ORAL HEALTH AND HEALTHY CHEWING FOR HEALTHY COGNITIVE AGING. A COMPREHENSIVE NARRATIVE REVIEW

Running title: Healthy chewing for healthy cognitive aging.

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ABSTRACT

Introduction: Aging leads to physiological cognitive decline that it is worsened in people with neurodegenerative diseases such as Alzheimer's Disease. Despite the ongoing search for a solution to this cognitive decline, no effective remedies have been established. It has been determined that modifiable external factors, such as oral health and occlusal function, prevent cognitive decline.

Objective: To analyze the primary interactions between occlusal function and cognitive functions.

Main findings: Masticatory function is related to cognitive functions. In particular, current evidence, from both animal and human studies, suggests that the activation of masticatory muscles and proper mastication, with natural teeth or dental prosthesis, induces the release of several mediators and the activation of specific brain areas. Together, they result in higher neuronal activity, neurotrophic support, blood flow and the prevention of amyloid beta plaque formation. Thus, all the components of the masticatory system must work together in order to preserve cognitive function.

Conclusions: Available evidence suggests that oral and cognitive health are more interconnected than previously thought. Therefore, maintenance and adequate restoration of the whole masticatory system are important for the prevention of cognitive decline. In summary, oral and chewing health lead to healthy cognitive aging.

Key words: mastication; dementia; cognitive dysfunction.

INTRODUCTION

Aging involves physiological cognitive decline. The deterioration of processing speed and memory, language, visuospatial, and executive functions, is normal as one ages [1]. However, the magnitude of this deterioration, the temporality, and the rate at which it occurs throughout life differ [1]. Certain situations or modifiable external factors either protect against this deterioration or accelerate the underlying mechanisms [2]. In fact, about 10% of the levels of neurodegenerative biomarkers (such as amyloid beta) may decrease spontaneously [3]. Furthermore, some factors have been identified as modifiable and reversible causes of cognitive deterioration [4].

Besides normal aging and the associated cognitive decline that does not affect daily normal activities, neurodegenerative diseases and dementia syndromes, such as Alzheimer's Disease (AD), induce more aberrant forms of deterioration [5]. Dementia syndromes are among the most devastating of all mental illnesses related to cognitive decline and are the most significant age-related disorders [6]. The deterioration affects several functions including motivation, social behavior and emotional control [7]. As a result, dementia syndromes cause a profound impact on quality of life and an economic burden from the need for a caregiver.

The effect on healthcare systems is significant as well. It costs almost €800 billion ($1 trillion) a year in Europe. This is greater than the cost of diabetes, cardiovascular diseases and cancer put together [8–10]. This cost will increase globally as longevity increases. This drives the urgency to search for effective strategies which modify its course in the adult population [11].

The literature describes various external modifiable factors that may affect the development of different dementia syndromes such as AD. These include smoking, alcohol, drug abuse, diet and stress [12]. Protective factors which reduce the progression of established AD include education, exercise [13] and active social commitments [12]. Moreover, some of these protective factors have been described as beneficial in slowing the normal physiological cognitive decline

associated with aging [14,15]. The absence of a clearly defined and studied strategy for addressing pathological cognitive deterioration [1] make this a very attractive field to explore.

An abundance of animal and human studies suggest that masticatory function is relevant to cognitive deterioration [16,17]. However, this relationship is complex and difficult to establish. Although data from animal studies seems to establish a causal relation, this has not been confirmed in longitudinal human studies. A deeper understanding of this relationship would give us the chance to institute new strategies that improve the course of cognitive deterioration in patients. This must be done by analyzing the available data while understanding its complexity.

Thus, it is the aim of the current review to describe the interactions between occlusal and cognitive functions presented in the literature and to propose how such interactions may benefit patients. This review offers a broad overview of this highly complex interaction that previously, has only been partially analyzed. We achieve this by conducting a search of the database Pubmed with the following search strategies ("mastication"[MeSH Terms] OR "mastication"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields]), ("mastication"[MeSH Terms] OR "mastication"[All Fields] OR "chewing"[All Fields]) AND ("hippocampus"[MeSH Terms] OR "hippocampus"[All Fields]), ("mastication"[MeSH Terms] OR "mastication"[All Fields] OR "chewing"[All Fields]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields]) and ("mastication"[MeSH Terms] OR "mastication"[All Fields] OR "chewing"[All Fields]) AND ("Cortex"[Journal] OR "cortex"[All Fields]).

MASTICATORY AND COGNITIVE FUNCTIONS IN ANIMALS

Many animal studies have linked aspects of chewing function with alterations in areas of the brain related to cognitive function [18]. This has been done by modifying the masticatory system to create different dysfunctions for comparison. Masticatory dysfunction is a common

technique used to study the connection between chewing and cognitive function. This is often done by extracting teeth (in part or completely), providing a soft (powder or liquid) or hard (solid) diet or raising the bite by adding a hard permanent material to the occlusal surface.

In mice, these masticatory changes cause alterations in learning and memory by reducing the number and activity of neurons in the hippocampus [19–21], especially in the cornus Ammonis 1 (CA1) and CA3 regions [22,23]. Reducing the chewing function of mice is also found to reduce neuronal activity and neurogenesis in the subgranular zone (SGZ) [24] and subventricular zone (SVZ) of the hypothalamus. These are involved in connecting the central nervous system with the periphery, [25].

A soft diet reduces expression of the brain-derived neurotrophic factor (BDNF), c-Fos and bromodeoxyuridine (BrdU) + cells in areas such as the motor M1, CA1, 2 and 3, dentate gyrus (DG), piriform cortex and the SVZ and SGZ zones [20,22,26,27]. This causes a reduction in neurogenesis, neuronal activity, neuronal trophic activity and synaptic formation (**Figure 1**). Insufficient masticatory activity (induced with a powdered diet) during development and aging restrains hippocampal neurogenesis in adulthood [26].

Reducing mastication by extracting all teeth induces mice to have longer escape latencies. This is possibly due to a reduction in cell proliferation and newborn cell survival and differentiation in the hippocampal DG. This also reduces the expression of hippocampal BDNF [28–30]. Reduced masticatory function in early life causes chronic stress which impairs the ability to recognize novel objects [31]. Tooth loss in mice also causes reduced volume of the frontal association cortex and nucleus accumbens [32], two structures related to cognition (**Figure 2**).

Excessive occlusal loading, from the placement of a hard permanent material to the occlusal surface, for example, reduces the number of newborn BrdU+ cells in the hippocampal DG. Additionally, the survival of these newborn cells is reduced, the apoptotic cells in the hippocampal DG are increased [33] and the number of dendritic spine numbers in CA1 are

lowered [34]. This malocclusion also reduces glucocorticoid receptors-mRNA, which impairs the hypothalamic-pituitary-adrenal feedback inhibition, especially in CA3 [34] (**Figure 2**).

As a summary, the link between cognitive decline and altered masticatory function seems plausible. However, direct translation to humans must be made with caution as many of the functions described above do not occur in the same way, as presented below.

MASTICATORY AND COGNITIVE FUNCTIONS IN HUMANS

Aging leads to physical and functional deterioration in older individuals. In addition to esthetic and social problems [35], tooth loss causes stress [36] which may trigger the activation of neuroinflammatory pathways related to oxidation [37]. Tooth loss also contributes to multiple other pathologies that are associated to functional and physical deterioration [38,39], and dietary changes that lead to worse nutrition [40–43]. The association between the loss of teeth and general health could be even greater considering that aging implies a deterioration in the chewing ability for other reasons as well (see [44] for review). For example, the masticatory muscles are weakened [45], more natural teeth are lost [46], swallowing patterns change [47], and there is an increase in the number of scars in the mouth and throat that make chewing difficult [48]. Oral health also affects "quality of life", altering the management of emotions, self-esteem and self-confidence [49–51].

Number of natural teeth and cognitive function: The periodontal pathway

Tooth loss is often the consequence of periodontal disease. More than 60% of adults over the age of 65 suffer from moderate to severe periodontal disease [52]. It is the 6th most prevalent disease in the world [53]. The inflammatory process around the teeth is usually caused by accumulated microbial plaque from poor oral hygiene, which elderly people are less competent to maintain [54]. Moreover, the presence of periodontal disease has been associated with cognitive impairment regardless of age, sex, or education level [55]. Although reverse causation may be suspected (cognitive impairment results in poor oral hygiene that leads to periodontal disease),

longitudinal studies have found that periodontitis is associated with an increase in cognitive impairment [56] and risk of AD development [57]. These studies have short follow-up periods; only 6 months and 3 years, respectively.

The possible pathway linking both diseases might be the low-level but chronic systemic inflammation that accompany peripheral infections, such as periodontal disease [58] (**Figure 3**). Lower mini-mental state examination (MMSE) results are related to a higher state of periodontal deterioration as measured by the levels of cytokines produced by exposure to bacteria lipopolysaccharides (LPS), such as interleukin (IL) 1beta, IL6, IL10 and Tumor Necrosis Factor (TNF) alfa [59]. Periodontitis and the associated inflammatory mediators have also been associated with higher levels of tau protein [60,61], and plasma levels of amyloid beta (Aβ) -$_{1-42}$ [62] and Aβ_{1-40} [63], which may reinforce the inflammatory hypothesis. Both tau protein and Aß are associated with AD when they become hyperphosphorylated and form fibrillar structures in the form of plaques, respectively.

However, most of the studies referenced above focus on few inflammatory markers, such as the C-reactive protein (CRP) [63]. It may be suspected that a subject susceptible to periodontal disease has a higher inflammatory response profile. An increased inflammatory response would not occur only in the periodontium but everywhere. Thus, the connection between periodontitis and cognitive impairment could be a spurious association due to a confounding factor, the inflammatory response potential of the patient. This inflammatory response is, in fact, a necessary cause for both periodontitis and cognitive impairment.

It has recently been reported that 29 markers of systemic inflammation which normally increase with periodontitis are not as relevant as previously thought for cognitive impairment [64]. This study supports the idea that the most probable relationship between cognitive functions and oral health can be caused by the loss of teeth caused by periodontal disease, but not inflammation

itself. This leads to the study of other parameters in oral health such as the number of natural teeth remaining in the mouth.

The number of remaining natural teeth is directly related to cognitive function [65–68] and the presence of less than 9 teeth is related to dementia [65] and cognitive impairment [67]. Furthermore, the number of remaining natural teeth is related to lower activities of daily living (ADL), quality of life scores, and cognitive function as well as depression and food deficiency [69]. Tooth loss has also been associated with cognitive impairment regardless of nutrition [70]. Different hippocampus-based cognitive processes have been evaluated by episodic and semantic memory tasks which find that a lower number of natural teeth resulted in worse scores [66]. It is important to note that most of these studies are cross-sectional in nature, the reported associations must be considered carefully without assuming causality. Thus, a reduced number of teeth might be a consequence of an already impaired capacity for ADL, as previously stated.

Interestingly, after the 2007 study, Stein and co-workers found a significant interaction between tooth loss and the prevalence of dementia through ApoE allele (one of the most studied markers of AD). From the study, 21.5% of the participants had dementia at baseline which was directly related to the number of remaining teeth (0-9) [71]. The authors pointed out that the participants with at least one ApoE allele and fewer teeth had lower scores at the first cognitive examination which declined quicker than participants with no or one risk factor [71]. The risk of developing AD was also found to be inversely related to the number of remaining teeth in another longitudinal study [72]. These studies were conducted in community-dwelling settings, which could have other co-lateral factors possibly not controlled for.

Chewing ability and cognitive function: more than natural teeth

It may seem logical to think that more natural teeth will induce better masticatory abilities. These can be measured by color-changing gums, mandibular excursions (ranges of distances that the mandible moves in the open, lateral, and forward directions), bite force, number of

occluding pairs (pairs of upper teeth that contact with lower teeth when closing the mandible) and complaints of the masticatory system (facial pain, headaches/migraines). Better masticatory abilities are related to improved cognitive function [73].

However, there are patients that are already so deteriorated that they lack adequate masticatory function regardless of the number of teeth. Some studies have determined that the relationship between masticatory function and cognition is not influenced by the number of natural teeth or the type of prosthetic rehabilitation (complete or partial, removable or fixed), but the masticatory function itself [70,74–77]. The local distribution of the masticatory forces seems to be important as well [78].

Episodic memory is predicted by masticatory performance in individuals with complete dentures [74]. However, this study does not address the direction of the association and masticatory performance was self-assessed. Furthermore, poor chewing ability is related to lower cognitive functions, measured with different cognitive tests such as MMSE, Hasegawa Dementia Scale-Revised (HDS-R) and Frontal Assessment Battery (FAB) [69,76]. Likewise, other executive functions, such as word fluency, Stroop color word test or trail-making B, can be predicted by from masticatory system issues such as headaches and migraines [74]. However, not all dentures provide these benefits. Patients who wear complete dentures often complain of issues such as bad adjustment, more limited range of ingestible food, discomfort and dissatisfaction. As a consequence, the cerebral blood flow is reduced [79]. To solve some of the limitations associated with standard complete dentures, implant-retained overdentures can be prescribed. This treatment option increases the amplitude and power of alpha waves and cognitive scores (cognitive performance (MMSE) and brain function (EEG)) [80].

Multiple interactions have been explored to explain this association. The treatment of edentulism with adequately adjusted dentures increases the occlusal contact area and increases

occlusal force. This situation leads to an increase in the brain function activity measured with electroencephalography (EEG) [81].

In summary, edentulous subjects with good occlusal function after an adequate rehabilitation should maintain correct cognitive functions. Understanding this hypothesis and the possible physiological mechanisms of this link are key to understanding potential improvements in current therapies.

Chewing ability and release of myokines

In recent years, the effect that the contractions of skeletal muscles, from general exercise, exert on cognitive functions has been well studied [82–84]. Considering that the musculature related to chewing is also skeletal, it could be assumed that the relationship between occlusal function and cognitive functions may imply similar pathways. Confirmation of such similarities is crucial.

The beneficial effect of exercise on cognition could be explained by increased levels of neurotrophins such as BDNF, especially in the hippocampus [85]. This increase could be explained by the activation of muscle-released myokines such as fibronectin type III domain-containing protein 5 (FNDC5) (released to the bloodstream as irisin) and cathepsin B (CTSB) that cross the Blood Brain Barrier generating an up-regulation of BDNF in the brain [86,87]. This has been proven in human studies [85] and has been linked with neurogenesis in the dentate gyrus of the hippocampus in animal models. However, in humans it has been recently discussed that in the adult dentate gyrus, neurogenesis is a rare and isolated event [88]. Others support the idea that adult neurogenesis in humans is persistent in both physiological and pathological aging [89]. Thus, there could be other ways that the influence of exercise is transferred to cognitive improvement.

BDNF has an important role in the maintenance of cognitive functions [90]. High levels of this neurotrophin are associated with greater neuronal plasticity [91], maintenance of hippocampal volume [92] and an improvement of trophic support, thus reducing the susceptibility of neurons to oxidative stress and the dysfunction caused by neurotoxic species such as amyloid beta plaques [91]. Elevated levels of BDNF also play a protective role in the pathogenesis of AD. It allows a non-amyloidogenic pathway in which the amyloid precursor protein (APP) is cleaved by a gamma secretase (ADAM10 or ADAM17 / TACE) preventing the formation of amyloid-beta insoluble peptides [93,94].

Thus, in summary, myokines such as FNDC5 and CTSB released in the medium by the contraction of the skeletal muscles during its activation improve superior cognitive functions thanks to the BDNF neurotrophic roles and their involvement in the establishment of a non-amyloidogenic pathway in the processing of APP.

Chewing ability and activation of Locus Coeruleus

Locus Coeruleus (LC) activation through trigeminal sensory inputs is another possible interaction pathway between occlusion and cognitive functioning.

The LC is part of the Ascending Reticular Activating System (ARAS). It is composed of noradrenergic neurons [95] that connect with virtually all brain structures [96–98]. The stimulation of LC neurons favors cognitive processes through the modulation of the noradrenergic system [15,99] and regulates neuroinflammatory processes by stimulating phagocytosis of Aß plaque through microglia [97,98]. It is important to note that pathological changes of LC neurons have been observed as an early sign of AD [100].

The LC receives sensory inputs from different sources, including the trigeminal nucleus [101]. The trigeminal sensory inputs originate in, among other structures, the periodontal fibers [102,103] and in the proprioceptive jaw muscle spindles, whose function will depend on the type of

activity, i.e., the type of diet or occlusal stimulation [101]. The alteration in the activity of the masseter muscles caused by a malocclusion generates an alteration in the ascending trigeminal sensorimotor information. This causes an asymmetry in the LC excitability and a change in cognitive performance [104,105]. Unilateral or bilateral tooth loss without occlusal rehabilitation leads to a malocclusive situation. This problem also generates structural changes in the chewing muscles. The loss of unilateral function due to a right-left edentulism generates a masseter atrophy of the edentulous side accompanying the absence of teeth [106,107]. The rehabilitation of the lost occlusal function allows masticatory performance recovery and the function of the musculature on that side [108]. However, we must keep in mind that the adjustment of removable prosthesis does not always allow a complete recovery of occlusal functionality. In contrast, fixed prosthetic rehabilitation better preserves the physiology of the mandibular muscles [109]. However, a specific comparison of both denture types has not been analyzed.

Chewing ability and direct activation of brain areas

Chewing also involves the activation of numerous brain areas that intervene in the initiation and perpetuation of masticatory movements. Functional magnetic resonance imaging (fMRI) studies show that chewing produces significant bilateral functional connections between motor cortices [110]. They also embrace motor, premotor and somatosensory cortices and supplementary motor areas (SMA). In addition, motor cortical seeds show bilateral functional connections with the posterior cerebellar lobes, precuneus, cuneus and cingulate cortex. Both cerebellar hemispheres show functional connectivity paths with each other.

Other masticatory tasks, including uni- or bi-lateral chewing of gum, show activity in several areas of the brain, including the right prefrontal cortex, left insula, thalamus, bilateral anterior cerebellar hemispheres, vermis, SMA, medial cingulate gyrus, primary motor (M1) and premotor cortices, and bilateral primary (S1) and secondary (S2) cortices [111]. Interestingly,

these authors found no differences in the activation of brain areas when they compare unilateral chewing and bilateral occlusion, considering that all subjects were evaluated fully dentated.

To clarify this aspect, the activation of brain areas in subjects with bilateral absence of molars (Kennedy class I) has also been investigated [112]. Two different situations were analyzed within the same 11 patients: FDA (full dental arch, with the removable prosthesis, and, therefore, total dentition) and SDA (shortened dental arch, with edentulous posterior sections, Kennedy class I, without the partial prosthetic rehabilitation). Statistically significant differences in the activation of different areas of the brain occurred in both situations during mastication. Chewing gum with FDA generated activation in the middle frontal gyrus, primary sensorimotor cortex extending to the pre-central gyrus, SMA, putamen, insula and cerebellum. However, during gum chewing with the SDA the activation of the middle frontal gyrus was not observed.

In summary, some areas of the brain, characteristically altered in cognitive ageing, are also involved in the chewing processes, particularly the posterior cingulate gyrus, fusiform gyrus, cuneus, primary motor, somatosensory cortices, precuneus and caudate nucleus as well as the hippocampus, amygdala, temporal fusiform cortex, planum plare, cingulate gyrus, lateral ventricle, precuneous cortex, superior temporal gyrus, post central gyrus and central opercular cortex (**Figure 4**). Thus, if cognitive impairment and chewing share target brain regions, it would seem clear that alterations in mastication or occlusion may also have some role in cognitive decline by reducing the activity of those areas.

INTEGRATIVE REMARKS

This review offers a broad overview of the highly complex interaction between oral health and cognitive function that has only been partially analyzed. We have evaluated the direct effects that oral health and mastication may have on cognitive health.

As a general summary (**Figure 5**), chronic low-level systemic inflammation classically made responsible for this association has recently been considered with caution. The absence of teeth or proper occlusal rehabilitation that could lead to reduced chewing abilities is being investigated with great interest. Reduced mastication generates a reduction in specific mediators released from masticatory muscles that are associated with neuronal activities and amyloid plaque removal in the hippocampus. Furthermore, trigeminal inputs as a consequence of masticatory function are also able to activate neurons in the Locus Coeruleus, which are implicated in regulating neuroinflammation and neurotrophic support. Finally, during mastication, the areas that get activated receive more blood flow. Some of these areas are also commonly affected in cognitive deterioration. Thus, it seems logical to think that if those areas are properly stimulated and receive adequate blood supply by masticatory functions, they would be less prone to deteriorate, and, so, less prone to induce cognitive decline.

It is important to remember that because of the complexity of the association and the long period between cause and effect, results that link proper masticatory function to better cognitive health are difficult to be achieved. Other indirect connections must also be accounted for, from considering mastication as the first step of digestion to, of course, reduced stress and better social interactions, which are also important in cognitive maintenance and brain function. Thus, all the components of the masticatory system must work together to maintain cognitive function.

CONCLUSION

The current review summarizes the available evidence suggesting that the association between oral and cognitive health involves much more than a single interaction. We are not only referring to oral health as the absence of inflammation or trying to restore teeth once they are lost from an esthetic or social perspective; we are proposing a completely new tool: adequately restoring functional mastication to prevent cognitive decline.

REFERENCES

1. Harada CN, Natelson Love MC, Triebel KL, Love MCN, Triebel KL. Normal Cognitive Aging. *Clin Geriatr Med*. 2013;29(4):737-752. doi:10.1016/j.cger.2013.07.002.Normal

2. Dorszewska J, Prendecki M, Oczkowska A, Dezor M, Kozubski W. Molecular Basis of Familial and Sporadic Alzheimer's Disease. *Curr Alzheimer Res*. 2016;13(9):952-963. doi:10.2174/1567205013666160314150501

3. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128. doi:10.1016/S1474-4422(09)70299-6

4. Assaf G, Tanielian M. Mild cognitive impairment in primary care: a clinical review. *Postgrad Med J*. 2018;94(1117):647-652. doi:10.1136/postgradmedj-2018-136035

5. Petersen RC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol*. 2004;62(7):1160-1163; discussion 1167. doi:10.1001/archneur.62.7.1160

6. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's Dement*. 2013;9(1):63-75.e2. doi:10.1016/j.jalz.2012.11.007

7. World Health Organization. WHO Dementia. http://www.who.int/news-room/fact-sheets/detail/dementia. Accessed July 15, 2018.

8. Smith K. Trillion-dollar brain drain. *Nature*. 2011;478(7367):15-15. doi:10.1038/478015a

9. Wimo A, Guerchet M, Ali G-C, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's Dement*. 2017;13(1):1-7. doi:10.1016/j.jalz.2016.07.150

10. Prince M, Wimo A, Guerchet M, Ali G, WU Y, Prina M. *World Alzheimer Report 2015 The Global Impact of Dementia. Alzheimer's Disease International*.; 2015. https://www.alz.co.uk/research/world-report-2015. Accessed July 15, 2018.

11. Alzheimer Association. 2016 Alzheimer's disease facts and figures. *Alzheimer's Dement*. 2016;12(4):459-509. doi:10.1016/j.jalz.2016.03.001

12. Qiu C, De Ronchi D, Fratiglioni L. The epidemiology of the dementias: An update. *Curr Opin Psychiatry*. 2007;20(4):380-385. doi:10.1097/YCO.0b013e32816ebc7b

13. Guitar NA, Connelly DM, Nagamatsu LS, Orange JB, Muir-Hunter SW. The effects of physical exercise on executive function in community-dwelling older adults living with Alzheimer's-type dementia: A systematic review. *Ageing Res Rev*. 2018;47(July):159-167. doi:10.1016/j.arr.2018.07.009

14. Batista M, Honório SA, Serrano J, Petrica J, Santos J. Benefits of physical activity in neurotrophic factors. *Minerva Ortop e Traumatol*. 2018;69(3):84-89. doi:10.23736/S0394-3410.18.03883-3

15. McMorris T. Developing the catecholamines hypothesis for the acute exercise-cognition interaction in humans: Lessons from animal studies. *Physiol Behav*. 2016;165:291-299. doi:10.1016/j.physbeh.2016.08.011

16. Chuhuaicura P, Dias FJ, Arias A, Lezcano MF, Fuentes R. Mastication as a protective factor of the cognitive decline in adults: A qualitative systematic review. *Int Dent J*. 2019;69(5):334-340. doi:10.1111/idj.12486

17. Weijenberg RAF, Delwel S, Ho B Van, van der Maarel-Wierink CD, Lobbezoo F. Mind your teeth—The relationship between mastication and cognition. *Gerodontology*. 2019;36(1):2-7. doi:10.1111/ger.12380

18. Frota de Almeida MN, de Siqueira Mendes FDCC, Gurgel Fel??cio AP, et al. Spatial memory decline after masticatory deprivation and aging is associated with altered laminar distribution of CA1 astrocytes. *BMC Neurosci*. 2012;13(1):23. doi:10.1186/1471-2202-13-23

19. Ono Y, Yamamoto T, Kubo K -y., Onozuka M. Occlusion and brain function: mastication as a prevention of cognitive dysfunction. *J Oral Rehabil*. 2010;37(8):624-640. doi:10.1111/j.1365-2842.2010.02079.x

20. Fukushima-Nakayama Y, Ono T, Ono T, et al. Reduced mastication impairs memory function. *J Dent Res*. 2017;96(9):1058-1066. doi:10.1177/0022034517708771

21. Tsai CY, Lee HP, Chang HM, Wu FC. Masticatory hypofunction effects induced by BTXA injection of hippocampal neurons in developing rats. *Arch Oral Biol*. 2018;96(250):122-129. doi:10.1016/j.archoralbio.2018.09.005

22. Okihara H, Ito J-I, Kokai S, et al. Liquid diet induces memory impairment accompanied by a decreased number of hippocampal neurons in mice. *J Neurosci Res*. 2014;92(8):1010-1017. doi:10.1002/jnr.23383

23. Aoki H, Kimoto K, Hori N, Toyoda M. Cell proliferation in the dentate gyrus of rat hippocampus is inhibited by soft diet feeding. *Gerontology*. 2005;51(6):369-374. doi:10.1159/000088700

24. Utsugi C, Miyazono S, Osada K, et al. Hard-diet feeding recovers neurogenesis in the subventricular zone and olfactory functions of mice impaired by soft-diet feeding. Soriano E, ed. *PLoS One*. 2014;9(5):e97309. doi:10.1371/journal.pone.0097309

25. Patten AR, Moller DJ, Graham J, Gil-Mohapel J, Christie BR. Liquid diets reduce cell proliferation but not neurogenesis in the adult rat hippocampus. *Neuroscience*. 2013;254:173-184. doi:10.1016/j.neuroscience.2013.09.024

26. Yamamoto T, Hirayama A, Hosoe N, Furube M, Hirano S. Soft-diet feeding inhibits adult neurogenesis in hippocampus of mice. *Bull Tokyo Dent Coll*. 2009;50(3):117-124. http://www.ncbi.nlm.nih.gov/pubmed/19887754. Accessed January 4, 2018.

27. Nose-Ishibashi K, Watahiki J, Yamada K, et al. Soft-diet feeding after weaning affects behavior in mice: Potential increase in vulnerability to mental disorders. *Neuroscience*. 2014;263:257-268. doi:10.1016/j.neuroscience.2013.12.065

28. Kondo H, Kurahashi M, Mori D, et al. Hippocampus-dependent spatial memory impairment due to molar tooth loss is ameliorated by an enriched environment. *Arch Oral Biol*. 2016;61:1-7. doi:10.1016/j.archoralbio.2015.10.006

29. Takeda Y, Oue H, Okada S, et al. Molar loss and powder diet leads to memory deficit and modifies the mRNA expression of brain-derived neurotrophic factor in the hippocampus of adult mice. *BMC Neurosci*. 2016;17(1):1-10. doi:10.1186/s12868-016-0319-y

30. Su S, Qi T, Su B, Gu H, Wang J, Yang L. Tooth loss inhibits neurogenesis in the dentate gyrus of adult mice. *Neural Regen Res*. 2014;9(17):1606-1609. doi:10.4103/1673-5374.141786

31. Kawahata M, Ono Y, Ohno A, Kawamoto S, Kimoto K, Onozuka M. Loss of molars early in life develops behavioral lateralization and impairs hippocampus-dependent recognition memory. *BMC Neurosci*. 2014;15(1):4. doi:10.1186/1471-2202-15-4

32. Avivi-Arber L, Seltzer Z, Friedel M, et al. Widespread Volumetric Brain Changes following Tooth Loss in Female Mice. *Front Neuroanat*. 2017;10(January). doi:10.3389/fnana.2016.00121

33. Mori D, Miyake H, Mizutani K, et al. Effects of occlusal disharmony on the hippocampal dentate gyrus in aged senescence-accelerated mouse prone 8 (SAMP8). *Arch Oral Biol*. 2016;65:95-101. doi:10.1016/j.archoralbio.2016.01.015

34. Kubo K ya, Kojo A, Yamamoto T, Onozuka M. The bite-raised condition in aged SAMP8 mice induces dendritic spine changes in the hippocampal region. *Neurosci Lett*. 2008;441(2):141-144. doi:10.1016/j.neulet.2008.05.027

35. Heydecke G, Thomason JM, Lund JP, Feine JS. The impact of conventional and implant supported prostheses on social and sexual activities in edentulous adults Results from a randomized trial 2 months after treatment. *J Dent*. 2005;33(8):649-657. doi:10.1016/j.jdent.2005.01.003

36. Vancampfort D, Koyanagi A, Ward PB, et al. Perceived Stress and Its Relationship With Chronic Medical Conditions and Multimorbidity Among 229,293 Community-Dwelling Adults in 44 Low- and Middle-Income Countries. *Am J Epidemiol*. 2017;186(8):979-989. doi:10.1093/aje/kwx159

37. Olivenza R, Moro MA, Lizasoain I, et al. Chronic stress induces the expression of inducible nitric oxide synthase in rat brain cortex. *J Neurochem*. 2000;74(2):785-791. doi:10.1046/j.1471-4159.2000.740785.x

38. Emami E, de Souza RF, Kabawat M, Feine JS. The impact of edentulism on oral and general health. *Int J Dent*. 2013;2013:498305. doi:10.1155/2013/498305

39. Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. *J Periodontol*. 2013;84(4 Suppl):S8-S19. doi:10.1902/jop.2013.1340010

40. Lee IC, Yang YH, Ho PS, Lee IC. Chewing ability, nutritional status and quality of life. *J Oral Rehabil*. 2014;41(2):79-86. doi:10.1111/joor.12115

41. Allen VJ, Methven L, Gosney MA. Use of nutritional complete supplements in older adults with dementia: systematic review and meta-analysis of clinical outcomes. *Clin Nutr*. 2013;32(6):950-957. doi:10.1016/j.clnu.2013.03.015

42. Gil-Montoya JA, Ponce G, Sanchez Lara I, Barrios R, Llodra JC, Bravo M. Association of the oral health impact profile with malnutrition risk in Spanish elders. *Arch Gerontol Geriatr*. 2013;57(3):398-402. doi:10.1016/j.archger.2013.05.002

43. Gil-Montoya JA, Subirá C, Ramón JM, González-Moles MA. Oral Health-Related Quality of Life and nutritional status. *J Public Health Dent*. 2008;68(2):88-93. doi:10.1111/j.1752-7325.2007.00082.x

44. Kumar A, Kothari M, Grigoriadis A, Trulsson M, Svensson P. Bite or brain: Implication of sensorimotor regulation and neuroplasticity in oral rehabilitation procedures. *J Oral Rehabil*. 2018;45(4):323-333. doi:10.1111/joor.12603

45. Newton JP, Yemm R, Abel RW, Menhinick S. Changes in human jaw muscles with age and dental state. *Gerodontology*. 1993;10(1):16-22.

46. Ueno M, Yanagisawa T, Shinada K, Ohara S, Kawaguchi Y. Masticatory ability and functional tooth units in Japanese adults. *J Oral Rehabil*. 2008;35(5):337-344. doi:10.1111/j.1365-2842.2008.01847.x

47. Daniels SK, Corey DM, Hadskey LD, et al. Mechanism of sequential swallowing during straw drinking in healthy young and older adults. *J Speech Lang Hear Res*. 2004;47(1):33-45. doi:10.1044/1092-4388(2004/004)

48. Yoshikawa M, Yoshida M, Nagasaki T, et al. Aspects of swallowing in healthy dentate elderly persons older than 80 years. *J Gerontol A Biol Sci Med Sci*. 2005;60(4):506-509. http://biomedgerontology.oxfordjournals.org/content/60/4/506.full.pdf.

49. Fiske J, Davis DM, Frances C, Gelbier S. The emotional effects of tooth loss in edentulous people. *Br Dent J*. 1998;184(2):90-93; discussion 79.

50. Naik A V, Pai RC. Study of emotional effects of tooth loss in an aging north Indian community. *ISRN Dent*. 2011;2011:395498. doi:10.5402/2011/395498

51. Rodrigues SM, Oliveira AC, Vargas AM, Moreira AN, EF EF. Implications of edentulism on quality of life among elderly. *Int J Env Res Public Heal*. 2012;9(1):100-109. doi:10.3390/ijerph9010100

52. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of Periodontitis in Adults in the United States: 2009 and 2010. *J Dent Res*. 2012;91(10):914-920. doi:10.1177/0022034512457373

53. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *J Dent Res*. 2014;93(11):1045-1053. doi:10.1177/0022034514552491

54. Gil-Montoya JA, Sánchez-Lara I, Carnero-Pardo C, et al. Oral hygiene in the elderly with different degrees of cognitive impairment and dementia. *J Am Geriatr Soc*. 2017;65(3):642-647. doi:10.1111/jgs.14697

55. Gil-Montoya JA, Sanchez-Lara I, Carnero-Pardo C, et al. Is periodontitis a risk factor for cognitive impairment and dementia? A case-control study. *J Periodontol*. 2015;86(2):244-253. doi:10.1902/jop.2014.140340

56. Ide M, Harris M, Stevens A, et al. Periodontitis and cognitive decline in Alzheimer's disease. *PLoS One*. 2016;11(3):1-9. doi:10.1371/journal.pone.0151081

57. Holmer J, Eriksdotter M, Schultzberg M, Pussinen PJ, Buhlin K. Association between periodontitis and risk of Alzheimer′s disease, mild cognitive impairment and subjective cognitive decline: A case–control study. *J Clin Periodontol*. 2018;45(11):1287-1298. doi:10.1111/jcpe.13016

58. Olsen I, Singhrao SK. Can oral infection be a risk factor for Alzheimer's disease? *J Oral Microbiol*. 2015;7(1):1-16. doi:10.3402/jom.v7.29143

59. Sochocka M, Sobczyński M, Sender-Janeczek A, et al. Association between Periodontal Health Status and Cognitive Abilitie s. The Role of Cytokine Profile and Systemic Inflammation. *Curr Alzheimer Res*. 2017;14(9):978-990. doi:10.2174/1567205014666170316163340

60. Kamer AR, Fortea JO, Videla S, et al. Periodontal disease's contribution to Alzheimer's disease progression in Down syndrome. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2016;2:49-57. doi:10.1016/j.dadm.2016.01.001

61. Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, de Leon MJ. Inflammation and Alzheimer's disease: Possible role of periodontal diseases. *Alzheimer's Dement*. 2008;4(4):242-250. doi:10.1016/j.jalz.2007.08.004

62. Gil-Montoya JA, Barrios R, Santana S, et al. Association between periodontitis and amyloid β peptide in elderly people with and without cognitive impairment. *J Periodontol*. 2017;88(10):1051-1058. doi:10.1902/jop.2017.170071

63. Leira Y, Carballo Á, Orlandi M, et al. Periodontitis and systemic markers of neurodegeneration: A case–control study. *J Clin Periodontol*. 2020. doi:10.1111/jcpe.13267

64. Gil Montoya JA, Barrios R, Sanchez-Lara I, et al. Systemic inflammatory impact of periodontitis on cognitive impairment. *Gerodontology*. 2020;37(1):11-18. doi:10.1111/ger.12431

65. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathology in the Nun Study. *J Am Dent Assoc*. 2007;138(10):1314-1322. doi:10.14219/jada.archive.2007.0046

66. Hansson P, Sunnegårdh-Grönberg K, Bergdahl J, Bergdahl M, Nyberg L, Nilsson L-G. Relationship between natural teeth and memory in a healthy elderly population. *Eur J Oral Sci*. 2013;121(4):333-340. doi:10.1111/eos.12060

67. Zuluaga DJM, Montoya JAG, Contreras CI, Herrera RR. Association between oral health, cognitive impairment and oral health-related quality of life. *Gerodontology*. 2012;29(2):e667-73. doi:10.1111/j.1741-2358.2011.00542.x

68. Cerutti-Kopplin D, Feine J, Padilha DM, et al. Tooth Loss Increases the Risk of Diminished Cognitive Function. *JDR Clin Transl Res*. 2016;1(1):10-19. doi:10.1177/2380084416633102

69. Kimura Y, Ogawa H, Yoshihara A, et al. Evaluation of chewing ability and its relationship with activities of daily living, depression, cognitive status and food intake in the community-dwelling elderly. *Geriatr*

Gerontol Int. 2013;13(3):718-725. doi:10.1111/ggi.12006

70. Elsig F, Schimmel M, Duvernay E, et al. Tooth loss, chewing efficiency and cognitive impairment in geriatric patients. *Gerodontology*. 2015;32(2):149-156. doi:10.1111/ger.12079

71. Stein PS, Kryscio RJ, Desrosiers M, Donegan SJ, Gibbs MB. Tooth loss, apolipoprotein E, and decline in delayed word recall. *J Dent Res*. 2010;89(5):473-477. doi:10.1177/0022034509357881

72. Takeuchi K, Ohara T, Furuta M, et al. Tooth Loss and Risk of Dementia in the Community: the Hisayama Study. *J Am Geriatr Soc*. 2017;65(5):e95-e100. doi:10.1111/jgs.14791

73. Ikebe K, Gondo Y, Kamide K, et al. Occlusal force is correlated with cognitive function directly as well as indirectly via food intake in community-dwelling older Japanese: From the SONIC study. Gil-Montoya JA, ed. *PLoS One*. 2018;13(1):e0190741. doi:10.1371/journal.pone.0190741

74. Scherder E, Posthuma W, Bakker T, Vuijk PJ, Lobbezoo F. Functional status of masticatory system, executive function and episodic memory in older persons. *J Oral Rehabil*. 2008;35(5):324-336. doi:10.1111/j.1365-2842.2007.01842.x

75. Lexomboon D, Trulsson M, Wardh I, et al. Chewing ability and tooth loss: association with cognitive impairment in an elderly population study. *J Am Geriatr Soc*. 2012;60(10):1951-1956. doi:10.1111/j.1532-5415.2012.04154.x

76. Cerutti-Kopplin D, Emami E, Hilgert JB, Hugo FN, Padilha DMP. Cognitive status of edentate elders wearing complete denture: Does quality of denture matter? *J Dent*. 2015;43(9):1071-1075. doi:10.1016/j.jdent.2015.07.008

77. 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 Prosthodont Res*. 2009;53(3):126-135. doi:10.1016/j.jpor.2009.02.005

78. Shin H, Cho M, Amano A, Song K, Choi Y. Association between mastication-related factors and the prevalence of dementia in Korean elderly women visiting senior centres. *Gerodontology*. December 2019:ger.12453. doi:10.1111/ger.12453

79. Sasaguri K, Otsuka T, Tsunashima H, Shimazaki T, Kubo K-Y, Onozuka M. Influence of restoration adjustments on prefrontal blood flow: A simplified NIRS preliminary study. *Int J Stomatol Occlusion Med*. 2015;8(1):22-28. doi:10.1007/s12548-015-0122-x

80. Banu FR, Veeravalli PT, Kumar A. Comparative Evaluation of Changes in Brain Activity and Cognitive Function of Edentulous Patients, with Dentures and Two-Implant Supported Mandibular Overdenture-Pilot Study. *Clin Implant Dent Relat Res*. 2016;18(3):580-587. doi:10.1111/cid.12336

81. Morokuma M. Influence of the functional improvement of complete dentures on brain activity. *Nihon Hotetsu Shika Gakkai Zasshi*. 2008;52(2):194-199. http://www.ncbi.nlm.nih.gov/pubmed/18467791. Accessed January 5, 2018.

82. Gomez-Pinilla F, Hillman C. The Influence of Exercise on Cognitive Abilities. In: *Comprehensive Physiology*. Vol 3. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2013:403-428. doi:10.1002/cphy.c110063

83. Nelson EE, Guyer AE. The development of the ventral prefrontal cortex and social flexibility. *Dev Cogn Neurosci*. 2012;1(3):233-245. doi:10.1016/j.dcn.2011.01.002.The

84. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic Exercise and Neurocognitive Performance: A Meta-Analytic Review of Randomized Controlled Trials. *Psychosom Med*. 2011;72(3):239-252. doi:10.1097/PSY.0b013e3181d14633.Aerobic

85. Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer's dementia. *Ageing Res Rev*. 2018;48(October):109-121. doi:10.1016/j.arr.2018.10.002

86. Wrann CD, White JP, Salogiannnis J, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metab*. 2013;18(5):649-659. doi:10.1016/j.cmet.2013.09.008.Exercise

87. Moon HY, Becke A, Berron D, et al. Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metab*. 2016;24(2):332-340. doi:10.1016/j.cmet.2016.05.025

88. Sorrells SF, Paredes MF, Cebrian-Silla A, et al. Human hippocampal neurogenesis drops sharply in

children to undetectable levels in adults. *Nature*. 2018;555(7696):377-381. doi:10.1038/nature25975

89. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat Med*. 2019;25(4):554-560. doi:10.1038/s41591-019-0375-9

90. Bekinschtein P, Cammarota M, Medina JH. BDNF and memory processing. *Neuropharmacology*. 2014;76(PART C):677-683. doi:10.1016/j.neuropharm.2013.04.024

91. Tapia-Arancibia L, Aliaga E, Silhol M, Arancibia S. New insights into brain BDNF function in normal aging and Alzheimer disease. *Brain Res Rev*. 2008;59(1):201-220. doi:10.1016/j.brainresrev.2008.07.007

92. Erickson KI, Prakash RS, Voss MW, et al. BDNF is Associated With Age-Related Decline in Hippocampal Volume. *J Neurosci*. 2011;30(15):5368-5375. doi:10.1523/JNEUROSCI.6251-09.2010.BDNF

93. Nigam SM, Xu S, Kritikou JS, et al. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. *J Neurochem*. 2018;142(2):286-296. doi:10.1111/jnc.14034.Exercise

94. Rohe M, Synowitz M, Glass R, Paul SM, Nykjaer A, Willnow TE. Brain-Derived Neurotrophic Factor Reduces Amyloidogenic Processing through Control of SORLA Gene Expression. *J Neurosci*. 2009;29(49):15472-15478. doi:10.1523/JNEUROSCI.3960-09.2009

95. Jones BE. Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. *Prog Brain Res*. 2004;145:157-169. doi:10.1016/S0079-6123(03)45011-5

96. Vermeiren Y, De Deyn PP. Targeting the norepinephrinergic system in Parkinson's disease and related disorders: The locus coeruleus story. *Neurochem Int*. 2017;102:22-32. doi:10.1016/j.neuint.2016.11.009

97. Heneka MT, Galea E, Gavriluyk V, et al. Noradrenergic depletion potentiates beta -amyloid-induced cortical inflammation: implications for Alzheimer's disease. *J Neurosci*. 2002;22(7):2434-2442. doi:20026222

98. Kong Y, Ruan L, Qian L, Liu X, Le Y. Norepinephrine Promotes Microglia to Uptake and Degrade Amyloid Peptide through Upregulation of Mouse Formyl Peptide Receptor 2 and Induction of Insulin-

Degrading Enzyme. *J Neurosci*. 2010;30(35):11848-11857. doi:10.1523/JNEUROSCI.2985-10.2010

99. Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: Therapeutic implications. *J Psychopharmacol*. 2013;27(8):694-718. doi:10.1177/0269881113480988

100. Braak H, Del Tredici K. Where, when, and in what form does sporadic Alzheimer's disease begin? *Curr Opin Neurol*. 2012;25(6):708-714. doi:10.1097/WCO.0b013e32835a3432

101. De Cicco V, Tramonti Fantozzi MP, Cataldo E, et al. Trigeminal, Visceral and Vestibular Inputs May Improve Cognitive Functions by Acting through the Locus Coeruleus and the Ascending Reticular Activating System: A New Hypothesis. *Front Neuroanat*. 2018;11(January):1-17. doi:10.3389/fnana.2017.00130

102. Trulsson M. Sensory-motor function of human periodontal mechanoreceptors. *J Oral Rehabil*. 2006;33(4):262-273. doi:10.1111/j.1365-2842.2006.01629.x

103. Türker KS, Sowman PF, Tuncer M, Tucker KJ, Brinkworth RSA. The role of periodontal mechanoreceptors in mastication. *Arch Oral Biol*. 2007;52(4):361-364. doi:10.1016/j.archoralbio.2006.11.014

104. De Cicco V, Barresi M, Tramonti Fantozzi MP, Cataldo E, Parisi V, Manzoni D. Oral Implant-Prostheses: New Teeth for a Brighter Brain. Lebedev MA, ed. *PLoS One*. 2016;11(2):e0148715. doi:10.1371/journal.pone.0148715

105. de Cicco V, Cataldo E, Barresi M, Parisi V, Manzoni D. Sensorimotor trigeminal unbalance modulates pupil size. *Arch Ital Biol*. 2014;152(1):1-12. doi:10.12871/000398292017126

106. Aoun G, Nasseh A, Sokhn S, Rifai M. Apparent Diffision Coefficient Measurement in Mediatinal Lymphadenopathies-Differentiation between Benign and Malignant Lesions. *J Clin Imaging Sci*. 2017;7(12):1-10. doi:10.4103/jcis.JCIS

107. Mayil M, Keser G, Demir A, Pekiner FN. Assessment of Masseter Muscle Appearance and Thickness in Edentulous and Dentate Patients by Ultrasonography. *Open Dent J*. 2018;12(1):723-734. doi:10.2174/1745017901814010723

108. Eberhard L, Oh K, Eiffler C, et al. Adaptation to new complete dentures—is the neuromuscular system outcome-oriented or effort-oriented? *Clin Oral Investig*. 2018;22(6):2309-2317. doi:10.1007/s00784-017-2331-8

109. Guzmán-Venegas RA, Palma FH, Biotti P JL, de la Rosa FJB. Spectral components in electromyograms from four regions of the human masseter, in natural dentate and edentulous subjects with removable prostheses and implants. *Arch Oral Biol*. 2018;90(September 2017):130-137. doi:10.1016/j.archoralbio.2018.03.010

110. Quintero A, Ichesco E, Schutt R, Myers C, Peltier S, Gerstner GE. Functional connectivity of human chewing: An fcMRI study. *J Dent Res*. 2013;92(3):272-278. doi:10.1177/0022034512472681

111. Lotze M, Domin M, Kordass B. Symmetry of fMRI activation in the primary sensorimotor cortex during unilateral chewing. *Clin Oral Investig*. 2017;21(4):967-973. doi:10.1007/s00784-016-1858-4

112. Shoi K, Fueki K, Usui N, Taira M, Wakabayashi N. Influence of posterior dental arch length on brain activity during chewing in patients with mandibular distal extension removable partial dentures. *J Oral Rehabil*. 2014;41(7):486-495. doi:10.1111/joor.12169

FIGURE LEGENDS

Figure 1. Graphical summary of the alterations that occur in memory and learning functions in animal models due to an occlusal dysfunction with the deprivation by soft diet.

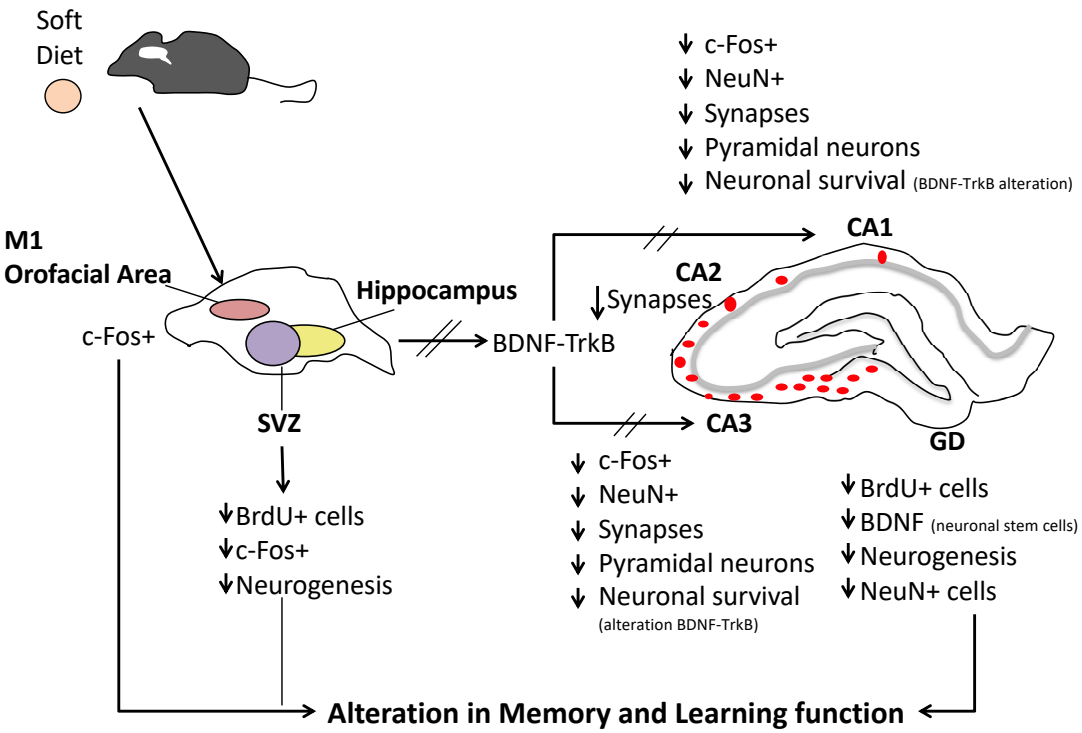

Figure 2. Graphical summary of the interaction between the occlusal condition and the alteration of structures such as the hippocampus through the chronic stress generated by an experimental occlusal alteration in the animal model.

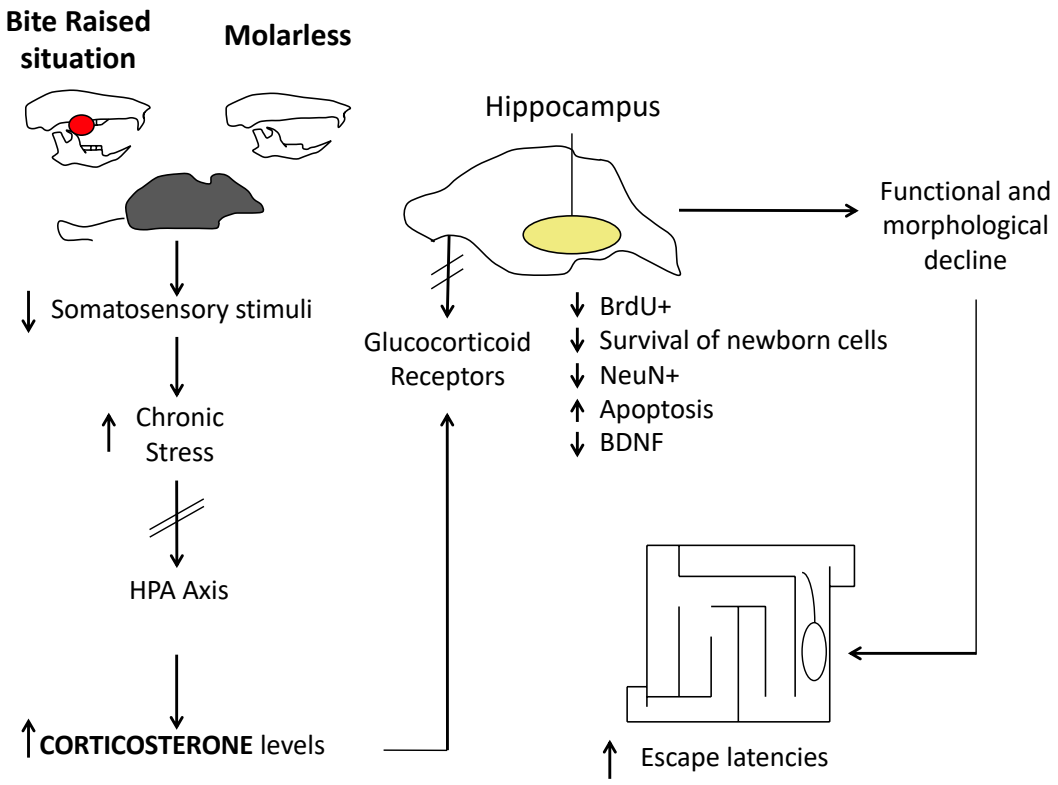

Figure 3. Periodontopathogens generate neuroinflammation through an increase in the levels of local and systemic inflammation that results in neurodegeneration and cognitive decline by an increase in the accumulation of Aß and P-Tau.

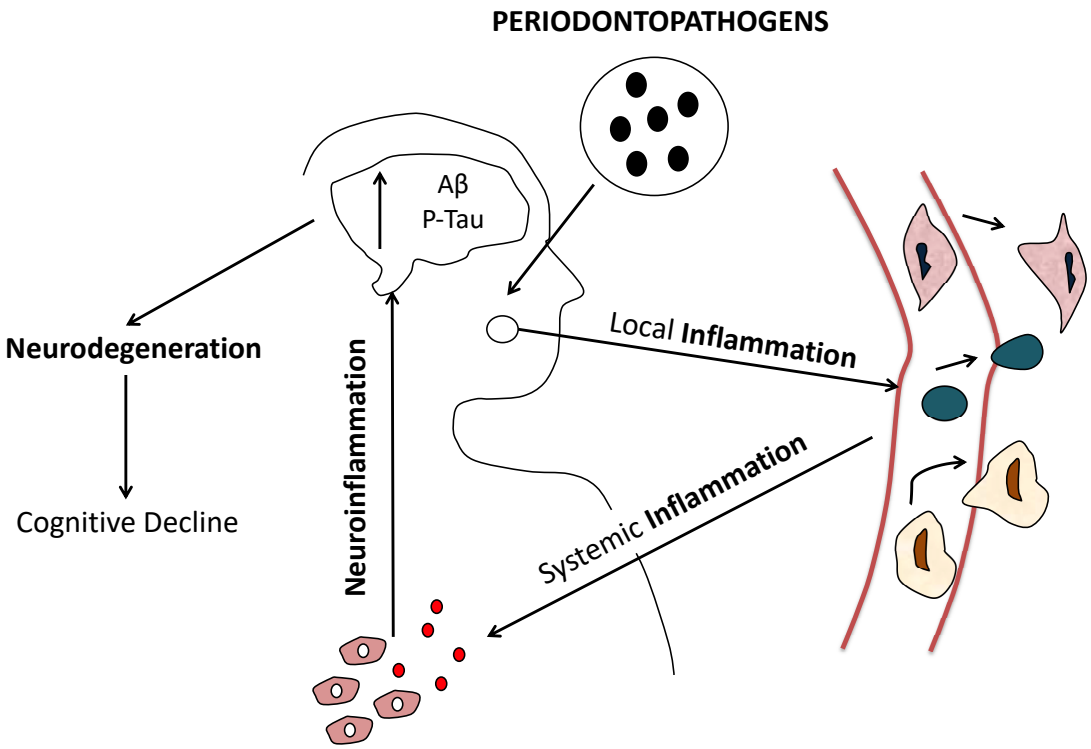

Figure 4. Overlapping of the brain areas involved in chewing processes (blue) or sensible to cognitive ageing effects (red). Violet indicates common areas to both processes.

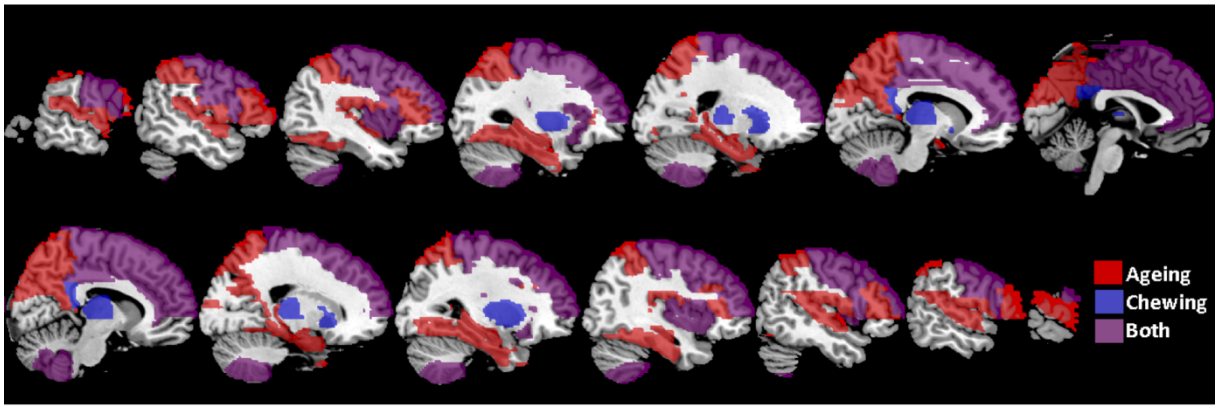

Figure 5. Graphical summary of the different pathways by which the occlusal function influences cognitive performance and AD pathogenesis.