Review Article

Edentulism (missing teeth) and brain central nervous system (CNS) deafferentation: a narrative review

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Background and Objective: Edentulism is a major public health issue that poses plenty of systemic health ramifications. The absence of teeth impairs an individual's ability to speak and alters their facial aesthetics negatively. Moreover, edentulism undermines the ability to adequately chew food, particularly those with firmer textures, which are often nutrient-dense fruits and vegetables. Nevertheless, the dental deafferentation (DD) that characterize tooth loss and its deleterious impact on the brain is a budding paradigm. The objective of this narrative review is to explore the effects of edentulism on the central nervous system (CNS) via the process of deafferentation.

Methods: We reviewed the literature from 1985 to 2021 to identify all relevant studies published regardless of study design across PubMed. Studies in languages other than English were excluded.

Key Content and Findings: The process of DD secondary to tooth loss eliminates several peripheral afferent neural inputs, which can cause central reorganization of the sensory and motor cortices. Adequate mastication with complete dentition reinforces such neural functional streams. As such, DD and the resulting, impaired mastication forces the brain to undergo neuroplastic changes, which are often accompanied by detrimental effects. When the DD impacts neural networks associated with the facial and vestibulocochlear nerves, taste and hearing deficits may result respectively. Cognitive decline may follow DD and edentulism—the impaired cerebral blood flow that follows suboptimal mastication, the poor, nutrient-sparse diets of edentulous individuals, and the chronic inflammation associated with periodontitis among edentulous individuals are the key mechanisms behind this link. The neural stresses imposed by DD and edentulism in excess can damage the brain to an extent enough to trigger Alzheimer's disease (AD).

Conclusions: The neural implications edentulism on the brain are vast, from sensory deficits to cognitive decline, extending far beyond facial aesthetics and ability to chew. The neural interconnectedness among the teeth, mastication, and the brain suggest novel interventions that can be taken to promote brain health and prevent the exacerbation of neurodegenerative disease.

Keywords: Edentulism; mastication; dental deafferentation (DD); central nervous system (CNS)

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Introduction

Edentulism is the unconditional and irreversible state of losing all natural (i.e., permanent) teeth. Deemed the dental equivalent of mortality—the terminus of periodontal disease and dental caries, edentulism is certainly a major public health issue (1). The incidence of edentulism is higher among certain populations: older, poor female individuals with a high school education or less who smoke. This is relative to wealthier, male individuals with a higher level of education who do not smoke (2,3). Additionally, arthritis, asthma, diabetes, and insufficient visits/access to a dental center were independently associated a decreased incidence of edentulism (4,5).

A testament to advances in preventative dentistry, edentulism has fortunately been on a steady decline over the years. From 18.9% in 1957–1958, the prevalence of edentulism significantly declined to a trivial 4.9% in 2009–2012 (6). This decline was particularly marked among the more affluent households. Further, this decline appears to persist over the upcoming years. In a study that utilized data five national cross-sectional health surveys, Slade *et al.* project that the prevalence of edentulism will reach as low as 2.6% by the year 2050—this continual decline is, however, counteracted by the ever increasing world population, especially the elderly subpopulation, who are more likely to be edentulous (6).

The health ramifications of edentulism are plenty. More evidently, edentulism worsens an individual's facial appearance as well as several basic functions, such as the ability to eat and speak. Compromised mastication causes individuals to avoid fruits and vegetables, which are nutrient-dense foods. Reduced fiber intake can incite chronic inflammation of the gastric mucosa, peptic or duodenal ulcers, and even upper gastrointestinal and pancreatic cancer (7).

Ndegwa *et al.* conducted a prospective cohort study to determine whether an association existed between oral health and gastric cancer. The authors determined that subjects with fewest teeth at baseline had an increased risk of gastric cancer at follow-up relative to those with all examined teeth present This risk was greatest amongst the youngest age group and diminishes with older age groups (8). In the same vein, another prospective cohort study determined that tooth loss was associated with increased risk of gastric non-cardia cancer (9).

Insufficient antioxidants can warrant the development of cardiovascular disease (7). Taguchi *et al.* conducted a cross-sectional study to determine whether tooth loss was associated with hypertension amongst post-menopausal women. The authors determined that subjects with missing teeth had significantly higher diastolic blood pressure relative to subjects without missing teeth. After controlling for covariates (i.e., obesity, hypercholesterolemia, and hypertriglyceridemia), subjects with missing teeth were 3.59 times more likely to have hypertension relative to subjects without missing teeth. The authors believed this eventual result was largely due to a disparity in diet between the two study groups—subjects with missing teeth had decreased levels of vitamin C, an antioxidant (10). Further, abundant intake of heavily processed fat and carbohydrate-rich foods lead to obesity and obesity-related diseases, such as insulin resistance and diabetes (7).

Further, edentulous individuals electively avoid partaking in social activities due to the feelings of shame they could experience due to their facial appearance and impaired speaking ability. Igarashi *et al.* quantified the impact of tooth loss on an individual's social life. The authors conducted a cross-sectional study to determine whether vision, hearing and tooth loss were linked to decreased social interaction, which was defined as 'not meeting my friends'. Igarashi *et al.* determined that tooth loss, after adjusting for confounders, was associated with an increased risk of decreased social interaction (11).

This self-imposed social handicap that edentulism imparts on the individual jeopardizes his/her mental health, self-esteem, and wellbeing, psychologically predisposing him/her to hopelessness and depression (5). In a qualitative study on 50 edentulous individuals, Fiske *et al.* determined that denture wearers have reduced self-confidence, premature aging, altered self-image, insecurity over their prothesis, and diminished capacity to form close relationships (12).

A newly hypothesized paradigm of health ramifications secondary to edentulism entails the central nervous system (CNS). At the University of Pennsylvania School of Dental Medicine, Dr. Jou discussed the different means by which a process known as dental deafferentation (DD) damages the brain. In this article, we shall focus on the effects of edentulism on the process of deafferentation, particularly on the CNS. We shall explore the latest research that has been conducted on different aspects of this rather novel paradigm in oral and maxillofacial medicine. We aim to identify the different mechanisms by which a diseased stomatognathic system affects contributes to cognitive decline [e.g., Alzheimer's disease (AD)] and neurodegenerative diseases. We reviewed the literature to identify all studies published thus far regardless of study design across multiple databases. We present this article in accordance with the Narrative Review

Table 1 The search strategy summary

Items	Specification
Date of search	08/01/2021–11/01/2021
Databases and other sources searched	PubMed
Search terms used	Edentulism; tooth loss; dental deafferentation; edentulism and CNS damage; edentulism and cognitive; edentulism and senses
Timeframe	1985–2021
Inclusion and exclusion criteria	Inclusion criteria consisted of articles written in English that addressed the topic at hand. No particular study type was preferred. Excluded articles written in languages other than English
Selection process	The selection process was independently conducted by Dani Stanbouly

CNS, central nervous system.

reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-117/rc).

Methods

A narrative review was conducted to achieve the aims of the following study. PubMed was queried to identify all relevant articles. To enable a more comprehensive review, the inclusion criteria was not limited to a specific study design. Consistent with others (13), the authors also did not deem it necessary to critique the selected articles. The selection process was conducted by author D.S. using the following terms: edentulism; tooth loss; dental deafferentation; edentulism and CNS damage; edentulism and cognitive; edentulism and senses. Additionally, the references within the selected articles were screened to determine any more relevant articles that could supplement the review (*Table 1*).

What is DD?

DD is the process by which peripheral afferent neural inputs are eliminated in relation to dental and masticatory apparatuses. Tooth loss, local and/or generalized periodontal detachment, inadequate operative or prosthetic restorations, and orthodontic managements are all examples of DD. No correlation between DD and markers of brain damage has yet to be proven—the jury is out on this hypothesis as it is put to the test (14).

The typical case of DD is tooth loss, often after exodontia. Other dental treatments can induce DD, such as root canal therapy (RCT). However, the resultant DD from RCT differs from that in tooth loss. Unlike RCT, tooth loss from exodontia rids the dentition of various structural and functional aspects. Structural components that are lost after exodontia include the transeptal fibers, Sharpey's fibers, proprioceptive receptors, and mechanoreceptors. Functional aspects of the dentition that are lost include interdental coordination between adjacent teeth as well as interarch relationships where the opposing arch no longer completes the masticatory function (14).

Impaired mastication secondary to multiple tooth loss has been shown to influence several neurologic processes. The process of mastication, with a healthy dentition, exercises many cortical regions of the brain, including but not limited to primary somatosensory cortex (SI) and the primary motor cortex (MI). Onozuka *et al.* conducted a functional magnetic resonance imaging (fMRI) study to explore the relationship between chewing and brain regional activity in 17 subjects. The authors determined that chewing increased blood oxygenation level-dependent (BOLD) signals specifically in the sensorimotor cortex, supplementary motor area (SMA), insula, thalamus, and cerebellum (15). Takahashi *et al.* attempted to identify which cerebral areas are involved in mastication with changes in food hardness. The authors determined that there were selective activations of the SMA, dorsolateral prefrontal cortex (DLPFC), and superior temporal gyrus (STG) of the left hemisphere, and the premotor area (PM) and inferior parietal lobule (IPL) of the right hemisphere as the hardness of chewing gum varied widely in oral cavity during mastication (16).

You see, our brain integrates various sensory and motor information associated with mastication—the sensations experienced within the oral mucosa as well as the operations of the masticatory muscles are etched in our CNS. In so doing, our brain renders eating an effortless and pleasurable habit. Thus, several neurological complications secondary to edentulism have been hypothesized and studied on the premise of the vital role mastication plays in the brain and its cerebral activity (14).

DD and the senses

Taste and olfaction can progressively weaken with DD and impaired mastication (17-19). Utsugi *et al.* sought to assess the effects of mastication on neurogenesis at the accessory olfactory bulb (AOB) and pheromonal responses. The authors determined that soft diet-fed rats exhibited decreased neurogenesis at the AOB relative to hard diet-fed rats. The number of synthesized bromodeoxyuridine-immunoreactive (BrdU-ir) cells at the caudal half of the AOB was significantly lower in mice fed soft diets relative to mice fed hard diets. Regarding phermonal responses, the numbers of Fos-ir cells in the rostral and caudal halves of the AOB were lower in mice fed soft diets months than those of mice fed hard diet after four months (18).

Another study by Boucher *et al.* determined that impaired mastication in the context of DDs from RCT therapy can caused taste deficits. The authors compared electrogustometric (taste) threshold among six study groups designated according to the number DD teeth—that is, extracted teeth or teeth treated with RCT. Subjects with more than seven deafferented teeth had significantly higher taste thresholds than subjects with less than seven deafferented teeth (17).

Another sense that is affected by DD and impaired mastication is hearing (20-24). Lawrence *et al.* investigated whether an association existed between tooth loss and hearing acuity or not in a 20-year longitudinal study. The authors determined that subjects who went from having greater than 17 teeth at baseline to less than 17 teeth at follow were more than 1.6 times more likely to suffer hearing decline relative to those with no change in their dentition. Further, every tooth lost since baseline resulted in 1.04-fold odds of acquiring hearing decline relative to a stagnant dentition (21). In a cross-sectional study on 1,004 subjects aged 36 to 84 years in Japan, Tanaka *et al.* found that higher number of teeth is associated with decreased prevalence of hearing impairment. After adjusting for covariates, the authors determined that subjects with 26 to 27 teeth, and 22 to 25 teeth were 1.4 and 1.5 times respectively more likely to suffer from hearing impairment relatively to subjects with 28 teeth. Most notably, having less than 22 teeth imposed a 1.9-fold risk of developing hearing impairment (24).

Several mechanisms are believed to underly the link between DD and hearing impairment. Deafferentation of the stomatognathic system can have systemic implications in the brain, restructuring sensory and motor cortices. This reactive process can trigger and aggravate neurodegenerative diseases, such as hearing impairment (24). It has also been proposed that the reduced vertical dimension of occlusion amongst edentulous patients impacts ear canal resonance and hearing (22). Peeters *et al.* sought to explore the extent to which hearing ability varied across the number of teeth and/or the number of occluding tooth pairs. Subjects were classified according into four groups: (I) complete dentures wearers in both jaws; (II) shortened dental arches; (III) full dental arches in both jaws; (IV) no occlusal stops (i.e., no occlusal vertical dimension). The authors determined that both air and bone conduction was significantly worse for subjects without vertical occlusion relative to the three other groups. Because edentulous subjects without occlusal stops had worse hearing loss relative to edentulous subjects with complete dentures, Peeters *et al.* believes that it is the loss of vertical dimension that influences hearing loss (23).

Finally, the low bone mineral density that characterizes periodontal disease, the terminal stage of which is edentulism, may be the culprit behind the resulting hearing impairment. The demineralization is believed to systemically pervade the aspect of the temporal bone that encapsulates the cochlea (24). A cross-sectional study on postmenopausal Korean women showed that low bone mineral density was a risk factor for hearing impairment (25).

DD and cognitive decline

Tooth loss and impaired mastication also have deleterious effects on cognition (26-34).

A 13-year longitudinal study investigating the association between the number of existing teeth and cognitive decline in China revealed the importance of a health dentition as a requisite to a healthy mind. By Mini-Mental Status Examination (MMSE), subjects expectedly illustrated cognitive decline with age. That being said, possessing a greater number of teeth significantly stalled the rate of cognitive decline (26). Another study conducted in Ecuador ended up with similar results. The subjects were classified according to whether they had severe edentulism (less than 10 teeth) or not. Cognitive functioning was gauged using the Montreal Cognitive Assessment (MoCA). After controlling for various cofactors, including dementia, MoCA scores among subjects with severe edentulism were significantly lower than those without severe edentulism (31). A cross-sectional study by Avlund *et al.* sought to determine whether cognitive function was related to oral disease in the elderly—159 individuals over the age of 80 were dentally and cognitively examined. Individuals with low cognitive

exam score were four times more likely to neglect regular professional dental care. They also had a higher risk of coronal caries than individuals with higher cognitive exam scores (27).

The results of Avlund *et al.* were replicated in another study that investigated the reciprocal relationship between cognitive function and edentulism among individuals aged 45 or older. A total of 17,076 respondents participated in the baseline surveys that determined cognitive function and edentulism. At follow-up 4 years later, 14,038 subjects from the original sample responded to the same survey. Interestingly, the impact of edentulism at baseline led to significantly lower levels of cognitive function at follow-up amongst the elderly (60 or older). This was not the same for individuals aged 45–59 (29).

The most severe cognitive complication that is associated with edentulism is AD (35-38). Dioguardi *et al.* conducted a meta-analysis investigating the association been tooth loss and AD. Qualitative analysis of the eligible studies revealed that, relative to patients without AD, patients with AD were 1.5 times more likely to develop tooth loss and 2.3 times more likely to wind up edentulous. However, the converse is not true. The mechanism behind this causal relationship, the authors believe is the memory impairment that accompanies AD: afflicted patients unintentionally neglect their dental hygiene, which leads to the corresponding tooth loss and edentulism (35). This mechanism has been supported by study investigating the relationship between tooth loss and cognitive function. Avlund *et al.* determined that individuals with low cognition were five times more likely to not use dental services regularly (27). That being said, a prospective cohort study by Takeuchi *et al.* that illustrated the added risk of incurring AD amongst edentulous patients, was acknowledged and elaborated upon in the meta-analysis. The authors determined that an inverse association between the number of remaining teeth and risk of incurring AD. Further, after controlling for all potential confounders, the authors determined that patients with 10 to 19 teeth, patients with one to nine teeth, and edentulous were 1.6, 1.8, and 1.6 times more likely to incur all-cause dementia relative to patients with 20 teeth or more (39). Even more, the number of teeth was shown to be associated with the extent of gray matter atrophy, further supporting the paradigm of edentulism as a proxy for dementia and its progress (40).

Takeuchi *et al.* purported several mechanisms for this association between edentulism, most of which are identical to those concerning edentulism and cognitive function. Firstly, the process of mastication with adequate dentition stimulates cerebral blood flow, activates cortical areas, and increases blood oxygen levels (41,42). A systematic review that explored the protective role of mastication against cognitive decline revealed that mastication greatly activated the frontotemporal cortex, the caudate nucleus, and the thalamus. Further, partially edentulous participants exhibited significant deactivation of the prefrontal cortex when they chewed without a prosthesis. This systematic review also illustrated a positive association between mastication and in regional cerebral blood flow. As such, the authors concluded that mastication may be protective in patients with cognition impairment and neurodegenerative diseases (43). Hence, impaired mastication in the case of edentulism compromises the aforementioned vital processes.

Another mechanism that potentially underlies the association between edentulism and AD concerns nutrition. As was discussed earlier, edentulism can markedly influence an individual's diet. Nutrient dense foods, such as fruits and vegetables often have rigid textures that necessitate adequate dentition. In contrast, processed foods often have delicate textures that are easy to chew. Hence, individuals with a declining number of teeth progressively substitute nutrient dense foods for processed foods. Many studies have articulated the link between poor oral health and malnutrition (44-46). Ioannidou *et al.* determined that tooth loss strongly associates with malnutrition among sufferers of chronic kidney disease. The authors classified the patients into five groups according to their dentition as follows: group 0 = complete natural dentition; group 1 = complete mixed dentition (natural teeth and replaced teeth); group 2 = incomplete (natural or mixed) dentition; group 3 = fully edentulous with full dentures; and group 4 = fully edentulous with no dentures. The rate of individuals who had a low protein intake of <1.2 g/kg/day was significantly different among the five groups, being highest among group 4 (13.9%)—this rate was much greater than the rest of the groups (group 3, 2.0%; group 2, 1.3%; group 1, 1.0%; group 0, 1.3%). The same trend followed for fraction of individuals who had a low caloric intake of <30 Kcal/kg/day. Further, for every five teeth lost, patients were 1.42 times more likely to have a low protein intake of <1.2 g/kg/day and 1.38 times more likely to have a low caloric intake of <30 Kcal/kg/day (44).

Cognitive ramifications follow a poor diet. Several studies have illustrated the link between nutrition and cognitive decline or AD (47,48). Tucker *et al.* investigated

whether a low serum vitamin B level predicted cognitive decline in aging men. Serum levels of the relevant vitamins were determined among 321 subjects, of whom the mean age was 67. Cognitive testing that assessed working memory (backward digit span), recall (word list memory test), language (verbal fluency), and spatial copying (constructional praxis) was conducted at baseline and 3 years later. The authors determined that constructional praxis score (i.e., ability to spatially manipulate designs and patterns) was positively associated with serum levels of folate and vitamins B-6 and B-12 and negatively associated with serum levels of homocysteine. Constructional praxis scores were also negatively associated with dietary intake of folate and vitamins B-6 and B-12 at baseline. Further, Homocysteine was significantly negatively associated with recall memory scores. Homocysteine, an amino acid that is elevated in the presence of insufficient serum levels of folate, vitamin B-12, or vitamin B-6 (49).

The final mechanism that was put forth by Takeuchi *et al.* was discussed earlier: the impact of chronic inflammation on the onset and progression of dementia. A common cause of tooth loss and edentulism, periodontitis transpires through both local and a systemic inflammation marked by the rise of several cytokines, such as interleukin-1, interleukin-6, C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) (50). Systemic inflammation, per se, has been shown to be associated with cognitive decline. Holmes et al conducted a prospective study investigating the effect of systemic inflammation on the progression of AD. The study entailed three-hundred subjects with mild to severe AD who were administered blood tests to measure the level systemic inflammatory markers, namely TNF-α, at baseline, two months later, four months later, and six months later. Further, caregivers of subjects were interviewed to identify whether the subjects experienced incidents of systemic inflammatory event, which was defined as a transient infection or trauma separate from the CNS with a minimum consequent serum CRP level of 1 μg/mL. High levels of TNF-α at baseline increased the rate of cognitive decline by four times. In contrast, subjects who had low levels of serum TNF-α throughout the study exhibited no cognitive decline at the 6-month follow-up (51).

Conclusions

The neural implications of DD and edentulism on the brain are vast, from sensory deficits to cognitive decline. Indeed, these nervous system complications reflect the vitality of healthy dentition and functional mastication. The issues of edentulism are more profound than previously thought, extending far beyond facial aesthetics and ability to chew. The neural interconnectedness among the teeth, the action of eating, and the brain exhibited by recent investigations suggest novel interventions that can be taken to promote brain health and prevent the exacerbation of neurodegenerative disease. A perfect smile should be deemed a marker of brain health to a similar magnitude as it is deemed a marker of oral health.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-117/rc

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