Review

Tooth Loss and Brain Damage: Multiple Recurrent Cortical Remapping Hypothesis

Yi-Tai Jou, DMD
Director of
Pre-doctoral Endodontic Program
Endodontic Department
School of Dental Medicine
University of Pennsylvania
240 S. 40th Street
Philadelphia, PA 19104
Tel: 215-898-4927
FAX: 215-573-2148
ytj@dental.upenn.edu

Abstract

Basic biomedical knowledge of the neurobiological mechanisms of the deafferentation of stomatognathic systems has expanded greatly in recent decades. In both human and animal experimental trials, there are indications that the deafferentation of stomatognathic systems may be a critical factor in triggering and aggravating neurodegenerative diseases. This review explores basic neurobiological mechanisms associated with the deafferentation of stomatognathic systems; further included is a discussion on tooth loss and other oral-maxillofacial deafferentation (OMFD) mechanisms, with a focus on dental and periodontal apparatus that are associated with brain function and that may underlie the changes observed in the aging brain. A new hypothesis is proposed that tooth loss and changes in the functionality of teeth may cause brain damage due to recurrent remapping of the brain, and may even be a triggering and aggravating factor in the onset and progression of Alzheimer's disease. A growing understanding of the association of OMFD with brain aging may lead to solutions in treating and preventing cognitive decline and Alzheimer's disease.

Introduction

One of the greatest health threats of the twenty-first century has been cognitive frailty and cognitive decline of old age (Bishop et al., 2010). For adults over the age of 85, a predicted near-50% of this population segment will be afflicted with Alzheimer's disease. Recent advances in the biology of stomatognathic systems, together with human and animal experimental studies of the brain, are beginning to shed light on the neural mechanisms and their potential roles in cognitive decline. Clinicians may have to develop new concepts and strategies in coping with these new and challenging circumstances. Developing therapeutic interventions and preventive strategies for such conditions demands a greater understanding of the processes underlying normal and pathological brain aging related to stomatognathic systems.

The greatest risk factor for cognitive decline and Alzheimer's disease in older adults is age itself (Bishop et al., 2010). Cumulating scientific evidence have indicated a correlation between tooth loss and impaired brain functions such as memory loss, cognitive impairment, even prodromes of Alzheimer's disease and dementia (Avlund et al., 2004; Bergdahl et al., 2007; Gatz et al., 2006; Grabe et al., 2009; Kaye et al., 2010; Okamoto et al., 2010a, 2010b; Stein et al., 2007, 2010). Based on animal

trials and clinical research, a recent review (Weijenberg et al., 2011) has highlighted the causal relationship of mastication on cognitive functions. The correlation between the loss of teeth with memory loss, cognitive impairment, and prodromes of Alzheimer's disease and dementia has not yet been fully explored. Kondo et al. (1994) hypothesized that tooth loss leads to a deprivation of sensory information input during mastication. Inflammatory mediators, bacteria, and toxins associated with periodontitis have been hypothesized to enhance brain inflammation (Grabe et al., 2009; Kamer et al., 2008, 2012; Kim et al., 2007), though as yet no conclusive study has been completed. In combining the latest studies, a new hypothesis is proposed: Loss of teeth and changes in the functionality of teeth may cause serious damage to the function of the brain, and may even be a triggering and aggravating factor in the onset and progression of Alzheimer's disease and dementia.

Tooth and Memories Associated with the Function of Mastication

During the period of mixed dentition, the roots of the primary teeth begin absorption while permanent teeth begin growth and eruption. Post-eruption, the permanent teeth eventually complete occlusion and allow mastication. The sensory receptors inside the periodontal ligament of the permanent teeth adapt to various functions, including mastication (Trulsson, 2006, 2007; van der Glas et al., 2007). This growth continues as the function of occlusion-mastication matures and stabilizes. During the stabilization period, the periodontal sensory receptors of the teeth—including mechanoreceptors, proprioceptive receptors, nociceptive receptors, and other related receptors and nerve endings—build a functional neuronal connection with the sensory cortex, on both conscious and unconscious levels (Trulsson, 2006, 2007; van der Glas et al., 2007). The periodontal sensory receptors of the teeth coordinate with masticatory muscles and joints to form a very precise neuromuscular reflex (van der Glas et al., 2007). After accumulating years of functional memories, the matured and integrated occlusion-mastication function becomes a basic and even pleasurable physical act.

In the mature and integrated occlusion-mastication act, processing food is not the only mechanical function. Before eating an apple, for example, memories relating to this occlusion-mastication act remind us that when we bite into the apple, we may expect a crisp and juicy, fragrant and sweet sensory event. This feedforward memory and recognition result from the coordinated and synchronized crossmodal, multisensory recognition among visual sensory receptors, olfactory sensory receptors, gustatory sensory receptors (Boucher et al., 2006), periodontal mechanoreceptors (Trulsson, 2006, 2007) and even the central connection and organization of multiple sensory inputs by the cortical neurons (Hirano et al., 2008; Momose et al., 1997; Sesay et al., 2000; Takada et al., 2004, Trulsson et al., 2010). After we have bitten into and began chewing on the apple, all related sensory receptors began its recognize, evaluate, and enjoy the fruit. This simple process of ingesting food is a complex harmonization of conscious and unconscious recognition, memory, conditioned reflexes, and many other functions as multiple neural transmissions, evaluations, decisions, and executions happen simultaneously. In the comprehensive execution of this neural process, the teeth play a prominent role, as its nerve endings and sensory receptors enable the necessary precision in the massive and comprehensive coordination of diverse players in the occlusion-mastication act (Trulsson, 2006, 2007). In this occlusion-mastication "symphony orchestra," each tooth is a "musician" performing its indelible, intricate, and indispensable function in creating the overall harmony of occlusion-mastication. Should one or more "musician" (teeth) were to change their function or become missing, the orchestra's overall harmony is doubtlessly affected, creating temporary or long-term dissonances and increasing mental and physical stress. To adapt to alterations, cope with stress, and maintain the effectiveness of the occlusion-mastication function in the face of such changes, it is necessary for related sensory cortical and motor remapping (Avivi-Arber et al., 2010; Henry et al., 2005).

Tooth and Head/Neck Activities Associated with the Function of Mastication

As discussed previously, processing food is not the only aim of the occlusion-mastication act. Before, during, and after food ingestion, all twelve pairs of cranial nerves related to the head/neck sensory and motor functions

simultaneously coordinate and integrate all relevant information. Additionally, all masticatory muscles, as well as all the muscles of the head and the neck, participate directly and indirectly during the occlusion-mastication act. The exercise of these aforementioned muscles is necessary for survival; it is also a natural pattern of routine for the head and the neck. A growing body of literature suggests that physical activity beneficially influences brain function and executive cognitive processes (Ratey and Loehr, 2011). Evidence also indicates that mastication can affect regional cerebral blood flow (Hirano et al., 2008; Momose et al., 1997; Sesay et al., 2000; Takada et al., 2004).

The occlusion-mastication act can be changed locally and comprehensively by pain due to decay, periodontal disease, or removal of permanent teeth necessary in the occlusion-mastication act; this change may lead to subsequent changes in the motor patterns of the head and neck. In cases of multiple teeth loss, the motor function of the head and neck (in particular the quality and quantity of the masticatory muscular exercises) are also affected. Long-term negative effects of such a scenario have been shown in animal and clinical studies (Andoh et al., 2009; Kato et al., 1997; Kawanishi et al., 2010; Kaye et al., 2010; Makiura et al., 2000; Miura et al., 2003; Ono et al., 2010, Onozuka et al., 1999, 2000; Tsutsui et al., 2007; Watanabe et al., 2002; Yamazaki et al., 2008) and may be plausibly linked to an impaired learning abilities, loss of memory, and subsequent development into prodromes of Alzheimer's disease and dementia.

Tooth Loss and Hypothesized Multiple Recurrent Sensory and Motor Cortical Remapping

Tooth loss leads to change in the occlusion-mastication function, which in turn leads to sensory cortical and motor cortical remapping (Avivi-Arber et al., 2010; Henry, et al., 2005). The sensory cortex of permanent teeth holds the functional and mature memories of the occlusion-mastication-ingestion act. Once affected by the sensation of pain due to cavities or periodontal diseases, changes may take place, locally and centrally, in the occlusion-mastication act, causing transitional sensory cortical remapping (Iyengar et al., 2007). In other words, the loss of the functional and mature memories (due to the damage or removal of permanent teeth) may cause sustained, even permanent, sensory cortical and motor cortical remapping (Avivi-Arber et al., 2010; Henry et al., 2005). From the nerve endings and sensory receptors in the damaged permanent teeth, to the neurons in the central nervous system, all related functional connections undergo a cortical reorganization during the sensory cortical and motor cortical remapping. Simultaneously occurring are local cortical re-circuitry, regional cortical rewiring, even large-scale cortical restructuring (Iyengar et al., 2007). The process of the primary sensory cortical remapping may overlap into areas of proximate cortical units, which may in turn affect the cortical circuitries of teeth, gingiva, and oral mucous membrane proximate to the affected adjacent tooth or teeth (Henry et al., 2005). It is hypothesized that when neighboring or opposing teeth are lost subsequently, a secondary sensory cortical remapping is likely to occur, with an ever-expanding area being affected by the process of the cortical remapping. Ex analogia, multiple, sequential loss of adjacent teeth may cause tertiary and quaternary sensory cortical remapping. With each remapping, the affected cortical area grows larger, and with continuous cortical rewiring and rebuilding and little time for maturation, the new neuronal pathways become always further removed from the semblance of the original optimal connections, decreasing the efficacy of the sensory cortical and motor neuronal pathways for the occlusion-mastication related function and its associated memories and cognition.

In the primary motor cortical remapping process, the area affected by the remapping may expand to nearby cortical neurons, such as cortical neurons controlling the anterior belly of digastric muscle and geniglossus muscle (Avivi-Arber et al., 2010). It is hypothesized that if neighboring or adjacent teeth are lost subsequently, a secondary motor cortical remapping is likely to occur, with an ever-expanding area being affected by the process of the cortical remapping. With each remapping, the affected cortical area grows larger, and with continuous cortical rewiring and rebuilding and little time for maturation, the new neuronal pathways become yet further removed from the semblance of the original optimal connections, decreasing the efficacy of the sensory cortical and motor neuronal pathways for the occlusion-mastication function and its related memories and cognition.

Recent research studies have shown that a breakdown in the composition and organization appears clearly and definitively in anatomical regions of brain affected by Alzheimer's disease, thus forming the disconnection syndrome (He et al., 2009). The etiology of the disconnection syndrome correlates to the disruption of the neuronal integrity of large-scale brain networks. The memory, motor, and cognitive functions relating to the occlusion-mastication act covers multiple anatomical sub-areas of the brain, including the primary and secondary motor and sensory cortices, the temporal, parietal, and occipital lobes, and more (Hirano et al., 2008; Momose et al., 1997; Sesay et al., 2000; Takada et al., 2004, Trulsson et al., 2010). It is hypothesized that multiple teeth loss and subsequent changes in the occlusion-mastication function cause ever-expanding motor and sensory cortical remapping. Furthermore, the less efficient cortical rewiring and rebuilding of the large-scale brain networks, combined with aging (when breakdowns in cerebral composition and organization are more likely), may lead to a loss of plasticity and an increase in disconnection in the brain. As the disconnection syndrome progresses, it is likely that this sequence of events, which began with the loss of multiple teeth, is likely cause and worsening factor for Alzheimer's disease and dementia (Bergdahl et al., 2007; Gatz et al., 2006; Grabe et al., 2009; Kaye et al., 2010; Okamoto et al., 2010a, 2010b; Ono et al., 2010; Stein et al., 2007, 2010).

The Scope of Sensory cortical and Motor Remapping

When a tooth is lost, its periodontal and pulp sensory receptors (including mechanoreceptors, proprioceptive receptors, nociceptive receptors, and other related receptors and nerve endings) are also lost. The accompanying functions of these missing receptors and nerve endings are reassigned to adjacent teeth and tissues during the cortical remapping process (Henry et al., 2005). However, in the primary sensory cortical remapping process, the affected areas are not limited to the sensory receptors of the lost teeth, nor limited to its related areas: The sensory functions of adjacent oral mucosa, tongue, and taste buds are also affected and changed (Habre-Hallage et al., 2011, Boucher et al., 2006). Subsequently, functional changes may occur to the corresponding sensory cortex and the relay neurons of the central nervous system of these affected oral and lingual mucosa and tissues. Starting within the sensory and motor cortices, a massive cortical modification, reorganization, and reintegration begins in order to adapt all related nerve endings and receptor cells, even various relay neurons in the central nervous system (Jain et al., 2008). (A simultaneous rebuilding of the cortical nervous pathways may occur, including local, regional, and large-scale cortical rewiring and re-integration.)

Tooth Loss Leads to Difficult Retrieval, or Complete Loss of, Associated Memory

When a tooth is lost, its interior sensory receptors (including mechanoreceptors, proprioceptive receptors, nociceptive receptors, and other related receptors and nerve endings) are also lost. The accompanying functions of these missing receptors and nerve endings are reassigned to adjacent teeth and tissues during the cortical and sensory cortical remapping process. However, the dental sensory functions make up an important part in the precise neuromuscular reflex and all related and associated memories. A change or damage in the dental sensory function may cause a comprehensive change in the mastication and related function such as postural balance control (Cuccurazzu et al., 2007, Kushiro and Goto, 2011; Yoshida et al., 2009). It is hypothesized that after a certain amount of patching and adapting, the mastication function may partially return, but the precise dental sensory function, as well as the cumulated functional (reflex) memory and its related conscious and unconscious cognitive chewing-related memories, may be difficult to retrieve, gradually fading away or even no longer in existence. Additionally, the sensory functions of the adjacent oral membrane, tongue membrane, and taste buds are also affected and changed by tooth loss (Boucher et al., 2006). All related functional memory and conscious and unconscious cognitive memory are subsequently affected and changed, very possibly damaged, difficult to retrieve, or even permanently lost.

Possible Damage to Brain Functions Caused by Tooth Loss

A growing number of research evidence show that the loss of peripheral sensory

functions, along with age difference and puberty, correlates with the neuroplastic changes of the brain, and may even form crossmodal neuroplastic changes (Merabet and Pascual-Leone, 2010). The loss of peripheral sensory receptors and OMFD may also lead to behavioral adaptations causing multiple levels of impact and change in the brain (Cuccurazzu et al., 2007, Deriu et al., 2010; Jain et al., 2008; Kushiro and Goto, 2011; Yoshida et al., 2009).

When multiple teeth loss occurs, the subsequent sensory and motor cortical remapping, rewiring, and rebuilding of various neural pathways on multiple levels make it difficult in the extreme to return to the original optimal connections and precise neuromuscular and associated crossmodal multisensory functions. Furthermore, continuous cortical rewiring and rebuilding of neural pathways may result in serious non-ideal or over-detoured connections, thus losing the functions' original high efficacy level. It is hypothesized that long-term, regular use of these non-ideal connections is likely to cumulate in abnormal levels of burden, may result in producing excessive Beta - Amyloid, causing synaptic and extra-synaptic dysfunction (Bordji et al., 2010, 2011; Gladding and Raymond, 2011) and taxing the limits of the brain's neuroplasticity. In certain circumstances, all of these conditions may combine to form short circuits, becoming the proverbial final straw in breaking the last surviving normal brain functions.

Permanent teeth are equipped with mastication functions and mature memories and losing them causes functional changes in the brain. It is possible to adapt to these changes; however, as the brain ages, the plasticity of the brain decreases as well, and, it is hypothesized that should the brain's functions be further shocked by the loss of strategic molars, the brain may suffer varying degrees of impact on multiple levels. In the aging process, multiple losses of teeth and its consequent effects may lead to various levels of cognitive and memory loss in old age, even dementia or Alzheimer's disease (Avlund et al., 2004; Bergdahl et al., 2007; Gatz et al., 2006; Grabe et al., 2009; Kaye et al., 2010; Okamoto et al., 2010a, 2010b; Ono et al., 2010; Stein et al., 2007, 2010).

As shown by the above hypotheses and worthwhile leads, new light may be shed on the research on the etiology and treatment of Alzheimer's disease and new directions and strategies considered for future studies in the fascinating link between teeth loss and brain change.

References

1. Andoh T, Sakuma Y, Yamamoto S, Matsuno A, Maeda T, Kotani J. Influences of molar loss of rat on learning and memory. Journal of Prosthodontic Research 2009; 53: 155-60.
2. Avivi-Arber L, Lee J C, Sessle BJ. Effects of incisor extraction on jaw and tongue motor representations within face sensorimotor cortex of adult rats. The Journal of Comparative Neurology 2010; 518: 1030-45.
3. Avivi-Arber L, Lee JC, & Sessle BJ. Face sensorimotor cortex neuroplasticity associated with intraoral alterations. Progress in Brain Research Chapter 9 2011;188: 135-50.
4. Avlund K, Holm-Pedersen P, Morse DE, Viitanen M, Winblad B. Tooth loss and caries prevalence in very old swedish people: The relationship to cognitive function and functional ability. Gerodontology 2004; 21: 17-26.
5. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010; 464: 529-35.
6. BoucherY, Berteretche MV, Farhang F, Arvy MP, Azerad J, Faurion A. Taste deficits related to dental deafferentation: An electrogustometric study in humans. European Journal of Oral Sciences, 2006; 114: 456-64.
7. Breivik T, Thrane PS, Gjermo P, Cools A, Myhrer T. Effects of hippocampal lesioning on experimental periodontitis in wistar rats. Journal of Periodontal Research, 2002; 37: 360-5.
8. Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg S, Reynolds CA, et al. Potentially modifiable risk factors for dementia in identical twins. Alzheimer's & Dementia : The Journal of the Alzheimer's Association 2006; 2: 110-7.
9. Grabe HJ, Schwahn C, Volzke H, Spitzer C, Freyberger HJ, John U, et al. Tooth loss and cognitive impairment. Journal of Clinical Periodontology 2009;36: 550-7.
10. He Y, Chen Z, Gong G, Evans A. Neuronal networks in Alzheimer's disease. The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry 2009; 15: 333-50.
11. Henry EC, Marasco PD, Catania KC. Plasticity of the cortical dentition representation after tooth extraction in naked mole-rats. The Journal of Comparative Neurology 2005; 485: 64-74.
12. Iyengar S, Qi HX, Jain N, Kaas JH. Cortical and thalamic connections of the representations of the teeth and tongue in somatosensory cortex of new world monkeys. The Journal of Comparative Neurology 2007; 501: 95-120.
13. Kato T, Usami T, Noda Y, Hasegawa M, Ueda M, Nabeshima T. The effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats. Behavioural Brain Researc 1997; 83: 239-42.
14. Kawanishi, K., Koshino, H., Toyoshita, Y., Tanaka, M., & Hirai, T. Effect of mastication on functional recoveries after permanent middle cerebral artery occlusion in rats. Journal of Stroke and Cerebrovascular Diseases : The Official Journal of National Stroke Association 2010;19: 398-403.
15. Kaye EK, Valencia A, Baba N, Spiro A III, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. Journal of the American Geriatrics Society 2010;58: 713-8.
16. Makiura T, Ikeda Y, Hirai T, Terasawa H, Hamaue N, Minami M. Influence of diet and occlusal support on learning memory in rats behavioral and biochemical studies. Research Communications in Molecular Pathology and Pharmacology 2000;107: 269-77.
17. Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: The opportunity of change. Nature Reviews. Neuroscience 2010; 11: 44-52.
18. Miura H, Yamasaki K, Kariyasu M, Miura K, Sumi Y. Relationship between cognitive function and mastication in elderly females. Journal of Oral Rehabilitation 2003; 30: 808-11.
19. Momose T, Nishikawa J, Watanabe T, Sasaki Y, Senda M, Kubota

K, et al. Effect of mastication on regional cerebral blood flow in humans examined by positron-emission tomography with (1) O-labelled water and magnetic resonance imaging. Archives of Oral Biology 1997; 42: 57-61.

20. Okamoto N, Morikawa M, Okamoto K, Habu N, Hazaki K, Harano A, et al. Tooth loss is associated with mild memory impairment in the elderly: The fujiwara-kyo study. Brain Research 2010a; 1349: 68-75.
21. Okamoto N, Morikawa M, Okamoto K, Habu N, Iwamoto J, Tomioka K, et al. Relationship of tooth loss to mild memory impairment and cognitive impairment: Findings from the fujiwara-kyo study. Behavioral and Brain Functions 2010b; 6: 77.
22. Ono, Y., Yamamoto, T., Kubo, K. Y., & Onozuka, M. Occlusion and brain function: Mastication as a prevention of cognitive dysfunction. Journal of Oral Rehabilitation 2010;37: 624-40.
23. Onozuka M, Watanabe K, Mirbod SM, Ozono S, Nishiyama K, Karasawa N, et al. Reduced mastication stimulates impairment of spatial memory and degeneration of hippocampal neurons in aged SAMP8 mice. Brain Research 1999; 826: 148-53.
24. Onozuka, M., Watanabe, K., Nagasaki, S., Jiang, Y., Ozono, S., Nishiyama, K., et al. Impairment of spatial memory and changes in astroglial responsiveness following loss of molar teeth in aged SAMP8 mice. Behavioural Brain Research 2000; 108: 145-55.
25. Sesay, M., Tanaka, A., Ueno, Y., Lecaroz, P., & De Beaufort, D. G. Assessment of regional cerebral blood flow by xenon-enhanced computed tomography during mastication in humans. The Keio Journal of Medicine 2000;49 Suppl 1: A125-8.
26. Stein, P. S., Kryscio, R. J., Desrosiers, M., Donegan, S. J., & Gibbs, M. B. Tooth loss, apolipoprotein E, and decline in delayed word recall. Journal of Dental Research 2010;89: 473-7.
27. Ratey, J. J., & Loehr, J. E. The positive impact of physical activity on cognition during adulthood: A review of underlying mechanisms, evidence and recommendations. Reviews in the Neurosciences 2011; 22: 171-85.
28. Stewart, R., Sabbah, W., Tsakos, G., D'Aiuto, F., & Watt, R. G. Oral health and cognitive function in the third national health and nutrition examination survey (NHANES III). Psychosomatic Medicine 2008;70: 936-41.
29. Tsutsui, K., Kaku, M., Motokawa, M., Tohma, Y., Kawata, T., Fujita, T., et al. Influences of reduced masticatory sensory input from soft-diet feeding upon spatial memory/learning ability in mice. Biomedical Research 2007; 28: 1-7.
30. Watanabe, K., Ozono, S., Nishiyama, K., Saito, S., Tonosaki, K., Fujita, M., et al. The molarless condition in aged SAMP8 mice attenuates hippocampal fos induction linked to water maze performance. Behavioural Brain Research 2002;128: 19-25.
31. Weijenberg, R. A., Scherder, E. J., & Lobbezoo, F. Mastication for the mind--the relationship between mastication and cognition in ageing and dementia. Neuroscience and Biobehavioral Reviews 2011;35: 483-97.
32. Yamazaki, K., Wakabayashi, N., Kobayashi, T., & Suzuki, T. Effect of tooth loss on spatial memory and trkB-mRNA levels in rats. Hippocampus 2008;18: 542-7.