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ABSTRACT

Age-related changes in mastication-induced brain neuronal activity have been suggested. However, in humans, little is known about the anatomical regions involved. Using fMRI during cycles of rhythmic gum-chewing and no chewing, we have examined the effect of aging on brain regional activity during chewing in young adult (19-26 yrs), middle-aged (42-55 yrs), and aged (65-73 yrs) healthy humans. In all subjects, chewing resulted in a bilateral increase in the BOLD signals in the sensorimotor cortex, cerebellum, thalamus, supplementary motor area, and insula, and a unilateral increase in the right prefrontal area. In the first three regions, the signal increases were attenuated in an age-dependent manner, whereas, in the right prefrontal area, the converse was seen. The remaining two regions showed no significant differences with ages. These results indicate that chewing causes regional increases in neuronal activity in the brain, some of which are age-dependent.

KEY WORDS: fMRI, gum chewing, brain activation, aging, human.

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INTRODUCTION

In recent years, much effort has been devoted to evaluating the interaction between gum-chewing and blood circulation in the human brain. Chewing has been shown to result in an increase in cerebral blood flow due to changes in internal carotid arterial blood flow (Suzuki *et al.*, 1994; Nakata, 1998). Using xenon-enhanced computed tomography to map the location of cerebral blood flow changes, investigators have found chewing to induce widespread increases in blood flow in the fronto-temporal cortex, caudate nucleus, and thalamus (Sesay *et al.*, 2000). In addition, cerebral blood flow imaging, by positron emission tomography (PET), shows increased blood flow in the bilateral lower frontal and parietal lobes during gum-chewing (Momose *et al.*, 1997). Consistently in these studies, cerebral blood flow during chewing is reported to be higher in young adults than in the elderly, implying an age-related decline in the chewing-induced increase in cerebral blood flow. However, because of the low spatial resolution of xenon-enhanced computed tomography and PET, it is difficult to identify the fine anatomical regions activated during chewing.

Functional magnetic resonance imaging (fMRI) has provided a new tool for the testing of specific hypotheses about the anatomical regions involved in processing sensory and motor information in the human brain (Pulvermuller, 1999; Yancey and Phelps, 2001). Blood oxygenation level-dependent (BOLD) contrast fMRI not only detects small signal changes that are related to changes in the magnetization of protons within the blood (Ogawa *et al.*, 1992), but also provides enhanced spatial and temporal resolution (Meisenzahl and Schlosser, 2001).

In this study, we used fMRI to assess the effect of aging on brain regional activity associated with chewing in young adult, middle-aged, and aged intact humans.

MATERIALS & METHODS

Subjects

Three groups of neurologically healthy subjects were included in this study: a young adult group (age 19-26 yrs; seven males and four females), a middle-aged group (age 42-55 yrs; five males and three females), and an aged group (age 65-73 yrs; eight males and five females). One subject in the young adult group and three in the aged group were excluded from the analysis due to a significant motion artifact. The number of remaining teeth in the young adult, middle-aged, and aged groups (mean $\pm$ SE) was 28 $\pm$ 0.2, 25 $\pm$ 1.7, and 19 $\pm$ 1.8, respectively. In addition, the mean biting force (Kgf, mean $\pm$ SE), measured by means of an occlusal force-meter GM10 (Nagano Keiki Seisakusyo, Ltd., Nagano, Japan), was 77.5 $\pm$ 6.62 in the young adults, 53.4 $\pm$ 7.41 in the middle-aged, and 26.7 $\pm$ 4.07 in the aged groups, respectively. In all subjects, mastication work was functionally normal. However, if there were chewing abnormalities, the experiments were carried out

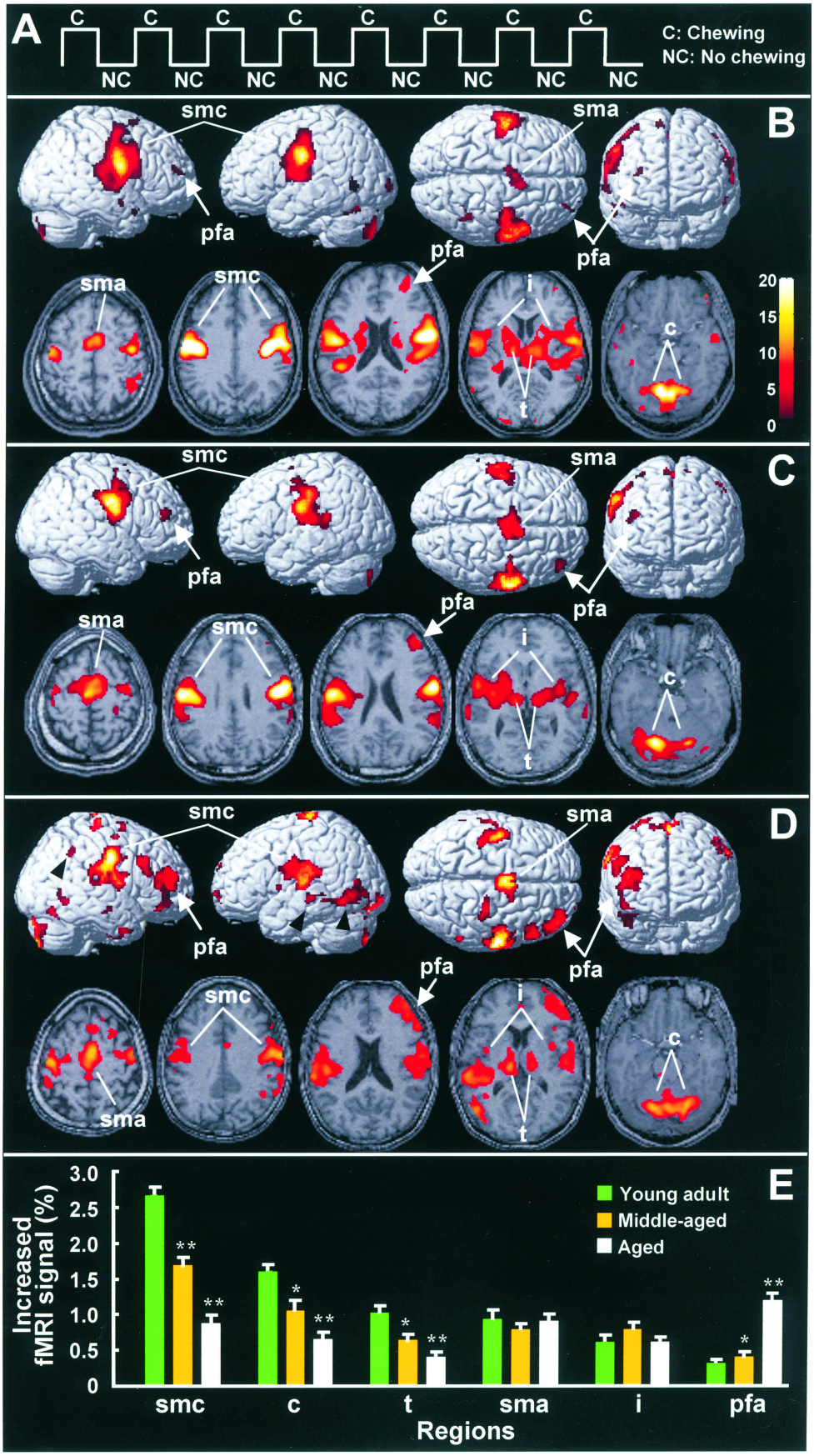

Figure. Effect of aging on brain regional activity during chewing. **(A)** The task paradigm used. **(B,C,D)** Significant signal increases associated with gum-chewing in a young adult subject (B), a middle-aged subject (C), and an aged subject (D). Upper section: Activated areas superimposed on a template ($p < 0.05$, corrected for multiple comparisons). Lower section: Activated regions superimposed on a T1 weighted MRI ($p < 0.001$, uncorrected for multiple comparisons). Abbreviations: smc, primary sensorimotor cortex; sma, supplementary motor area; i, insula; t, thalamus; c, cerebellum; pfa, prefrontal area. Arrowheads: Activated regions in the parietal, temporal, or occipital association cortices. Color scale: *t* value (degrees of freedom = 87.12). **(E)** Percentage increase in the fMRI signal in the young adult (Y, n = 10), middle-aged (M, n = 8), and aged (A, n = 10) groups. Each column represents the mean ± SE. *p < 0.05 compared with young adults. **p < 0.0001 compared with young adults.

after dental treatment (*e.g.*, repair of artificial crowns or the wearing of partial dentures). Written informed consent was obtained from each subject after a full explanation of the experiment, and the protocol for the use of human subjects was approved by the Ethics Committees of the Yoro Central Hospital.

Task Paradigm

The task paradigm was periods of rhythmic chewing, at a rate of approximately 1 Hz, measured by means of a metronome (Kemsley *et al.*, 2003), of moderately hard gum (5.6×10^4 poise) separated by periods of no chewing (see Suzuki *et al.*, 1994; Onozuka *et al.*, 2002). This gum, without odor and taste components, was specially prepared in the General Laboratory of Lotte Co. Ltd. (Saitama, Japan). Each subject performed 8 cycles of 32 sec of rhythmic chewing and 32 sec without chewing (see inset in Fig. A).

Image Acquisition

For each subject, functional (T_2* weighted) images, followed by an anatomical (T_1 weighted) image, were acquired by means of a 1.5-T Horizon MRI scanner (General Electric, Fairfield, CT, USA). The

functional images consisted of echo-planar image volumes which were sensitive to BOLD contrast in the axial orientation (TE = 44 ms, TR = 4000 ms). The volume covered the entire brain with a 64 x 64 matrix and 42 slices (voxel size = 3.75 mm x 3.75 mm x 4 mm, slice thickness = 3.8 mm, gap = 0.2 mm). Images with 64 volumes were acquired for this experiment.

Data Analysis

For data analysis, the first 8 volumes were discarded because of instability of magnetization. Head motion was monitored with the use of an analytical software package (MEDx, Sensor Systems, Inc., Sterling, VA, USA), and studies were rejected if a shift of greater than 0.75 mm (20% of voxel size) over the scanning time period was detected in any direction, since excess movement reduces both the spatial resolution and spatial fidelity. If head motion was < 0.75 mm, we applied a motion correction program, AIR 3.0, to the obtained images (Mazziotta and Cherry, 1993). Independently, a correction for head motion was also applied with the use of SPM99 software (Wellcome Department of Cognitive Neurology, London, UK). Furthermore, motion artifacts, which may have been due to chewing, were removed by a low-pass filter of 1.5 sec, with MEDx software. Finally, we confirmed that residual motion artifacts were less than 0.01 mm (0.267% of a voxel) in any direction.

The 128 successive functional images for each subject were normalized to the MNI template, provided by the Montreal Neurological Institute (Lutz *et al.*, 2000), and spatially smoothed with an 8-mm Gaussian kernel with the use of SPM99. Statistical analysis, based on the general linear model approach (Friston *et al.*, 1995), was used. Global changes in the BOLD signal were removed by proportional scaling. The resulting areas of activation were characterized in terms of peak height and spatial extent (> 20 voxels).

For quantitative evaluation of the increased fMRI signal seen during chewing, we calculated the difference between the signals while chewing and not chewing and expressed it as a percent change in the signal in the absence of chewing. The resultant data were analyzed by ANOVA followed by Scheffé's *post hoc* test.

Table. Significant Increases in the fMRI Signal during Gum-chewing: Anatomical Regions, Brodmann's Area (BA), and Maximal *t* Values (Degree of Freedom = 87.12) with Co-ordinates as Given in the **Talairach and Tournoux Atlas** (1988)

Subject	R/L	Region of Activation	BA	Maximal *t* Value	Talairach Coordinates of Max-voxel x	y	z
Young Adult	R	Supplementary motor area	6	11.69	6	4	54
	L	Sensorimotor cortex	3, 4	28.91	-48	-10	30
	R	Insula		4.92	36	4	6
	R	Thalamus		10.75	14	-16	4
	L	Cerebellum		23.82	- 8	-64	-18
	R	Prefrontal area	10, 46	5.32	34	58	14
Middle-aged	L	Supplementary motor area	6	8.27	-10	- 6	64
	L	Sensorimotor cortex	3, 4	18.36	-50	-10	42
	L	Insula		7.87	-40	-12	14
	R	Thalamus		7.60	22	-10	0
	L	Cerebellum		15.38	-10	-66	- 2
	R	Prefrontal area	10, 46	5.38	30	60	22
Aged	R	Sensorimotor cortex	6	13.11	2	- 8	70
	R	Supplementary motor area	3, 4	12.27	62	- 2	12
	L	Insula		8.05	-36	- 4	- 2
	L	Thalamus		7.00	-10	-20	6
	R	Cerebellum		11.42	24	-64	-22
	R	Prefrontal area	10, 46	8.21	40	54	18

RESULTS

In agreement with a previous finding (Onozuka *et al.*, 2002), in young adult subjects, gum-chewing was always associated with significant bilateral increases in the BOLD signal in the primary sensorimotor cortex, extending down into the upper bank of the operculum and insula (Fig. B). In addition, increases were seen in the supplementary motor area, thalamus, insula, cerebellum, and right prefrontal area. The locations of the most significant foci of activation for these regions are summarized in the Table, in which the anatomical regions with maximal *t* values in clusters and the coordinates, as given in the Talairach and Tournoux (1988) atlas, are shown. In contrast, in middle-aged subjects, the signal increase was lower in the primary sensorimotor cortex, thalamus, and cerebellum, and higher in the right prefrontal area, than in the young adults (Fig. C). In the aged subjects, these differences were even greater (Fig. D). Furthermore, in only the aged subjects, gum-chewing caused activation of the parietal, temporal, and occipital association cortices (Fig. D, arrowheads), the exact regions varying between subjects (data not shown).

Quantitative analysis revealed that the gum-chewing-induced increase in the signal in the primary sensorimotor cortex of middle-aged and aged subjects was, respectively, 63.3% (group effect: $F_{2, 25} = 59.41$, $p < 0.0001$) and 32.7% (group effect: $F_{2, 25} = 59.41$, $p < 0.0001$) of that seen in young adults, while the corresponding values for the cerebellum were 65.9% (group effect: $F_{2, 25} = 16.12$, $p < 0.05$) and 40.5% (group effect: $F_{2, 25} = 16.12$, $p < 0.0001$), and those for the thalamus were 62.0% (group effect: $F_{2, 25} = 12.34$, $p < 0.05$) and 38.5% (group effect: $F_{2, 25} = 12.34$, $p < 0.001$) (Fig. E). In the prefrontal area, the signal increase in middle-aged and aged subjects was, respectively, 174.3% (group effect: $F_{2, 25} = 27.58$, $p < 0.05$) and 412.7% (group effect: $F_{2, 25} = 27.58$, $p < 0.0001$) of that seen in young adults. However, no significant difference was seen in the supplementary motor area (group effect: $F_{2, 25} = 0.36$) or insula (group effect: $F_{2, 25} = 1.01$).

DISCUSSION

In this study, in agreement with previous PET (Momose *et al.*, 1997) and fMRI (Onozuka *et al.*, 2002) findings, gum-chewing significantly activated the oral region of the primary sensorimotor cortex, supplementary motor area, insula, thalamus, and cerebellum. These regions are believed to receive sensory information from the lips, tongue, oral mucosa, gingivae, teeth, mandibles, and temporomandibular joint and to control masticatory movement and the lingual and facial muscles

(Nakamura and Katakura, 1995; Nakata, 1998), and therefore may be called the masticatory center (Nakamura and Katakura, 1995).

Our new finding is that, in the primary sensorimotor cortex, cerebellum, and thalamus, the chewing-induced increase in the BOLD signal was attenuated in an age-dependent manner. Studies on aging and mastication have shown that the loss of teeth and the masticatory muscle power deficits seen with advancing age impair masticatory function, thereby causing a reduction in sensory input activity to the central nervous system (Okimoto *et al.*, 1991). In the present experiments, biting force was highest in the young adult group, followed by the middle-aged group, and lowest in the aged group. A similar age-dependent decline was seen in the number of remaining teeth. Taken together with the fact that age-related degeneration of various brain regions, including the somatosensory cortex, occurs in humans (Godde *et al.*, 2002), it may be suggested that the age-related attenuation of the signal seen in the above three regions results from an age-dependent decrease in both masticatory work and neuronal activity in the brain.

Surprisingly, our results indicate that, in all groups, gum-chewing resulted in an increased BOLD signal in the right prefrontal area, and in aged subjects, this increase was 4 times higher than that seen in young subjects. A previous PET study found that patients with early Alzheimer's disease show increased activity in the prefrontal regions compared with healthy age-matched controls during cognitive tasks (Grady *et al.*, 2001a). Furthermore, these authors also showed that increased right prefrontal cortex activity is associated with better memory performance in both groups (Grady *et al.*, 2001b); this has been interpreted as compensatory re-allocation of cognitive resources (Grady *et al.*, 2003). With respect to Alzheimer's disease and aging, the single most vulnerable circuit in the cerebral cortex is the projection referred to as the perforant path (Squire and Zola-Morgan, 1991), which originates in the entorhinal cortex and terminates in the dentate gyrus, thus providing the key interconnection between the neocortex and hippocampus (Amaral and Witter, 1989; Witter *et al.*, 1989). Thus, if the interpretation of Grady *et al.* is correct, it is possible that, in the elderly, chewing stimulates neuronal activity within a network between the right prefrontal cortex and the hippocampus, which might be useful in maintaining cognitive function.

However, the exact link between gum-chewing and activation of the parietal, temporal, and occipital association cortices is unclear at the present time, and further research is required.

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