

## Masticatory Deficiency and Deficit of Cognitive Function, Attention, Learning and Memory

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### Abstract

Numerous animal and human evidence to date demonstrates the Masticatory Act as an entity not only responsible for the grinding and processing of nutritious food, but as a complex and refined system of recognition and transmission of stimuli to the Central Nervous System (CNS) through multiple sensory inputs and a complex communication network between the brain and the stomatognathic system currently defined as the brain-stomatognathic axis.

Mastication triggers metabolic processes responsible for maintaining not only the physical health, but mainly for the intellectual preservation of the individual and it is closely linked to the cognitive function.

As well as, masticatory deficiency resulting from occlusal disharmony, soft food diet or the absence of teeth, as a chronic stress agent that activates the hypothalamus-pituitary-adrenal axis (HPA) and increased circulating glucocorticoids as a promoter of various pathologies.

In this work, we make a brief integrative review including radiological exams, serological and behavioral analysis of the past 20 years in animals and humans with clear influence of masticatory dysfunction on hippocampal-dependent cognitive decline. The review includes recent longitudinal cohort studies of tooth loss and cognitive decline in humans.

**Keywords:** *Chewing; Mastication; Brain Activity; Cognitive Function; Chewing and Dementia*

### Introduction

Recently oral health and mastication have been highlighted in the context of cognitive performance. Animal and human studies demonstrate mastication as a relevant peripheral sensory input to the brain and to hippocampal-dependent memory and learning function [22,23]. Those studies also describe masticatory deficiency resulting from tooth loss or occlusal disharmony as a cause of hippocampal morphological and functional changes [3], causing harmful systemic effects such as hippocampal-dependent cognitive deficits, hypertension, cardiovascular disorders and osteoporosis [10].

Cognitive performance deteriorates with aging, so in young people, masticatory deficiency may not compromise hippocampal functioning in the short term, as there are other peripheral sensory inputs; but in the elderly, with decreased locomotor activity and decreased peripheral sensory receptor function, we have hippocampal function alterations.

Therefore, it is important to maintain the masticatory organs for cognitive function, especially in the elderly [1,3,10].

Mastication has also been shown to be an important preventive to cognitive impairment and masticatory deficiency associated with a soft food diet as a risk for the development of dementia.

Some articles consider tooth loss alone as a factor in mastication deficiency, increasing the risk for senile dementia or Alzheimer disease [2,3,8,10,11,15,19].

Dementia is a chronic or progressive syndrome in which there is deterioration in cognitive function beyond what is expected with normal aging. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment. Consciousness is not affected and is commonly accompanied or preceded by deterioration in emotional control, social behavior or motivation. It was the 5th cause of death in 2016 (WHO).

Other authors also describe tooth loss as a risk for the decline of the cognitive functions [12,15-17,22].

That said, the present work proposes a brief integrative review to assess the relationship between masticatory deficiency and impairment of cognitive function, attention, learning and memory. It includes recent longitudinal cohort studies of the association between tooth loss and cognitive decline in humans.

### Mastication

Mastication, the rhythmic act and first stage of digestion, is the process of breaking down food into smaller particles and bolus, in preparation for swallowing.

Grinding also occurs as a process of occlusal recognition and awareness, texture and hardness of food by the oral structures, called proprioception, which via orofacial mechanoreceptors of the trigeminal nerve reach the sensory nuclei of the trigeminal, cerebellum, motor nuclei of the hypoglossal nerve and the reticular formation of the brain stem; this being the sensory afferent path [1].

Although it is semi-autonomous, it is a function of the CNS [18] that involves neural networks in the brain stem and brain regions to control and create masticatory patterns [23].

The reticular formation and the ascending reticular activator system are necessary for brain excitation in attention, perception and conscious learning [1,23].

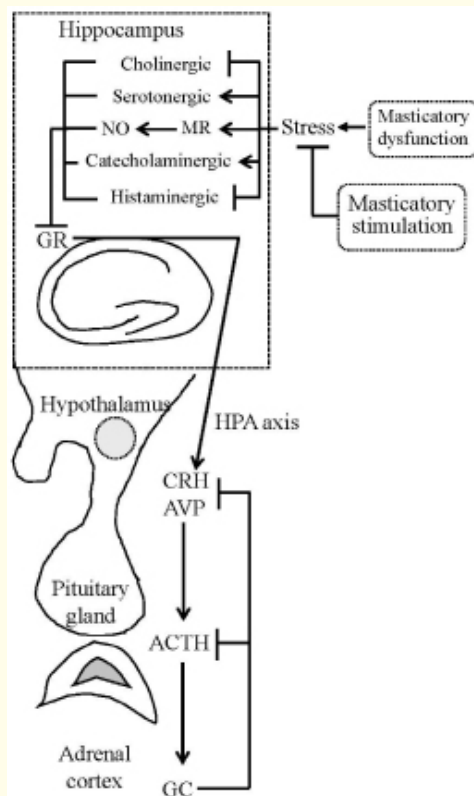
Mastication acts to stimulate the ascending reticular system, accelerating the cognitive process [2,5].

The neurons of the sensitive trigeminal nucleus reach the posterior ventral thalamic nucleus, the reticular formation and the hypothalamus. The information from the posterior ventral thalamic nucleus ends at the somatosensory cortex, whose neurons are projected into the somatosensory association area that has reciprocal projection with the entorhinal cortex. This is an important source for the hippocampal dentate gyrus (DG). That way, information from the masticatory organs reaches the hippocampus via the thalamus and the cerebral cortex. The hypothalamus receives input from the reticular formation and projects directly into the hippocampus as opioidergic and histaminergic fibers.

The hippocampus receives projections of noradrenergic, serotonergic and dopaminergic fibers from the locus coeruleus, raphe nuclei and ventral tegmental area that are part of the ascending reticular activation system [1].

During mastication, the mesencephalic trigeminal nucleus receives proprioceptive sensory stimuli of the trigeminal nerve from the muscle spindle of the masseter and periodontal ligaments [8].

The hypothalamic paraventricular nucleus (PVN) is a central component of the HPA axis containing neurons that secrete the corticotrophin-releasing hormone CRH and arginine vasopressin AVP. It receives afferent stimuli from various regions of the brain including the hippocampus, the amygdala and the prefrontal cortex [10].



**Figure 1:** Simplified diagram showing the relationship between mastication, the hippocampus, and hypothalamic-pituitary-adrenal (HPA) axis activity. Masticatory dysfunction, acting as a stressor, suppresses hippocampal choline and histamine levels, and elevates catecholamine, serotonin, nitric oxide (NO) levels, and mineralocorticoid receptor (MR) expression, and then reduces the hippocampal glucocorticoid receptor (GR) expression, leading to hypersecretion of hypothalamic corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), and HPA axis hyperactivity. Masticatory stimulation suppresses the hyperactivity of the HPA axis and thus ameliorates stress-induced disorders. ACTH, adrenocorticotrophic hormone; GC, glucocorticoid. Source: *Int J Mol Sci.* 2017 Aug; 18 (8): 1687 Published online 3 Aug 2017. Doi:10.3390/ijms18081687.

Mastication influences the functions of the hippocampus by regulating the HPA axis and its final product, the glucocorticoids [1,10]. And it increases the survival rate of the newly formed cells in the hippocampal dentate gyrus [23].

The organization of the HPA axis is highly conserved throughout the phylogeny of mammals and the fundamental aspects of the functioning of the HPA axis are similar throughout the phylogenetic path of rodents to humans [10].

Glucocorticoids Corticosterone (in rodents) and Cortisol (in humans) are present in almost all tissues and organs and regulate the intermediate metabolism, immune function, skeletal growth, cardiovascular function, reproduction and cognition. They also promote hepatic gluconeogenesis and increased glycogen storage in the liver. Excessive exposure to glucocorticoids promotes hyperglycemia and insulin resistance; they also influence the intestinal epithelial barrier, which is essential for the pathogenesis of inflammatory bowel diseases [10].

Corticosterone reduces cell proliferation and neurogenesis [7].

Therefore, activation of the HPA axis due to masticatory deficiency, recognized as a chronic stress agent, promotes an increase in circulating glucocorticoids and can trigger several diseases [10].

### Hippocampus

The term hippocampus is commonly used to describe two interconnected structures, the dentate gyrus and the Hippocampus proper or the Ammon's horn (CA). An internal trilaminar structure with two types of main cells: granule cells in the dentate gyrus and pyramidal cells in the regions CA1, CA2, CA3 in the Ammon's Horn.

The Hippocampus acts actively in the control of several hormones through the HPA (Hypothalamus-Pituitary-Adrenal) axis. It acts on CRH (Corticotropin-releasing Hormone) from the Hypothalamus, which promotes ACTH (Adrenocorticotropic Hormone) secretion by the anterior pituitary and corticosterone secretion by the adrenal cortex [1].

Target region of corticosterone action [3,9]. It contains a high density of Glucocorticoid receptors and is the target of the action of the stress hormone [1].

Spatial cognition is mainly controlled by the Hippocampus [8].

It is associated with learning, memory and mood. In humans, it is important for the formation and recovery of episodic memories [1,23].

It is also one of the two brain structures responsible for the formation of neurons, NEUROGENESIS in adults. That occurs in the SGZ (subgranular zone) in the hippocampal dentate gyrus and in the SVZ (subventricular zone) of the forebrain [1,20]. The neurogenic niche [1,7].

The hippocampal Dentate Gyrus (DG) plays a key role in decoding contextual and spatial information, separating patterns and detecting novelty [1].

CA1 and CA3 are critical areas in the recognition of a familiar item and in the detection of a new visual object in a temporal context [9].

Tsutui *et al.* reported that the sustained reduction in masticatory stimulation induces loss of pyramidal cells in CA1 and CA3 [3,9].

### Areas that are Activated During Mastication

Mastication promotes increased cerebral blood flow [5,8,10,15,16,21] and plasma oxygen [21] in the prefrontal cortex and in the hippocampus [1,11,16,23].

Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) studies in humans indicate that the following areas are activated during mastication:

Primary somatosensory cortex, primary motor cortex, supplementary motor area, premotor area, prefrontal cortex, insula, posterior parietal cortex, thalamus, striatum and cerebellum [3,19,23].

There is also an increase in blood flow in the bilateral lower frontal lobe and parietal lobes, right premotor cortex, precuneus, thalamus, hippocampus and in the lower parietal lobe while chewing gum [3].

Computed tomography and functional magnetic resonance imaging (CT and FMRI) also show increased bilateral blood flow in the frontal (lower portion) and parietal lobes while chewing gum, with activation in the somatosensory areas, motor cortex, insular cortex, thalamus and cerebellum [3,15,19].

However, several authors report that different brain areas are activated during mastication and that these areas differ during mastication cycles according to the hardness of the food, use of prosthesis and the individual's age range.

In 2003 Onozuka and colleagues in a study with fMRI [18] observed age-related differences in brain activation, during cycles of rhythmic mastication and without it.

With 3 age groups, young (19 to 26 years old), middle age (42 to 55) and elderly (65 to 73), the results revealed a central mastication network, including the sensorimotor cortex, thalamus, cerebellum, frontal cortex , supplementary motor area and premotor cortex [17]. Older individuals showed an increased activity in the prefrontal area and a decreased activity in the somatosensory cortex and cerebellum [19].

**Search criteria:**  
**1. Key word combination: (chewing OR mastication OR "tooth loss" OR "teeth loss") AND MRI and brain**  
**2. Language: English**  
**3. Publication date: 2012.10.15–2017.10.15**

Reference	Task	MRI findings
Inamochi et al. 2017 [78]	Chewing, before (Day 0) and after (Day 1/Day 7) inserting a palatal plate	Decreased activation in the bilateral face S1/M1, putamen, left ACC, and right medial posterior frontal cortex on Day 1 vs. Day 0. Activation in the right S1/M1 and putamen recovered to Day 0 level by Day 7.
Choi et al. 2017 [65]	Gum chewing	Brain activations at the entorhinal cortex and the parahippocampal cortex, based on an region-of-interest analysis
Lotze et al. 2017 [67]	Rubberdam chewing	Increased activation at bilateral S1, S2, M1, PMC, SMA and CG, anterior CB, INS, OFC, THA and left pallidum
Lin et al. 2017 [74]	Resting (task-free) condition	The older subjects presented a different functional network associated with masticatory performance, compared to the younger subjects
Lin et al. 2015 [72]	Resting (task-free) condition	Grey matter volume in the motor and frontal regions, and the functional connectivity of the cerebellum, was associated with masticatory performance
Viggiano et al. 2015 [71]	After vs. before a mastication exercise (gum chewing)	Increased perfusion at the principal trigeminal nucleus but not in the dorsolateral-midbrain
Jiang et al. 2015 [66]	Rhythmic chewing	Increased activation at sensorimotor cortex contralateral to the chewing side of preference (CSP), midbrain and brainstem for left CSP, and CB for right CSP
Shoi et al. 2014 [70]	Gum chewing	full arch (with a removable partial denture, RPD) vs. short-dental arch (SDR) Increased activation at middle FG, S1/M1, SMA, putamen, INS and CB for RPD group; no activation at middle FG in SDR group
Luraschi et al. 2013 [68]	Three tasks <sup>a</sup> , patients with a complete denture	(Across all three functional tasks) Increased activation at bilateral pre (M1) and post (S1) central gyrus
Hirano et al. 2013 [81]	Two back-to-back ANT sessions with or without gum chewing	(During chewing) increased activation at anterior CG and left FG for the executive network; motor-related regions for attentional networks
Quintero et al. 2013a [69]	Gum chewing	Increased activation at CB, motor cortex, caudate nucleus, CG, and brainstem
Quintero et al. 2013b [73]	Gum chewing	Increased FC between bilateral M1 and S1, CB, CG and precuneus; increased FC between CB and contralateral CB, bilateral sensorimotor cortex, left superior temporal gyrus, and left CG
Yu et al. 2013 [82]	Stress induced by loud noise; gum-chewing	Anterior INS -dACC FC was increased by noise to a lesser extent during gum-chewing (vs. no gum-chewing)

CB the cerebellum, CG the cingulate gyrus, dACC the dorsal anterior cingulate cortex, FC functional connectivity, FG the frontal gyrus, INS the insula, M1 the primary motor cortex, OFC orbitofrontal cortex, PMC the premotor cortex, S1/S2 primary/secondary somatosensory cortex, SMA supplementary motor area, THA thalamus

<sup>a</sup>The tasks included lip pursing, jaw tapping and jaw clenching

Figure 2: Publications of 5-year neuroimaging studies on mastication and brain activity [17].

In 2017 Chia-Shu Lin and colleagues assessed functional connectivity and masticatory performance, which is a clinical index that assesses the general masticatory function.

Based on the 12 bilateral brain regions related to mastication and fMRI at rest, 52 healthy adults, 26 older ( $\geq 54.5$  years) and 26 younger ( $\leq 54.5$  years).

In the young group, they observed a greater connection between sensorimotor areas, thalamus and cerebellum; in the elderly group this connection is sparse with a greater signal distributed over several centers outside the sensorimotor areas spread over the superior parietal lobe, anterior insula and the anterior dorsal cingulate cortex.

Also, in the elderly, including the right superior parietal lobe, right superior insula and the bilateral superior cingulate cortex. Concluding that, in the elderly, the masticatory performance is in the activation of centers related to mastication and the connectivity between them. Young people chew automatically without additional effort to monitor their movements [18].

A Quintero and colleagues [18] in a fMRI study with healthy young humans chewing gum also demonstrated specific areas associated with mastication and that brain activation changes along the masticatory sequences in the cerebellum, motor and tail cortex, cingulate and trunk cerebral [4].

It was observed in rats model of Alzheimer, that the modulation of neurogenesis by the Hippocampus when influenced by the prolonged soft food diet promotes a decrease in neuronal proliferation and impaired learning and memory.

Just as a subsequent mastication with a hard food diet improves neurogenesis in mice [1,7,10,20]. And that masticatory deficiency decreased the hippocampal volume, not only causing neuronal degeneration, but also inducing an increase in astrocytes, which is associated with aging [1,3].

In addition, it has been shown that molar loss induces an increase in plasma corticosterone [20] and a decrease in glucocorticoid receptors (GR) and messenger glucocorticoids (RNA) in the hippocampus [3,9]. These changes are similar to those that occur in chronic stress or long exposure to corticosterone [3].

Also, recent research in animals and humans using neuroimaging, describes how in a short time oral changes due to loss of dental structures promote morphological and functional changes in the hippocampus, the main place of learning and spatial memory [7,9].

It also shows mastication as an important preventive to cognitive impairment and that masticatory deficiency associated with a soft food diet is a risk for the development of dementia. As well as, tooth loss alone, as a deficiency factor in the masticatory condition and a risk for senile dementia or Alzheimer's disease [2,3,8,10,11,15,19].

### Mastication and Stress

Mastication is an effective behavior for coping with stress [5,8,10,11,17,23].

Stress is a psychological and physiological response to harmful stimuli and environmental changes [8] that activate the autonomic and neuroendocrine system through the HPA axis [10], releasing hormones and corticosteroids [8,23]. It causes influx of  $Ca^{++}$  in neurons via activation of corticosterone receptors, attenuation of cellular excitability and LTP (long-term potentiation) of the hippocampus [1].

Acute and chronic exposure to stress impairs the neurogenesis of the hippocampus, reduces the proliferation of progenitor cells and suppresses neuronal differentiation and cellular survival of the DG [10].

It negatively affects physical and mental health leading to illness.

The increase in corticosterone due to stress impairs the hippocampal-dependent learning and memory [8].

Studies with rodents and humans demonstrate that the hippocampus is not only involved in memory and is highly sensitive to aging and stress [1,3,8,10]. It is one of the first brain regions to be structurally and functionally modified by stress [8]. And, that the prefrontal cortex dominates the stress response system, including the HPA axis [10].

### Mastication

Attenuates the HPA axis [8,10,17], the main neuroendocrine response to stress [10], autonomic nervous system [3,8,11,23] and immune system [3]. It decreases plasma catecholamines and corticosterone that increase with stress and attenuates nitric oxide and neurotrophic factors [8,23]. It also attenuates the decrease in cell proliferation in the DG caused by stress [8] and improves the synaptic plasticity [10] that is involved in memory and learning.

Chewing gum increases relaxation [8] and the performance of cognitive function such as checking numbers and typing [5,6], Hollingworth 1939.

Chewing gum during exposure to loud noise, inhibits the propagation of noise-induced stress information to the brain [5,8] in a recent study using fMRI.

In stress, it prevents gastric ulcer [11] spatial cognitive deficit, anxiety and osteoporosis [8,10]

In animals, maternal mastication during the prenatal period prevents learning deficit induced by stress in the descended [8,10]. Stress does not only affect adult hippocampal neurogenesis, but has a transgenerational effect transmitted genetically to the offspring when the pregnant mother is exposed to stressful conditions [10]

In mice, chewing under stress attenuated the increase in the level of corticosterone, the induction of C-Fos, the phosphorylation of protein kinase 1/2 related to the extracellular signal, oxidative stress and nitric oxide in the paraventricular nucleus of the hypothalamus [1,3,8]. It attenuated plasticity deficiencies induced by stress in the hippocampus, activating long-term potentiation (LTP) mediated by N-methyl-D-aspartate (NMDA) [8] responsible for learning and memory [1].

Under stress it attenuates changes in blood pressure [8], core temperature and plasma adrenaline levels, then attenuates the response of the autonomic nervous system, decreases plasma levels of interleukin-1 beta, interleukin -6 and leptin, which occur during the stress [3].

It can promote inactivation of the histamine neurons through the ventromedial hypothalamus and the mesencephalic trigeminal sensory nucleus. The histamine system can modulate the activity of the sept hippocampal cholinergic system. Consequently, the change in acetylcholine release induced by mastication may be a key factor in the memory process [3].

Induces the release of the H1 histamine in the hippocampus, and the activation of the H1 receptor can recover the synaptic plasticity suppressed by stress. Increasing the concentration of histamine in the hippocampus increases satiety [8].

Reduces anxiogenic behavior in animals, similar to what occurs in humans, chewing gum relieves bad mood, reduces salivary cortisol in acute induced stress and reduces daily stress levels [3,5,8].

### Masticatory deficiency

Masticatory Dysfunction as a generic term, refers to a debilitating condition in which a normal masticatory function is compromised due to structural factors, like tooth loss for example, or functional factors such as a weak bite force or a worse chewing performance [17].



Masticatory deficiency is a result of tooth loss, unsuitable dental prostheses and restorations, splints and occlusal dental retainers, which in association with a soft food diet for a long time, cause impairment in the cognitive function of the hippocampus. It also damages the hippocampal morphology through neural circuits and the HPA axis. The reduced masticatory stimulation decreases the volume and promotes morphological changes in the Hippocampus [1,3].

Masticatory dysfunction due to an elevated bite or occlusal disharmony results in hyperactivity of the HPA and an increase in circulating levels of glucocorticoids. The maintenance of this increase impairs the regulation of the negative feedback of the HPA axis [1,10]. The negative feedback mechanism of the HPA axis reduces glucocorticoid secretion mainly by inhibiting hypothalamic and pituitary activities and by binding to glucocorticoid receptors in the hippocampus [8].

Tooth loss due to caries and periodontal disease, which is very common in the elderly population, reduces somatosensory stimuli in the oral cavity, inducing increases in circulating glucocorticoids [10].

Tooth loss can be a risk factor for the decline in cognitive functions [12,15-17,22].

Tooth loss vs. cognitive impairment: 3 possible mechanisms [15,16,22]:

- Periodontal disease - systemic inflammatory reactions.
- Decrease in nutritional status reduced by tooth loss with decreased macro and micronutrients.
- Reduction of sensory inputs of the trigeminal nerve.

### Imaging exams, serological analysis, behavior studies

In animals, some methods for assessing mastication include extraction of the molar teeth, occlusal disharmony or elevated bite with the addition of occlusal acrylic and a soft food diet.

In humans, the self-reported clinical status and masticatory difficulty, examination of the oral cavity, number of natural teeth, occlusion and periodontal status [1].

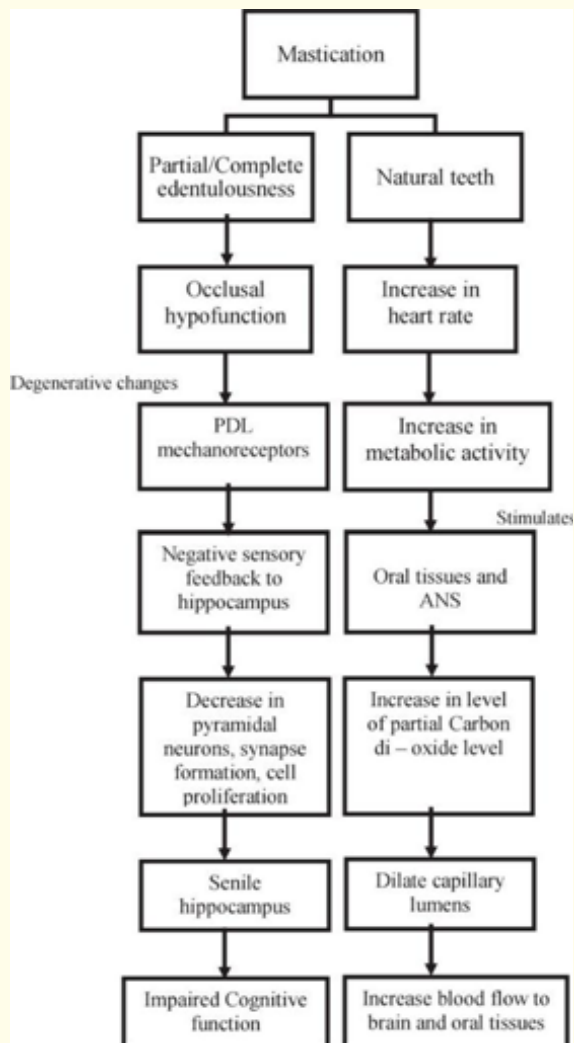
But it is not simple to assess the human condition, it is not a simple labyrinth test and considering the self-reported clinical status, it may not be reliable given the individual adaptive capacity.

In this sense, cerebral neuroimaging, including structural and functional magnetic resonance, fills the gap between animal and human study because it directly assesses the brain-stomatognathic axis, recording changes in functional activation and structural signatures [17].

Brain-stomatognathic axis is currently defined as a complex communication network between the brain, including cortical and subcortical structures and the stomatognathic system [17].

Electromyography (EMG) in humans aged 46.4 +/- 7.7 years with unilateral loss of 1st and 2nd right or left inferior molar, showed a decreased masticatory muscle activity and a reduced pupillary size during clenching on the side of loss due to a decrease in proprioceptive afferents of the trigeminal which leads to an imbalance in the activity of the locus coeruleus (LC) and an asymmetry in the brain activity. Replacement with implant-supported prosthesis reduces the imbalance of proprioceptive afferents and pupil size asymmetry, improves excitability and neuromotor performance and increases mydriasis associated with performing haptic tasks. Mydriasis reflects the excitation of mental effort in performing the task [2].





**Figure 3:** Relationship between masticatory and cognitive functions; PDL-Periodontal Ligament, SNA-Autonomic Nervous System *Jpn Dent Sci Rev.*2018 Nov; 54 (4): 169-173. Published online 2018 Aug 31. doi: 10.10.16/j.jdsr.2018.06.001.

Neuroimaging studies have also showed that both blood perfusion of the trigeminal nucleus and brain activation in somatosensory areas were associated with preference on the mastication side [17] and a greater mastication performance was associated with functional and structural brain individuality in masticatory function, including the greater volume of gray matter in the motor area and a greater functional connectivity between the cortex and the cerebellum [17,18].

When clenching, there was somatosensory brain activation with implant-supported prosthesis, but not with dentures. And with gum, the activation of the prefrontal cortex was reduced in the group with implant-supported prosthesis compared to the group with full prostheses [17].

With conventional removable partial denture, there was no activation in the middle frontal gyrus, corresponding to a lower mastication performance. Also, after placing the prosthesis, there was an increase in the brain activation in the somatosensory cortex during clenching,

which resulted in a greater masticatory efficiency. After the adaptation, there was an increase in the activation of the sensorimotor regions, translating the incorporation of the prosthesis as part of the body [17].

With the use of normal dentures, there was an increase in activation in the prefrontal cortex. And with implant-supported prosthesis that gives a better adaptation, it reduced the activation [17].

Functional Magnetic Resonance Imaging (fMRI) revealed that chewing affects cerebellar functions. The cerebellum may be involved in the masticatory rhythm [4] and motor control when motivated by proprioceptive stimuli [1,10] Increased cerebellar activity during chewing can improve hippocampal-dependent memory and cognition [1,10].

The association of tooth loss with a soft food diet in animals (SAMP8 rats) decreases the number of pyramidal cells (2.23), dendritic spines (2.23) and synapses in the hippocampus and parietal cortex, as well as decreasing the genes in neurons of the hippocampus, including the expression of the neurotrophic BDNF receptor and its receptor kinase B in the hippocampal CA1 and CA3 region [3]. There is also an intracellular alteration of the neuron cytoskeleton and astrocyte hyperplasia and hypertrophy (2.23) marked with proteins of glial fibrillary acid in the CA1 region and suppression of cell proliferation in the Gyrus Dentate.

Likewise, the increase in bite with acrylic by 0.1 mm decreased the number of neurons and increased the hyperplasia and hypertrophy of astrocytes marked with proteins of glial fibrillary acid in the CA3 region. This process is similar to the changes associated with old age. In conclusion, masticatory dysfunction can accelerate the aging process of the hippocampus-dependent cognitive function [1,3,10].

Mastication increases the production of BDNF (brain-derived neurotrophic factor) and Neurotrophin-3 by the muscle tissue, which are important proteins for the neurons of Locus Coeruleus and their axons [2] and induces survival, development and function.

BDNF and its specific receptor, kinase B related to Tropomyosin (trKB) has an improvement effect on nerve transmission, synaptic plasticity and CNS development [1]. It is important in long-term potentiation, neurogenesis, dendritogenesis and activity-dependent neuroplasticity [8]. BDNF when infused by the hippocampus increases neurogenesis in the adult hippocampus [7].

In SAMP8 mice, masticatory dysfunction due to a non-molar condition caused a reduction in the number of neurons that express c-Fos (2.23) in CA1 [2]. Mitigated situation with artificial crowns [1,2].

The Fos protein is an indicator of neural plasticity [23] and is involved in the formation of memory [1].

Iinuma *et al.* observed a significant reduction in the expression of c-Fos due to occlusal disharmony [23].

Chizuru Itsugi and colleagues measured the difference in Fos immunoreactivity (Fos-ir) in the sensory nucleus of the main trigeminal, which receives intraoral touch information through the trigeminal nerve, in a study where the mice fed with a soft food diet showed low neurogenesis, while those fed with hard food or with hard food after a soft food diet, had normal or recovered neurogenesis. The results suggest that feeding with a hard food diet improves neurogenesis related to olfactory behaviors in SVZ [20].

The molar loss in rats and the consequent increase in plasma glucocorticoids, [3,9] led to the suppression of the synaptic plasticity of the hippocampus neurons.

Bordji *et al.* and Gladding and Raymond, in an animal study with multiple tooth losses, observed that reconnecting motor and sensory information to their original neuromuscular pathways becomes difficult, which can result in altered connections and can accumulate abnormal levels of beta-amyloid, causing loss of the function synaptic [23].

In a 4-year prospective cohort study in elderly people living in Ohasama, Japan, pre-existing multiple tooth loss increased the risk of cognitive impairment over that period regardless of age, sex, hypertension, diabetes, cardiovascular, cerebrovascular disease, hypercholesterolemia, depressive symptoms, BMI, smoking, drinking status, duration of education and baseline MMSE score. The development of dementia was observed in a control group without initial cognitive impairment [15].

MMSE (Mini mental status exam) - commonly used for cognitive impairment in older adults. Scores vary from 0 to 30 and lower scores indicate worse cognitive performance and greater cognitive impairment [12].

In another 4-year prospective cohort study in Aichi, Japan, demonstrated that individuals aged  $\geq 65$  years with few teeth and without dentures had an increased risk of dementia compared to those with  $\geq 20$  teeth; but the risk was not significantly high in individuals with few teeth, but who used dentures [15].

In South Korea, a prospective study of 2.4 years, with elderly people of  $\geq 65$  years without dementia showed that dental shortage was associated with the onset of dementia and Alzheimer's [15].

Another 5-year prospective cohort study with elderly people aged  $\geq 65$ , the Fujiwara-Kyo study, associated tooth loss with mild memory loss [15].

In China, the first longitudinal study among the elderly, (8,153 participants) who were followed for 13 years (1998 to 2011), evaluated the association between the number of remaining teeth and cognitive decline. Average number of teeth 17.5 and basal cognitive function 27.3 (MMSE). It was concluded that more teeth were associated with better cognitive function and slower decline than those with fewer teeth, after controlling for other covariates such as demographic characteristics, age, sex, ethnicity, marital status, socioeconomic status in adults, childhood, health conditions and health behaviors [22].

The loss of molar or high bite in elderly mice promoted a decrease in cell proliferation in the DG. Metyrapone, a blocker of corticosterone synthesis, attenuated neuronal degeneration due to chronic stress [1,10].

Rats with extracted molars exhibit reduced release of acetylcholine in the cerebral cortex and deficiencies in spatial memory [15]. Spatial memory impairment in rats may be due to a decrease in trKB (tropomyosin-related kinase B) levels in the pathways located in the trigeminal nerve to the Hippocampus [1].

Rats without a molar and with a long-term soft diet, submitted to learning tests, have deficiency in spatial learning and memory [13] and an accelerated aging depending on the time that elapses from tooth loss. Process was attenuated after restoration with artificial crowns [1,3].

In OFT open field test and ORT object recognition test with SAMP8 mice; with removal of the upper molars and with their masticatory function impaired, they developed rotational lateralized behavior and locomotor hyperactivity common in dysfunction of the dopaminergic system with impairment of selective attention and recognition, in the prefrontal cortex and hippocampus [9].

SAMP8 mice are animals prone to accelerated senescence, with an approximate lifespan of 12 months compared to other strains that live 2 to 3 years, which have normal maturation up to 6 months and then accelerate aging, [10,13]. They are used as an animal model for old age to assess mastication and brain function [20].

Open field test (OFT) is a test on rats and mice to assess locomotor activity, anxiety and willingness to explore.

Object recognition test (ORT).

In humans, in a case of malocclusion with dental splints, malocclusion has been shown to affect the processing of emotion in the brain, anterior cingulate cortex and amygdala [3].

In rodents and monkeys, occlusal disharmony with the addition of acrylic layers in the incisors, occlusal splint in the maxilla or composite in the upper molars with an increase in the Vertical Occlusion Dimension (0.1mm) induced an increase in plasma and urinary corticosterone and urinary cortisol, respectively, induced by acute and chronic stress [3,10,23].

As well as increased dopamine and norepinephrine in the hypothalamus and frontal cortex, reduction of tyrosine hydroxylase, GTP cyclohydroxylase I and immunoreactive serotonin in the cerebral cortex, caudate nucleus, black substance, locus coeruleus and dorsal raphe nucleus in rodents [3].

This masticatory dysfunction resulting from occlusal disharmony promoted hyperactivity of the HPA axis with an increase in circulating glucocorticoids [3,10,23].

In monkeys, the increase in urinary cortisol induced by occlusal splints returns to the baseline value when they are removed [3,13,23].

In young adult rats, interference with masticatory function for 10 days significantly decreases long-term potentiation in neurons of the hippocampus CA1, increased corticosterone and plasma norepinephrine [9]. These catecholaminergic changes are also similar to the changes induced by chronic stress [3,9].

It is worth remembering that the hippocampus is innervated by the noradrenergic, serotonergic and dopaminergic systems, therefore, changes induced by occlusal disharmony can affect the hippocampal function [1,3].

With all this evidence, we can conclude that oral rehabilitation and sensorimotor and cognitive stimulation can help protect human beings from age-related cognitive decline [15].and that these interventions would be more effective if implemented as early as possible [13].

### Methodology

To carry out this work, the following research bases were used: PMC file and Pubmed free.

First selection: English language. Exclusion: Articles not directly related to chewing, parafunctions and humans with pathologies. Keywords: Chewing, Mastication, Brain activity, Cognitive function.

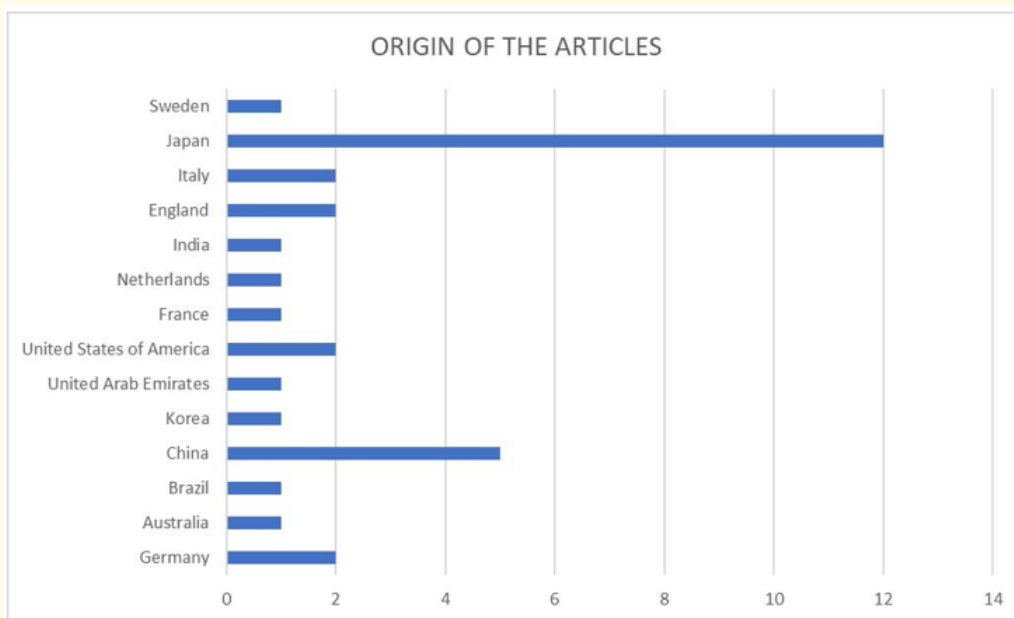
Second selection: English language not restricted to humans and publications in the last 20 years. Key words: Chewing And Dementia

Articles were selected that showed radiological, serological and behavioral tests.

### Results

The research provided 381 articles of which 46 were selected, the abstracts were read and those that met the inclusion criteria were recovered in full.

The prevalence of Asian authors, more specifically Japanese, was observed. According to the International Institute for Applied Systems Analysis (IIASA), Japan holds the world's oldest population, followed by Italy, Germany, Portugal and Finland. It also has the largest number of cases of Dementia (WHO).



Figure

**Discussion and Conclusion**

These undeniable evidences highlight Mastication, through a complex neural network of sensory input from the Masticatory Apparatus to the brain, as an important means of preserving brain structures and, as such, of the individual’s physical and mental health.

They also point to cognitive decline as a result of individual and behavioral structural factors, because despite being associated with aging, it is not part of normal aging and is also related to other modifiable factors that are capable of intervention.

According to data from the World Population Prospects: the 2019 Review in 2050, one in six people in the world will be over 65 (16%) and over one in 11 in 2019 (9%). The number of people over 80 is expected to almost triple from 143 million in 2019 to 426 million in 2050.

WHO currently accounts for about 50 million cases of dementia worldwide and estimates that it will triple to 152 million by 2050.

Almost 10 million people develop dementia each year. 6 million in low- and middle-income countries, (Tendros Adhanom Ghebreyesus - Director-General of WHO).

WHO recognizes Dementia as a public health priority and in 2017 created the Global Dementia Observatory (GDO) an international surveillance platform to share data about this disease with countries to exchange information and create policies for health systems, social assistance and for research.

Therefore, and given the proprioceptive refinement of the oral cavity, our enormous responsibility as oral health professionals in the treatment and maintenance of oral organs, true neural receptors, as well as in the preventive work of raising the population's awareness of not only nutritional eating habits, but effectively masticatory to the detriment of a modern diet, sometimes devoid of texture and hardness, as an aid in preventing aging and maintaining the hippocampus-dependent cognitive function.

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