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Original article

# Effects of tooth loss on brain structure: a voxel-based morphometry study

Takuya Kobayashi[a], Masafumi Kubota[a], Toshiyuki Takahashi[a], Ayaka Nakasato[a], Taro Nomura[a], Junichi Furuya[b], Hisatomo Kondo[a,*]

[a] Department of Prosthodontics and Oral Implantology, School of Dentistry, Iwate Medical University, Morioka, Japan,
[b] Department of Oral Health Science for Community Welfare, Faculty of Dentistry, Tokyo Medical and Dental University, Tokyo, Japan

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ABSTRACT

*Purpose:* One of the most prominent issues in a super-aging society is the rapid increase in dementia patients. Cross-sectional studies in dentistry have indicated that patients with dementia have worse oral health compared to healthy people. The purpose of this study was to clarify the influence of tooth loss on brain structure by comparing the volumes of gray matter (GM) and white matter (WM) between edentulous and dentulous subjects.

*Methods:* Subjects were recruited from the Denture Clinic at Iwate Medical University Hospital Dental Center. Experiments were performed on edentulous (5 males, 8 females, 81.8 ± 1.24 years) and dentulous subjects (4 males, 7 females, 77.1 ± 4.25 years). Patients with dementia were excluded from this study. Brain volumes of GM and WM in edentulous and dentulous subjects were compared using intracranial volume, age, gender and history of hypertension as covariates. Analyzed brain areas were identified by transforming the Montreal Neurological Institute coordinate into the anatomical coordinate in edentulous subjects.

*Results:* The analysis of WM structural images found no morphological differences between dentulous and edentulous subjects. However, significant atrophy of GM was observed in the hippocampus, caudate nucleus and temporal pole of the right hemisphere in edentulous subjects.

*Conclusions:* The results of this study suggest that tooth loss was a causal factor for volume reduction in brain areas related to memory, learning and cognition.



## 1. Introduction

Recently, it has become a big issue that rapid increase in the need for nursing care due to the extension of the average life expectancy in advanced countries. Dementia is one of the main causes of being in needs of care. According to the 2015 World Alzheimer Report, the total number of patients with dementia is estimated to reach 132 million people in 2050, that will be 3 times the current population. Cross-sectional studies in dentistry have been conducted to investigate the relationship between oral condition and dementia. It has been previously reported that patients with dementia had more carious teeth, missing teeth, periodontal disease, unstable dentures and unclean oral cavities than healthy subjects [1–8]. These unfavorable oral conditions could be attributed to the patient's inability to obtain routine oral care [3,4,8,9]. Kikutani et al. reported the relationship between oral condition and dementia, suggesting that oral care and rehabilitation could inhibit the decline of cognitive function in dementia patients [10]. Another study also indicated that there was a negative correlation between the number of residual teeth and the risk of acquiring dementia [11]. In addition, it was shown that few teeth without dentures and lack of regular dental care were related to dementia onset in the elderly [12]. However, cross-sectional studies do not show a causal relationship between dental health status and factors for the development of dementia.

Animal studies have suggested that molar tooth loss might produce neuronal cell loss in the hippocampus and consequently induce memory impairment [13]. Moreover, Riviere et al. pointed out the relationship between oral infection and Alzheimer's disease (AD), on basis of the detection of oral Treponema in the human brain [14]. Although there are a large number of studies showing close relationships between oral and brain function [15–19], its association with dementia remains unknown.

* Corresponding author at: Department of Prosthodontics and Oral Implantology, School of Dentistry, Iwate Medical University, 1-19 Uchimaru, Morioka, Iwate 020-8505, Japan.
*E-mail address:* hkondo@iwate-med.ac.jp (H. Kondo).

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**Table 1**
Characteristics of the subjects.

| | Dentulous | Edentulous |
|---|---|---|
| Subjects | $n = 13$ | $n = 11$ |
| Age | $81.8 \pm 1.24$ | $77.1 \pm 4.25$ |
| Sex (male/female) | 5/8 | 4/7 |
| Weight (kg) | $55.0 \pm 6.1$ | $55.4 \pm 10.7$ |
| ICV ± S.D. | $1417717.7 \pm 135227.5$ | $1425501.6 \pm 136498.8$ |
| Hypertension | $n = 2$ | $n = 1$ |
| Diabetes | 0 | 0 |
| Cranial disease | 0 | 0 |
| Nervous disease | 0 | 0 |

In contrast, Onozuka et al. have investigated the effects of recovery of oral condition and function on higher brain function. Elderly people activate more brain areas while masticating, compared to younger adults [20]. Furthermore, in our preliminary study normal activations of the basal nucleus and cerebellum were observed in dentate subjects, which are related to adjustment of masticatory patterns and cognitive functions, but no activations were found during mastication in edentulous subjects.

With the expansion of medical imaging technology, voxel-based morphometric (VBM) studies have recently gained attention as a method to investigate changes in brain morphology. The VBM method is used as a morphological diagnostic imaging technique based on three-dimensional magnetic resonance imaging (MRI) and is capable of detecting both gray matter (GM) and white matter (WM) alterations by evaluating each voxel. Previous studies employing VBM showed atrophy of the hippocampus, parahippocampal gyrus, entorhinal cortex, middle temporal gyrus and anterior and posterior cingulate gyrus in Alzheimer's disease patients [21–23]. Moreover, another VBM study showed atrophy in the area from the hippocampus to the parahippocampal gyrus in patients with mild cognitive impairment [24]. Thus, VBM can be used to assess brain atrophy, and is a minimally invasive and observational method to assess dementia. In this study, we attempted to elucidate the effects of tooth loss on brain tissue, comparing the volume of GM and WM between edentulous and dentulous subjects by VBM. Results of this study might propose importance of teeth maintenance to prevent brain atrophy.

## 2. Materials and methods

### 2.1. Subjects

Subjects were recruited from the Denture Clinic at the Iwate Medical University Hospital Dental Center. They were divided into edentulous who have been in edentulous condition at least for 10 years (6 males, 8 females, $78.5 \pm 4.90$ years [mean ± SD]) and dentulous subjects who have more than 20 teeth and belong to type A of Eichner classification (5 males, 9 females, $81.1 \pm 2.62$ years). Exclusion criteria included subjects showing diffuse marked atrophy or enlargement of the perivascular space over 10 mm from a MRI brain image. In addition, subjects were questioned about hypertension, diabetes, encephalopathy and neurological disease. No subjects had past histories of diabetes, encephalopathy or neurological disease, but some had past histories of hypertension. For this reason, hypertension was used as a covariate. To exclude patients with dementia, the mini-mental state examination (MMSE) was performed (Table 1).

Three subjects were consequently excluded from this study; therefore, experiments were performed on 13 edentulous (5 males, 8 females, $81.8 \pm 1.24$ years) and 11 dentulous subjects (4 males, 7 females, $77.1 \pm 4.25$ years) (Fig. 1). All the edentulous subjects have worn upper and lower complete dentures with stable occlusal condition. This study was approved by the Ethical Committee for Human Research of the Faculty of Iwate Medical University (No. 01071) and the subjects gave informed consent according to institutional guidelines.

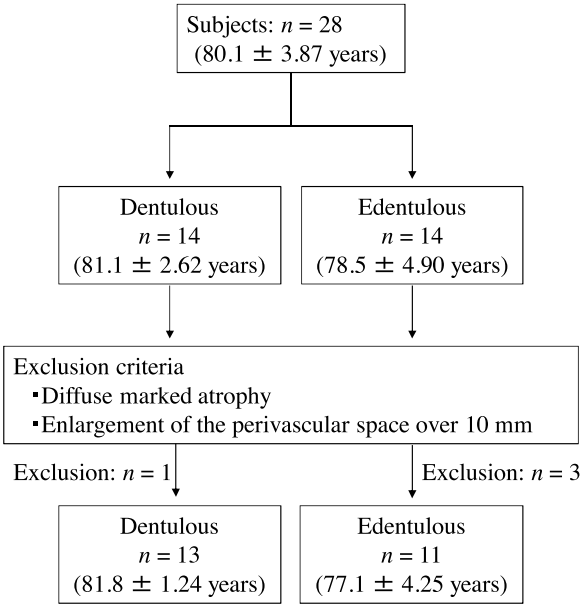


**Fig. 1.** Flow diagram of the selection of subjects and exclusion criteria.

### 2.2. Brain MRI scans and data analysis

The MRI scans were performed using a 3.0 T MR scanner (Signa EXCITE HD, GE, Medical Systems, Milwaukee, WI, USA). Structural data were captured by T1-weighted imaging according to image acquisition protocol, repetition time (TR): 7.6 ms, echo time (TE): 1.56 ms, flip angle (FA): 15°, field of view (FOV): $240 \times 240$ mm, slice thickness: 1.4 mm, slice gap: 1.4 mm, matrix size: $256 \times 256$ and voxel size $0.94 \times 0.94 \times 1.40$. Using statistical parametric mapping (SPM) 12 (Wellcome Department of Imaging Neuroscience, University College, London, UK), the brain volume of edentulous subjects was compared to dentulous subjects, applying VBM analysis.

The following processes were preparatory for VBM in SPM12. Digital imaging and communications in medicine (DICOM) acquired by the MR scanner was transferred from imaging data to the Neuroimaging Informatics Technology Initiative (NIfTI) file, and three-dimensional T1-weighted images were segmented into GM, WM and cerebrospinal fluid. To achieve higher registration accuracy, the diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) was used to calibrate a group template. Finally, the images were smoothed with a Gaussian kernel of 8 mm full-width at half maximum to reduce individual variability. Brain volumes of GM and WM in edentulous and dentulous subjects were statistically compared in the point of view from intracranial volume, age, gender and history of hypertension as covariates. Analyzed brain areas were identified by superimposing the Montreal Neurological Institute coordinate on the anatomical coordinate.

## 3. Results

The mean MMSE scores of dentulous and edentulous subjects were 28.5 and 28.8 points, respectively (Fig. 2).

The analysis of WM structural images showed no morphological differences between dentulous and edentulous subjects. In

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