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Review

Mastication for the mind—The relationship between mastication and cognition in ageing and dementia

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ABSTRACT

The goal of this literature review has been to investigate the relationship between mastication and cognition, with a special focus on ageing and dementia, and its possible underlying mechanisms. Since the relationship between mastication and cognition is not yet firmly established, and is investigated in the context of a number of different disciplines, a comprehensive overview will contribute to our knowledge. The results of animal and human experimental studies suggest a causal relationship between mastication and cognition. Furthermore, correlations exist between mastication and activities of daily living and nutritional status. These findings have compelling implications for the development of prevention strategies by which medical and nursing staff may optimize their care for the frail and elderly, suffering from dementia.

Contents

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1. Introduction

The world population is ageing (United Nations, 2008). For example, the senior population (persons over the age of 60) in developed regions will increase from 264 million in 2009 to 416 million in 2050 (United Nations, 2008). Given the fact that ageing is one of the risk factors for developing dementia (Fernandez et al., 2008), an increase in patients suffering from dementia is to be anticipated (Wimo et al., 2003). There are several risk factors for developing dementias like Alzheimer's disease (AD), which is one of the most common subtypes of dementia (Kalaria et al., 2008). These risk factors include ageing, illiteracy, a lower level of education, lower socioeconomic status (Kalaria et al., 2008), head trauma (Plassman et al., 2000), genetic factors such as the apolipoprotein E4 (apoE4) allele (Cedazo-Mínguez, 2007), cardiovascular risk factors such as being overweight, smoking, hypertension and diabetes mellitus (Fillit et al., 2008), an inactive lifestyle (Kramer et al., 2003) and, perhaps surprisingly, loss of teeth (Kondo et al., 1994; Gatz et al., 2006). Loss of teeth has also been associated with malnutrition (Nordenram et al., 2001; Kim et al., 2007), mortality and disability (Holm-Pedersen et al., 2008), loss of cognitive function (Bergdahl et al., 2007) and prevalence of dementia (Kim et al., 2007).

This review will focus on the relationship between masticatory and cognitive function in ageing and dementia. The first question we would like to answer is whether the literature supports the existence of such a relationship and whether this relationship is causal, i.e. does a deterioration of the masticatory system impair cognitive functioning in older persons with and without dementia? A related question concerns the mechanisms underlying this relationship. To our knowledge, neither question has been addressed before, which is why a literature search was performed. The literature on the relationship of mastication and cognition that will be addressed in this review will be subdivided into several categories: animal experimental studies, usually with a strong neuroanatomical focus; human experimental studies, with healthy (and typically young) subjects; and clinical studies, either cross-sectional or longitudinal, with a patient population suffering from either age-related or pathological loss of the ability to perform activities of daily living. Both physiological and behavioral changes will be discussed, where applicable.

2. Outline

Before addressing the selected studies, age-related changes in both dental and cognitive domains will be described in order to provide a conceptual framework and explain nomenclature. Subsequently, animal experimental studies will be discussed, describing short- and long-term effects of diminished mastication. Possible underlying mechanisms will be discussed, such as reduced cell growth and diminished development due to sensory deprivation, disruption of the cholinergic system or disruption of the hypothalamic–pituitary–adrenal axis (HPA-axis), through functional disruption of the glucocorticoid response such as down regulation of glucocorticoid receptors (GR), which is a common response to chronic stress. This will be followed by a review of human studies, introducing another possible underlying mechanism, viz. the beneficial effect of increased systemic and cerebral blood flow as seen in response to exercise. Additionally, the acute and long-term effects of mastication on cognition will be discussed. Finally, to provide a full clinical perspective, the effect of loss of masticatory function on nutritional status and the ability to independently perform activities of daily living (ADL) of the elderly population will be addressed.

3. Age-related changes in the human dental and cognitive domain

3.1. Age-related changes in the dental domain

Edentulism (i.e. not having any remaining teeth) is a common dental state amongst institutionalized older persons (Adam and Preston, 2006). Mentally healthy older persons living in a care facility are often in need of dental care (Wyatt, 2002; Unluer et al., 2007), while neurodegenerative diseases such as dementia inhibit proper oral care and make it difficult to retain and control dentures (Kieser et al., 1999). Furthermore, ageing coincides with a high prevalence of systemic diseases which can complicate dental treatment (Scully and Ettinger, 2007) or cause additional problems such as bone necrosis (Edwards and Migliorati, 2008). Medicine-induced xerostomia (dry mouth due to a lack of saliva) (Abdollahi et al., 2008) can lead to coronal and root caries (Chiappelli et al., 2002). The consequences of diminished dental function and oral care for older persons are diverse; for example, an increased risk of infective endocarditis (Wilson et al., 2007; Ito, 2006) and fatal pneumonia (Adachi et al., 2002; Yoneyama et al., 2002). Pneumonia is a major, if not the primary, cause of death for patients with dementia, whereas in the general population, it is only rarely fatal (Brunnstrom and Englund, 2009). Loss of masticatory function is furthermore associated with loss of physical fitness and functional status (ability to perform activities of daily living (ADL), Shimazaki et al., 2001), and nutritional status (Budtz-Jorgensen et al., 2001; Walls and Steele, 2004). These topics will be discussed in more detail later on.

In order to analyze reports on age-related changes in mastication, a distinction between two commonly used measurements techniques of masticatory performance will be made: (1) masticatory *efficiency*, which is the objective assessment of masticatory function (Boretti et al., 1995; Zhao and Monahan, 2007) and (2) masticatory *ability*, which is the self-assessed (also called subjective) masticatory function (Boretti et al., 1995). Masticatory efficiency assessments can include measurements of tangible parameters such as bite force, jaw muscle strength, maximal mandibular excursions (i.e. maximal mouth opening and maximal movement of the lower jaw in the horizontal plane) (Zhao and Monahan, 2007) and number of teeth (Van Der Bilt, 2002). Masticatory ability is usually measured by interviewing subjects, with or without the aid of questionnaires (Boretti et al., 1995). For example, the question "Are you ordinarily able to chew or bite fresh carrots?" can be used as an indicator of masticatory ability (Locker, 2002). For assessment of masticatory ability, the individual's response to such questions does not need to be verified by an objective assessment of masticatory efficiency. However, the two different measures of masticatory function do show agreement (Boretti et al., 1995; Miura et al., 1998). For example, masticatory ability is related to the presence and amount of teeth (Gotfredsen and Walls, 2007), and the ability to eat a certain type of artificial food correlates – albeit weakly – to the ratings on an 18 item questionnaire regarding appreciation of denture functionality (Slagter et al., 1992).

Normal human ageing is associated with diminished masticatory efficiency, such as loss of jaw muscle cross-sectional area and density (Newton et al., 1993) and loss of natural teeth (Ueno et al., 2008), both more pronounced in women (Newton et al., 1993; Ueno et al., 2008). Furthermore, changed swallowing patterns (Daniels et al., 2004), and increased occurrence of residual debris in the mouth and throat (Yoshikawa et al., 2005) are age-related. There is a lengthening of chewing sequence by adding about 3 cycles for every decade of ageing (Peyron et al., 2004). The chewing frequency (1.45 Hz for men and 1.77 Hz for women, Peyron et al., 2004), generated by the central pattern generator which is located in the

medulla and pons (Lund and Kolta, 2006), remains stable throughout the lifespan (Karlsson and Carlsson, 1990; Peyron et al., 2004). Bite force shows both gender-related variation (Bakke et al., 1990) and age-related variety (Bakke et al., 1990; Fontijn-Tekamp et al., 2000) and is highest in young men (Miyaura et al., 1999). Bite force is also related to number of teeth (Miyaura et al., 1999), occlusal support (i.e. type and size of the contact area of opposing teeth) (Ikebe et al., 2005) and denture use (Ikebe et al., 2005; Alajbeg et al., 2006). Age-related changes in masticatory ability are reported as well. A cohort of seniors with a mean age at baseline of 63 years, subdivided in a "young" group (age equal to or under 64 years) and an "old" group (age 65 years and over) was studied over the course of seven years (Locker, 2002). The ability to eat fresh or boiled fruits, vegetables and firm meats diminishes in both young and old, in both dentate and edentulous persons; however, the greatest decline in masticatory ability was reported by the group of older, edentulous subjects (Locker, 2002).

For research purposes, assessment of masticatory efficiency rather than masticatory ability is preferred when examining (changes in) masticatory function, although for clinical evaluations, the patient-based assessments of masticatory ability can be of relevance as well (Boretti et al., 1995; Feine and Lund, 2006).

3.2. Age-related changes in the cognitive domain

Executive functions include the ability to perform more than one task simultaneously (divided attention), set-shifting (disengaging attention and focusing attention to relevant stimuli), and inhibition (suppression of irrelevant stimuli in order to focus attention to relevant stimuli) (Heyder et al., 2004; Duke and Kaszniak, 2000). Brain areas (grey matter) that play an important role in executive functions such as the prefrontal cortex (PFC), the striatum, and the cerebellum, are sensitive to ageing (Salat et al., 2004; Raz et al., 2003; Sullivan and Pfefferbaum, 2006) as is the white matter (pathways) connecting these areas (Raz et al., 2005). Another area that is both sensitive to ageing and functionally connected to the PFC (Grady et al., 2003), through the striatum, is the hippocampus (medial temporal lobe) (Raz et al., 2004). A dysfunction of the hippocampus causes impairment in episodic memory (Viard et al., 2009). Particularly, learning new information and retrieving information from memory becomes more difficult throughout the ageing process (Burke and Mackay, 1997; Guillaume et al., 2009). Ageing may also impair the level of activity of the entire brain, called arousal, controlled by the Ascending Reticular Activating System (ARAS) (Robbins and Everitt, 1995). Lowering the activity level in the brain may result in slower and less flexible cognitive functioning; two clinical symptoms that are characteristic for normal ageing (Velanova et al., 2007). Taken together, major characteristics of cognitive ageing imply impairment in executive functions (divided attention, set-shifting, inhibition), episodic memory (learning new information and retrieving information from memory) and arousal (level of brain activity).

4. Masticatory function and cognition: is the relationship causal?

To establish causality in any relationship, certain criteria need to be met (Spilker, 1991). First of all, bias, chance, and confounding influences must be eliminated. Also, the association must be consistent (throughout the literature). Of course, the cause must precede the effect, and the presence of a dose–response gradient is another strong indicator of causality. Finally, the association must be specific and should make epidemiological sense (although it might be added that new associations could provide new insight into the etiology of the disease). In the following paragraphs, studies that can elucidate causality in the relationship between mastication and cognition, such as animal and human experimental studies, will be discussed first. More descriptive, clinical studies will be discussed thereafter; they provide information about the consistency of the results.

4.1. Animal experimental studies

4.1.1. Behavioral response to impaired mastication

Animal experimental studies, using the Senescence Accelerated Mouse (SAM), a murine model for ageing (Takeda, 1999; Takeda, 2009), specifically the P8 strain which is an accepted model for AD (Morley, 2002); have shown that impaired mastication leads to long-lasting behavioral aberrations. For example, when masticatory efficiency is impaired by either cutting off the crown of the upper molars (Onozuka et al., 1999; Watanabe et al., 2002) or completely removing them (Onozuka et al., 2000, 2002a, 2002b; Watanabe et al., 2001), it leads to impairment of learning and spatial memory (viz. worse performance in a Morris water maze test, D'Hooge and De Deyn, 2001) (Watanabe et al., 2001, 2002; Onozuka et al., 1999, 2000, 2002a). Besides by cutting or removing molars, mastication can also be impaired by offering animals only soft food (Yamamoto and Hirayama, 2001), thus limiting the masticatory ability. The authors compared groups of 6-month-old SAMP8 mice to the senescence-resistant strain (SAMR1) that were fed either hard (pelleted) food or soft (powder) food. The resistant mice outperformed the prone, yet diet-matched, counterparts in an eight arm radial maze, showing the genetic advantage of the resistant strain. Hard diet-fed mice (-H) gave more correct responses than soft diet (-S) strain-matched individuals for both the R1 and P8 strain, indicating the negative influence of the soft diet (Yamamoto and Hirayama, 2001). Support for the chronic deleterious effect of soft diet on learning also emerges from other animal studies (Tsutsui et al., 2007; Kushida et al., 2008).

4.1.2. Physical responses to impaired mastication and possible mechanisms

Impaired masticatory efficiency produces long-term physical changes (Onozuka et al., 1999, 2000, 2002a, 2002b; Watanabe et al., 2001) which aggravate when the molarless condition persists for a longer period (Onozuka et al., 1999, 2000; Watanabe et al., 2002). Young specimens do not seem to suffer the negative effect of reduced mastication, whereas middle-aged (Watanabe et al., 2001) and old animals do (Watanabe et al., 2001; Tsutsui et al., 2007; Ichihashi et al., 2007). Interestingly, the negative effect of molar crown loss on cognitive performance can be partially reversed by fitting a prosthetic crown on the remaining molar root (Watanabe et al., 2002). Several explanatory mechanisms possibly underlying the relationship between impaired mastication and the responses described above surface from the literature. They will be discussed below in more detail.

A first explanation might be that reduced sensory input influences neurogenesis. Reduction of masticatory ability through a soft diet induces a synaptic density reduction at the cerebral cortex, in particular the parietal regions (Yamamoto and Hirayama, 2001), and reduces the pyramidal hippocampal cell count (Tsutsui et al., 2007). A powder-fed group of C57BL/6 mice showed reduced neuronal proliferation, and a powder-fed and molarless group had both lowered neuronal survival rates and neuronal differentiation (Mitome et al., 2005). In young Wistar rats, it was found that a powder diet led to a decrease in proliferation of newly formed cells in the dentate gyrus of the hippocampus for all age groups (i.e. 7 weeks, 16 weeks and 24 weeks old) with the oldest group showing the strongest effect, in line with the age-related decrease in neuron number found in the control groups (Aoki et al., 2005). Since a complex, enriched environment can facilitate synaptogenesis

Table 1
Behavioral and physical responses to impaired mastication in animals.

Author	*N*	Age at onset	Animal	Intervention	Time span	Response
Yamamoto and Hirayama (2001)	*	0–28 days	SAMP8 mouse and SAMR1 mouse	Powdered diet	2–12 months	BR: Spatial learning ability decreased compared to age matched controls (at 6 months old) in eight arm radial maze. PR: STRAIN effect: Synaptophysin levels lower for prone strain (P8) compared to resistant strain (R1) age matched controls. Less synapses and decreased density of immunoreactive terminals in hippocampus and parietal cortex of P8 group compared to R1 diet matched controls. DIET effect: Soft diet reduced synaptophysin levels in both strains. Density reduction and reduction of synapses in hippocampus and parietal cortex in both strains compared to hard diet fed strain matched controls.
Aoki et al. (2005)	42	0–28 days	Wistar Rat	Powdered diet	0–21 weeks	BR: n/a. PR: Number of BrdU positive cells (i.e. generated within 2 h after BrdU injection) in dentate gyrus subfield decreased in each group (7, 16 and 24 weeks old) compared to younger controls. Soft diet condition aggravates aging effect.
Tsutsui et al. (2007)	109	0–28 days	B6C3Fe-a/a mouse	Powdered diet	27–53 weeks	BR: 360 days group: 2nd and 3rd training day; soft diet group spatial learning ability decreased. PR: Hippocampal (pyramidal) neuron loss in 360 days old soft diet group, compared to all other groups.
Kushida et al. (2008)	38	0–28 days	Wistar Rat	Powdered diet	9 weeks	BR: Learning ability and memory decreased compared to age matched controls in step-through passive avoidance task. PR: No difference in basal level dopamine release in hippocampus; lower maximum increase of dopamine in response to K^+, compared to hard diet fed controls.
Mitome et al. (2005)	54	0–28 days	C57BL/6 mouse	Extraction of all molars AND powdered diet	10–17 weeks	BR: n/a. PR: 5 weeks after last BrdU injection: less newborn cells and lower survival rates in both powder diet groups (soft diet only/soft diet AND molar extraction) compared to hard diet controls. Less differentiation into neurons in the molarless soft diet fed group compared to hard diet controls.
Kato et al. (1997)	*	1–4 months	Wistar rat	Extraction of all molars AND powdered diet	137–146 weeks	BR: Spatial learning ability decreased compared to age matched controls in radial maze. PR: No difference in basal level of extracellular ACh in parietal cortex compared to controls. Lower maximum increase of extracellular acetylcholine in response to K+ compared to controls.
Terasawa et al. (2002)	84	5–9 months	Wistar Rat	Removal of crowns of upper molars AND powder diet	15–35 weeks	BR: n/a. PR: Lower ACh concentration in hippocampus in soft diet AND molarless group compared to age matched controls at 15 weeks but not 35 weeks. Less ChAT positive neurons in NDB/MS in both age groups in soft diet AND molarless group compared to age matched controls. *Note*: No effect for soft diet alone.
Watanabe et al. (2001) (1)	35	0–28 days	SAMP8 mouse	Extraction of maxillary molars	17 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.
Onozuka et al. (2000) (1)		1–4 months	SAMP8 mouse	Extraction of maxillary molars	17 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.
Onozuka et al. (2002b)	56	1–4 months	SAMP8 mouse	Extraction of maxillary molars	21 days	BR: n/a. PR: No effect compared to age matched controls.
Ichihashi et al. (2007) (1)	12	1–4 months	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.

Kubo et al. (2007) (1)	20	1–4 months	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.
Watanabe et al. (2001) (2)	35	5–9 months	SAMP8 mouse	Extraction of maxillary molars	17 days	BR: Spatial learning ability decreased in aged controls compared to young controls. Molarless condition aggravates aging effect. PR: Less neurons in CA1 in middle-aged controls compared to young controls. Molarless condition aggravates aging effect. Number of GFAP positive cells increased compared to age matched controls.
Ichihashi et al. (2007) (2)	12	5–9 months	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.
Kubo et al. (2007) (2)	20	5–9 months	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: No effect compared to age matched controls. PR: No effect compared to age matched controls.
Onozuka et al. (1999)	20	9 months and up	SAMP8 mouse	Cutting of crowns of maxillary molars	14–28 days	BR: Spatial learning ability decreased compared to age matched controls; increasing impairment with duration. PR: Decrease of pyramidal cells in CA1 compared to controls 10 days after surgery; increasing loss with increasing duration of molarless condition (7 days vs. 21 days postoperative).
Onozuka et al. (2000) (2)	34	9 months and up	SAMP8 mouse	Extraction of maxillary molars	17 days	BR: Spatial learning ability decreased in aged controls compared to young controls. Molarless condition aggravates aging effect. PR: Hippocampal hypertrophy of GFAP+ astrocytes and shorter fibers, and increase in the number of astrocytes in CA1 compared to young controls. Molarless condition aggravates aging effect.
Onozuka et al. (2000) (3)	60	9 months and up	SAMP8 mouse	Extraction of maxillary molars	14–28 days	BR: Spatial learning ability decreased compared to age matched controls. Prolongation of molarless condition aggravates impairment. PR: Increase of GFAP positive cells in all molarless groups compared to operation-day and age matched controls. Within molarless group: Density of GFAP labeled cells in CA1 higher in 21 days post-op group vs. 7 day post-op. After 21 days of molarless condition: resting membrane potential hypertrophied astrocytes not different from normal; lower response to increasing K^+ concentration in hypertrophied cells.
Watanabe et al., 2001 (3)	35	9 months and up	SAMP8 mouse	Extraction of maxillary molars	17 days	BR: Spatial learning ability decreased in aged controls compared to young controls. Molarless condition aggravates aging effect. PR: Less neurons in CA1 compared to young controls. More GFAP positive cells compared to age matched controls. Number of GFAP positive cells also increased in aged controls compared to young and middle-aged controls. Molarless condition aggravates aging effect.
Onozuka et al. (2002b)	61	9 months and up	SAMP8 mouse	Extraction of maxillary molars	21 days	BR: n/a. PR: Lower ACh release triggered by KCl compared to age matched controls. Decrease in hippocampal ChAT activity in aged controls compared to young controls. Less ChAT positive cells in medial septal region and vertical limb of the diagonal band of Broca (vDBB) in aged controls compared to young controls. Molarless condition aggravates aging effect (not in vDBB).
Onozuka et al. (2002a)	48	9 months and up	SAMP8 mouse	Extraction of maxillary molars	10 days	BR: n/a. PR: Increased plasma corticosterone levels compared to age matched controls.

Table 1 (*Continued*)

Author	*N*	Age at onset	Animal	Intervention	Time span	Response
Onozuka et al. (2002a)	30	9 months and up	SAMP8 mouse	Extraction of maxillary molars	11 days	BR: Spatial learning ability decreased compared to both control groups. Molarless and metyrapone injected animals equal to controls injected with vehicle. PR: Lower neuron count in CA1; and increased plasma corticosterone levels compared to both control groups (molarless + metyrapone and control + vehicle).
Watanabe et al. (2002) (1)	20	9 months and up	SAMP8 mouse	Cutting of crowns of maxillary molars	17 days	BR: Spatial learning ability decreased compared to age matched controls. PR: Fewer Fos positive cells in CA1 subfield compared to age matched controls.
Watanabe et al. (2002) (2)	55	9 months and up	SAMP8 mouse	Cutting of crowns of maxillary molars	14–28 days	BR: n/a. PR: Decrease of Fos positive cells in molarless group between 7 and 21 days.
Watanabe et al. (2002) (3)	21	9 months and up	SAMP8 mouse	Cutting of crowns of maxillary molars	27 days	BR: Spatial learning ability decreased compared to age matched controls. After restoration partial improvement. PR: After restoration; Fos induction improved compared to compare to molarless group but still decreased compared to controls.
Ichihashi et al. (2007) (3)	12	9 months and up	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: Spatial learning ability decreased in aged controls compared to young controls. Bite raised condition aggravates aging effect. PR: Less GR immunoreactive cells in CA1 and DG and lower expression of GRmRNA in CA1, CA3 and DG compared to age matched controls.
Kubo et al. (2007) (3)	20	9 months and up	SAMP8 mouse	Adding a layer of resin on maxillary molars	14 days	BR: Spatial learning ability decreased in aged controls compared to young controls. Bite raised condition aggravates aging effect. PR: Plasma corticosterone levels elevated and pyramidal cell density in CA3 lower compared to age matched controls.
Ichihashi et al. (2008)	10	9 months and up	SAMP8 mouse	Adding a layer of resin on maxillary molars	Unknown	BR: n/a. PR: Less GR-immunoreactive cells in CA1 and DG compared to age matched controls. Fewer GR-immunoreactive cells dorsal vs. ventral DG.

N = *; data not provided; Response: BR: behavioral response; PR: physical response BrdU = bromodeoxyuridine; ACh = acetylcholine; ChAT = cholineacetyltransferase; GFAP = glial fibrillary acidic protein; GR = glucocorticoid receptors; GRmRNA = glucocorticoid receptor messenger ribonucleic acid. CA1 = hippocampal subfield CA1; CA3 = hippocampal subfield CA3; DG = hippocampal subfield dentate gyrus. *Note*: All studies: male animals, except (Mitome et al., 2005): females; in case of surgery: controls undergo same procedure except no actual extraction/cutting/adding layer; anesthesia with pentobarbital sodium, except (Mitome et al., 2005): ketamine and xylazine; standard housing, free access to (pellet) food and water. If powdered; powder diet contains same components; i.e. difference only in hardness of food. No difference in spontaneous locomotion, food intake nor body weight. No difference in swimming speed or visual ability (although not assessed in all studies). Behavioral testing if not otherwise specified: Morris maze: 4 trials per day, 7 consecutive days. Performance = time needed to find platform; if otherwise specified: Eight Arm Radial Maze: 3 days habituation, followed by 14 consecutive days testing. Performance = number of correct responses in first eight trials. Radial maze: 3 days habituation, followed by 16 consecutive days testing, 1 trial per day. Step-through passive avoidance task: assessment 24 h later. Performance = time until stepping through door. Ad (Onozuka et al., 2002a): Injection of corticosterone synthesis inhibitor metyrapone, first injection 1 day preoperative, every 2 days following. Assess at day 10 post-operation. Studies are separated into age groups/experiments indicated by numbers between brackets. BrdU is marker for cell proliferation; Fos induction is proxy for neuronal activity; GFAP is proxy for ageing and/or neuronal degeneration.

(Churchill et al., 2002), it might be possible that the impoverished sensory input caused by a soft diet (Tsutsui et al., 2007) led to these negative effects.

A second explanatory mechanism might be a disruption of the hypothalamic–pituitary–adrenal axis (HPA-axis). Aged SAMP8 mice all show circadian variation in their plasma corticosterone levels, with molarless specimens exhibiting significantly more elevated levels in the dark period (Onozuka et al., 2002a). After injection with metyrapone (an inhibitor of stress-induced elevation of plasma corticosterone), the molarless mice no longer showed raised plasma levels, nor did they exhibit the neuron loss or learning deficits. Metyrapone apparently protects against the negative effects of the molarless condition by preventing increased corticosterone plasma levels (Onozuka et al., 2002a). Higher plasma levels of corticosterone (Kubo et al., 2007) and lower levels of hippocampal glucocorticoid receptors (Ichihashi et al., 2007, 2008) were also found when masticatory efficiency was impaired by adding a layer of resin to the molars. Reduced expression of hippocampal (cytosolic) glucocorticoid receptors is associated with chronic stress (Sapolsky et al., 1984; Mizoguchi et al., 2003), indicating that the stress response might very well mediate the influence of impaired mastication on memory. In fact, regions such as the hippocampus and PFC are known for their responsiveness to stress (McEwen, 2008). Impaired mastication might cause stress, or, given that chewing is reported to relieve stress in humans (Scholey et al., 2009) and animals (Ono et al., 2008), it might offer a counteractive mechanism for stress, which is lost when mastication is inhibited.

A third possible underlying mechanism is the functional disruption of the cholinergic neurotransmitter system due to impaired masticatory efficiency, caused for example by cutting or extracting molars. Aged molarless SAMP8 mice have a lower evoked hippocampal acetylcholine response, and an aggravated age-related decline of both choline acetyltransferase (ChAT) and ChAT-positive cells (Onozuka et al., 2002b). Hippocampal acetylcholine (ACh) is associated with spatial memory function in rodents (Stancampiano et al., 1999). A disruption of the cholinergic system related to impaired learning was also found in rats (Kato et al., 1997; Terasawa et al., 2002). Toothless rats made more errors while learning a spatial memory task compared to the controls and showed a decrease in releasing ability of ACh stimulation with K+ (Kato et al., 1997). The molar crown-less condition lowered the hippocampal ACh concentration compared to control animals (Terasawa et al., 2002). No effect was found with the powder diet only group (Terasawa et al., 2002). The abovementioned and related studies not addressed here are summarized in Table 1.

Several comments with regard to these results can be made. First of all, some studies set out with young animals (Yamamoto and Hirayama, 2001; Terasawa et al., 2002; Aoki et al., 2005; Mitome et al., 2005; Tsutsui et al., 2007; Kushida et al., 2008) whereas others have worked with aged specimens (Onozuka et al., 1999, 2002a; Watanabe et al., 2001, 2002; Ichihashi et al., 2008), or both (Kato et al., 1997; Onozuka et al., 2000, 2002b; Ichihashi et al., 2007; Kubo et al., 2007). In young animals, the *developmental* effect of impaired mastication is studied, e.g. Yamamoto and Hirayama (2001), whereas in the older groups, the *degenerative* consequences are brought forward.

Second, some of the studies found an effect in aged groups only; however, those interventions typically lasted only for a short period of time, for example 14 or 21 days (Ichihashi et al., 2007). Possibly, older animals are more sensitive to the detrimental effects of impaired mastication, since they respond to the same treatment that the younger ones do not respond to. Only when the impaired mastication condition lasts longer, e.g. 9 weeks or more (Kushida et al., 2008; Yamamoto and Hirayama, 2001), young animals start to exhibit deficits in behavior and physiology as well.

Third, whereas the average lifespan of a mouse can be 2 years, e.g. male C57BL/6 mice can live up to 26.6 months (Rowlatt et al., 1976), the average lifespan of the SAMP8 mouse is about 1 year (Takeda, 2009). The Wistar rat can even live up to 3 years (Snyder et al., 1990). So while a 10-month-old SAMP8 mouse is indeed an aged specimen, a rat that has lived 60 weeks by the end of the experimental period, as was seen in one study (Terasawa et al., 2002), can be classified as middle aged at best (Snyder et al., 1990). This could explain the lack of results for a soft diet alone in that study (Terasawa et al., 2002). Indeed, in a similar investigation (Tsutsui et al., 2007) with mice, only the aged group, and not the middle-aged group, showed a response to a soft diet. Apparently the effect of a soft diet needs a longer time to become apparent.

Fourth, the effect that cutting or extracting teeth has on an animal's well being must be considered. Pain or inflammation might be of influence. Although the results are not published, Onozuka et al. (2002a) mention that inflammation of the alveolar bone was ruled out, since interleukine and interferon levels were normal. While disruption of occlusion by applying a layer of resin to the teeth could cause chronic discomfort (Christensen, 1970), others (Watanabe et al., 2002) point out that the absence of distressed behavior such as not eating was not seen after cutting the upper molar crowns. A further argument against pain playing a part in the process is the fact that results deteriorate as the condition lasts longer, instead of improving during the subsequent healing process, e.g. Onozuka et al. (1999).

In conclusion, a decrease in masticatory activity coincides with chronic deterioration in behavioral and physiological functions. Learning ability and (spatial) memory decline, and lower levels of cell proliferation and neuron density are found. There are alterations in biochemistry and an increase in stress hormone levels. Furthermore, the effects are age-related. We argue that the relationship is causal as the cause precedes the effect, a dose–response gradient is present, and the association is both specific and makes epidemiological sense.

4.2. Human experimental studies

The acute effect of chewing gum on cognition and the effect of mastication on (cerebral) blood flow have been the topic of several studies. Since changes in (cerebral) blood flow may affect cognitive performance in both young and older adults (Duschek and Schandry, 2007; Birns et al., 2005), these changes will be discussed first.

When describing results, the following definitions for age-groups will be used: "young" adults are individuals with an age under or equal to 30 years; "middle-aged" adults are individuals with an age equal to or higher than 30 years, but lower than 50 years; "senior" adults are individuals with an age equal to or higher than 50 years, but lower than 70 years and "aged" adults are individuals with an age equal to or higher than 70 years. When a study did not specify ages, but did include only senior and/or aged subjects, they are referred to as "old" or "older". When considered of particular relevance, specific ages are mentioned.

4.2.1. Acute cardiovascular effects of mastication

Mastication has been shown to acutely lead to higher heart rates in young adults (Wilkinson et al., 2002; Shiba et al., 2002; Nitta et al., 2003). Chewing a piece of gum for 20 min at 1.33 Hz increases heart rate and blood pressure in young adults (Farella et al., 1999). Maximal measurements include an increase of 11 beats/min for heart rate, and a rise in systolic blood pressure with 14 mmHg and in diastolic blood pressure with 11 mmHg. The higher the bolus resistance, the larger the effect (Farella et al., 1999). Although maximal values are found after 10 min of chewing, as soon as 2 min after onset, heart rate and blood pressure changes are present; 10 min

Table 2
Brain areas that are activated during mastication, as measured in regional cerebral blood flow.

Study	*N*	Age in years (range or mean)	Scanning technique	Protocol	PFC	PMA	SMA	SMC	FTC	PC	Ins	Cing	Hippo	Amyg	Thal	Stri	Caud	Cere	Prec
Momose et al. (1997)	*n* = 12	18–40	PET	S: at rest before chewing; during chewing for 150 s; at rest 15 min and 30 min after chewing. Compare task to all resting states.			X	X			X					X	X	X	
Sesay et al. (2000)	*n* = 7	24–57	Xe-CT	S: during chewing and at rest 20 min after chewing.					X	NS	NS	NS			X		X	NS	
Onozuka et al. (2002c)	*n* = 17	20–31	fMRI	S: during 4 cycles of; 32 s chewing – 32 s rest. Compare task vs. rest.			X	X			X				X			X	
Onozuka et al. (2003) (1)	*n* = 11	19–26	fMRI	S: during 8 cycles of: 32 s chewing 32 s rest. Compare task vs. rest.	R		R	L			R				R			L	
Onozuka et al. (2003) (2)	*n* = 8	42–55	fMRI	idem	R		L	L			L				R			L	
Onozuka et al. (2003) (3)	*n* = 13	65–73	fMRI	idem	R		R	R			L				L			R	
Tamura et al. (2003)	*n* = 14	Not given	fMRI	S: during 5 cycles of: 25 s chewing, 25 s rest. Compare to 250 s rest.				X											
Takada and Miyamoto (2004)	*n* = 12	20–28	fMRI	S: during 4 cycles of: 28 s rest, 224 s on task. Tasks are: chewing, empty chewing and rest. Compare all; results unique for actual mastication with bolus.	X					X									
Sasaguri et al. (2004) (1)	*n* = 42	19–26	fMRI	S: during 4 cycles of: 32 s chewing 32 s rest. Compare task vs. rest. C: visual memory task, compare before and after 2 min chewing.			X	X			X			X	X			X	
Sasaguri et al. (2004) (2)	*n* = 33	61–72	fMRI	idem			X	X			X		X	X	X			X	
Shinagawa et al. (2004)	*n* = 6	24–31	fMRI	S: before, and after chewing 5 min (scan 10 min later and 20 min later); pushing forwards and sideways with tongue during all scans. Compare before and 10 min after.[a]				X											
Kordass et al. (2007)	*n* = 13	24.6	fMRI	S: for each task during 9 cycles of: 24 s on task, 24 rest. Tasks are: tapping on teeth, chewing left, chewing right, tapping on splint. Compare all with rest.				I											
Hirano et al. (2008)	*n* = 18 (2 back task)/13 (3 back task)	24.5/24.8	fMRI	S: assessment at rest before chewing (2×), and after chewing 60 s. C: Working memory task, execute during rest and after chewing.	X	R				R			R		R				R

Scanning technique: fMRI = functional Magnetic Resonance Imaging; PET = Positron Emission Tomography; Xe-CT = xenon-enhanced computed tomography PROTOCOL: S = scanning procedure; C = cognitive assessment; min = minutes; s = seconds. Brain areas: PFC = prefrontal cortex; PMA = premotor area; SMA = supplementary motor areas; SMC = sensori-motorcortex; FTC = frontotemporal cortex; PC = parietal cortex; Ins = insula; Cing = cingulate cortex; Hippo = hippocampus; Amyg = amygdale; Thal = thalamus; Stri = striatum; Caud. = caudate nucleus; Cere = cerebellum; Prec = precuneus. Lateralisation: X: activation bilateral/not specified; R: activation right hemisphere; L: activation left hemisphere; I: activation ipsilateral; NS: reported but not significant. *Note*, studies separated into age groups indicated by numbers between brackets.

[a] *Note*: No difference between rest and 20 min later.

after ending the chewing task, the heart rate is still elevated, blood pressure (both systolic and diastolic) however, returns to resting levels (Farella et al., 1999). Since increased heart rate increases cerebral blood flow (CBF) in young adults (Ono et al., 2007), mastication is likely to change CBF as well. The above discussed studies have included young adults only, so it is unknown whether similar results would be obtained in older persons. Studies regarding CBF cover subjects of all ages. In these studies, which will be discussed in detail below, the results seem to be unaffected by age. Therefore, we assume that the same would hold true for the results discussed above, which allows us to generalize these outcomes to the senior population. Clearly, further research to investigate this assumption is required.

CBF does in fact increase as a result of mastication in young adults (Kordass et al., 2007; Ono et al., 2007; Hasegawa et al., 2007), in a group of adults with ages ranging from 18 to 40 years (Momose et al., 1997) and as a result of clenching the jaws at maximal force in seniors (Miyamoto et al., 2005). These acute perfusion effects are studied either cortex-wide (general) or within certain regions of interest. In young adults, exercise in the form of mastication elevates heart rate and middle cerebral arterial blood flow velocities (MCAV; outcome for TransCranial Doppler ultrasound) (Ono et al., 2007; Hasegawa et al., 2007). The masticatory response is immediate, bilateral (Ono et al., 2007; Hasegawa et al., 2007) and ends immediately after the task ends (Ono et al., 2007). Clenching leads to a MCAV response at the working side only (i.e. right side clenching leads to increased blood flow in the right middle cerebral artery) and increased heart rate (peak at 20 s) (Hasegawa et al., 2007). The increase in blood volume is higher in senior participants when they are wearing their dental prosthesis, compared to not wearing a dental prosthesis (Miyamoto et al., 2005). Increased CBF is often observed in older subjects during exercise (Deslandes et al., 2009), and many studies indicate the benefits of exercise, even leisure time activity, on the brain in both young adults and older adults (e.g. Ferris et al., 2007; Churchill et al., 2002; Heyn et al., 2004; Rovio et al., 2005; Laurin et al., 2001; Larson et al., 2006; Larson, 2008; Kramer et al., 2005; Kramer and Erickson, 2007; Benedetti et al., 2008; Yaffe et al., 2001). Although mastication might not be the same as strenuous cardiovascular exercise, muscle activity is increased during mastication in all three groups in a study (mean ages 26.7, 60.9, and 65.7 years) (Alajbeg et al., 2006) and increases of heart rate and blood pressure also occur in young adults (Wilkinson et al., 2002; Shiba et al., 2002; Farella et al., 1999). We would argue that at least some of the effects of mastication on cognition and general health are due to exercise-induced changes in CBF as described in senior adults (Brown et al., 2008). Changes in regional rather than general CBF as a result of mastication have also been investigated. Chewing a piece of gum at 1 Hz promptly leads to an increase in blood flow in several brain areas such as the primary sensorimotor cortex, cerebellum, and striatum in adults (age range 18–40 years) (Momose et al., 1997). The hyper-perfusion ends within 15 min of cessation of chewing (Momose et al., 1997); increased cerebral activation in the sensorimotor cortex only lasts 10 min after cessation of chewing in adults (age range 24–31 years) (Shinagawa et al., 2004). The above addressed and related studies are summarized in Table 2.

The results of the studies presented in Table 2 suggest an acute mastication-related activation of several brain areas such as the PFC (3/10 studies), supplementary motor area (4/10), sensory-motor cortex (7/10), parietal cortex (2/10), insula (4/10), cerebellum (4/10) and the thalamus (5/10). Several comments with regard to these results can be made. The specific involvement of the hippocampus is studied and observed in two studies, in both of which participants were scanned during a memory task (Sasaguri et al., 2004; Hirano et al., 2008). Since the hippocampus is known for its involvement in memory (Viard et al., 2009), this activation might not be related to the masticatory activity, but to the cognitive aspect of the task. The chewing condition did enhance an already present activity, caused by the memory task. Both hippocampal activity and performance on the memory task in aged participants increased after chewing (Sasaguri et al., 2004) and mastication also augmented concentration levels and achievement (Hirano et al., 2008). We could speculate that mastication amplifies brain-area-specific, task-induced activation.

Several studies had the subjects performing unusual (i.e. not resembling normal) behavior, such as pushing the tongue forward or sideways inside the mouth or chewing on a rubber strip (Shinagawa et al., 2004; Kordass et al., 2007). The exact effects of performing trained behavior are not known, as opposed to habitual mastication. In the light of the focus of this paper on ageing, one study is of particular interest. Onozuka et al. (2003) have compared the mastication-related activation patterns from young, middle-aged and aged adults (age ranges 19–26, 42–55, and 65–73 years respectively). Besides differences in lateralization, they observed differences in the amount of signal increase between the different age groups. There was an increase of activity in the PFC for the two older groups, with the highest increase in the oldest group (Onozuka et al., 2003). Mastication-induced increased activity of the PFC could be associated with better performance, since over-recruitment of brain areas has been seen in older adults with better cognition (Grady, 2008). Indeed, both frontal activation and positive effects of mastication on cognition have been found as an acute effect of mastication in adults (age range 20–39 years) (Hirano et al., 2008).

4.2.2. Acute cognitive effect of mastication

Young, healthy volunteers immediately show improvement in self-rated attention (Hirano et al., 2008) and performance in cognitive tasks increases in adults (age range 18–46 years) when chewing on a piece of gum (Wilkinson et al., 2002; Stephens and Tunney, 2004b; Baker et al., 2004; Tucha et al., 2004b; Hirano et al., 2008). Self-rated attention levels as well as performance on two successive memory tasks lowered during the second task when the subjects were not chewing. Performance and concentration levels increased during the subsequent chewing trial (Hirano et al., 2008). Chewing gum enhanced working memory and episodic long-term memory, and improved attention and processing speed in one out of four tests (Stephens and Tunney, 2004b). Chewing during the first learning session improves learning, as shown in better delayed recall in a between-subjects study (Baker et al., 2004). Furthermore, mastication improves immediate and delayed word recall, and spatial and numeric working memory (Wilkinson et al., 2002). A control group in this experiment, pretending to chew without having an actual bolus in the mouth ('empty chewing') also scored better than 'quiet' controls on numeric working memory reaction times; however they performed worse on simple reaction times. The authors argue that this may be a result of performing the unusual behavior of empty chewing (Wilkinson et al., 2002). However, enhanced performance (Tucha et al., 2004b; Johnson and Miles, 2007; Miles and Johnson, 2007) and improved attention and processing speed (Stephens and Tunney, 2004b; Wilkinson et al., 2002) are not consistent findings. A positive effect of chewing gum was observed for sustained attention, but reaction times and number of errors increased in both chewing and empty chewing conditions (Tucha et al., 2004b). The authors explain the discrepancies with the Wilkinson study in terms of design (repeated measures vs. different groups without baseline to eliminate possible between-group differences). They do not regard the results contradictory, but emphasize to interpret the results with caution (Tucha et al., 2004a) A discussion unfolded in the literature in 2004 (Scholey, 2004; Stephens and Tunney, 2004a; Tucha et al., 2004a) and possible explanations for the differences in results between studies are

given, such as the use of different gums, methodological differences (between cross-over design, small samples, lack of baseline testing, non-parametric testing vs. ANOVA), (un)familiarity with chewing gum, and context-effects.

A repetition of the Baker study (Johnson and Miles, 2007) and a re-examination study to control for all possible artifacts by the same authors (Miles and Johnson, 2007) led to a clear conclusion: neither enhancing effects of chewing gum on memory, nor a context-dependent memory effect were found. In fact, the best performance was found for the group that did not chew at any time (Johnson and Miles, 2007) On the other hand, a third study (Johnson and Miles, 2008) with a between-subjects design showed that chewing during a memory task, whether only at encoding or at recall or at both, did lead to improved performance. Similar results were obtained for eating a mint-flavored strip; the group that only received a flavored strip at recall performed as well as the group that received a flavored strip at both encoding and recall. The authors concluded that chewing gum or receiving mint flavor at any point can improve memory (Johnson and Miles, 2008). There is additional support for the suggestion that flavor plays a role in the effect of mastication on memory through arousal in young adults (Zoladz and Raudenbush, 2005; Masumoto et al., 1998) and younger middle-aged adults (age range 27–33 years) (Morinushi et al., 2000) although underlying mechanisms are not yet identified.

Clearly there are inconsistencies in the above described findings, as well as questions that still need to be answered. The following comment can be made: the studies above have focused on the acute effect of mastication on cognition in young adults. Since the highest increase in PFC activity as a result of mastication was seen in elderly persons rather than in young adults (Onozuka et al., 2003) and the PFC is involved in cognitive function (Moritz-Gasser and Duffau, 2009), we might assume that similar findings could be acquired when investigating older adults. In fact, we could speculate that this phenomenon should be even more pronounced in older adults. Further research should clarify this.

In conclusion, both systemic responses (in young adults) and cerebral cardiovascular responses (in both young and older adults) occur robustly and quickly after the onset of mastication. As shown by fMRI and PET studies, several brain areas are activated during mastication. Brain regions that react specifically to mastication (in contrast to mimicking chewing without an actual bolus in the mouth) include the dorsolateral prefrontal cortex, ventral prefrontal cortex and parietal cortex; the frontal area shows a stronger response with higher age. An acute, positive effect of mastication on cognitive performance is still a topic of discussion. With regard to causality, the literature on physiological effects seems consistent and fits the other requirements for causality (cause must precede the effect; presence of a dose–response gradient) leading to the conclusion that mastication causes an increase in systemic and cerebral circulation. Furthermore, mastication is associated with changes (either positive or negative) in cognition. To understand what aspects of mastication and cognition are related, especially in the senior population, clinical studies regarding this relationship in the older population are of paramount importance.

4.3. Clinical studies

The relationship between cognition and masticatory function (i.e. both efficiency and ability) and oral health in older adults will be discussed below. These studies are either cross-sectional, observational, or longitudinal and experimental of nature. Therefore, all effects reported can be considered chronic (i.e. non-acute).

4.3.1. Cognition and masticatory efficiency

Cognition relates to maximal bite force and maximal mandibular excursions in full dental prosthesis wearing aged persons (Scherder et al., 2008). Cognitively impaired aged older women show a lower bite force, a smaller occlusal contact area, lower numbers of teeth (Miura et al., 2003), and are more often edentulous (Nordenram et al., 1996) than healthy age matched controls. Edentulism is related to worse cognitive performance in seniors and aged adults (Bergdahl et al., 2007; Stewart and Hirani, 2007) while retention of some teeth relates to better cognitive functioning in aged nursing home residents (Nordenram and Ljunggren, 2002). Loss of teeth is even recognized as a risk factor for developing AD in seniors and aged adults (Kondo et al., 1994). Having only a few teeth (0–9) increases the risk for developing dementia one decade later, in aged non-apolipoprotein E4 carriers (Stein et al., 2007). Furthermore, being edentulous and not using a denture is a risk factor for becoming mentally impaired over a 6-year period in aged adults (Shimazaki et al., 2001).

4.3.2. Cognition and masticatory ability

One study compared the masticatory ability of aged females suffering from dementia to matched healthy women (Miura et al., 2003). The cognitively impaired group clearly indicated a diminished ability to chew certain foods. The cognitively impaired females could chew 50% of the items on a 35-item rating list, while the healthy controls indicated to be able to chew 77.6% (Miura et al., 2003). Cognitive achievement of aged edentulous denture wearers could be predicted by complaints of pain in the face, head, and mandible (Scherder et al., 2008), which might be indicative of lowered masticatory ability. No correlation between cognitive limitation and prosthetic status (e.g. being dentate or wearing a partial denture versus wearing a complete denture) was found in community-dwelling aged adults (Weyant et al., 2004). The relationship between masticatory ability, rather than prosthetic status, with cognitive functioning has not been examined in that study.

4.3.3. Cognition and oral health

A healthy dentition, preferably with nine or more occluding pairs, is needed for good masticatory function in adolescents and adults of all ages (Gotfredsen and Walls, 2007). Bad oral health, such as having periodontal disease, can lead to tooth loss in the older population (Kossioni and Dontas, 2007) causing loss of masticatory function. Therefore, the effects of oral health on cognition must be considered as well. Receiving oral care for 24 months seems to preserve the mental status of aged persons in a long-term care facility; scores on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) deteriorate slower compared to a group not receiving oral care (Yoneyama et al., 2002). The MMSE is a screening instrument for global cognitive functioning (Folstein et al., 1975). Several cross-sectional studies have also reported a negative relation between cognition and oral health (missing teeth and presence of periodontitis) in senior adults (Wu et al., 2008a) and in aged adults between cognition and dental treatment need (Nordenram and Ljunggren, 2002); between cognition and caries incidence (Ellefsen et al., 2008; Avlund et al., 2004) and between cognition and use of dental healthcare (Avlund et al., 2004). Declining cognition might lead to under-appreciation of oral health and need for care, leading to deterioration of the oral environment (Wu et al., 2008b). Despite support for these negative relationships, no differences were found between decayed, missing and filled teeth (DMFT) scores of two groups of aged nursing home residents, although they differed in cognitive status—not or mildly demented versus more severely impaired (Adam and Preston, 2006). However, denture use and stability were lowered in the more severely impaired group (Adam and Preston, 2006), thus compromising masticatory function.

4.3.4. Non-cognitive issues related to masticatory function and oral health

Cognition and the loss of cognition in relation to mastication has been the primary focus of this review. However, besides cognition, a person's nutritional status and the ability to perform activities of daily living (ADL) can be affected by changes in oral health and masticatory function. The relationship between mastication and nutrition is especially relevant since malnutrition itself is also associated with prevalence of dementia and loss of cognition in older persons (Ramos et al., 2005; Smith and Refsum, 2009), and adequate intake of certain nutrients seems to protect against mental decline in older adults (Del et al., 2006), especially when combined with exercise (van Praag, 2009). These related outcomes will be briefly addressed below.

Several studies reported that good masticatory function and oral health are needed for adequate and varied nourishment in older persons (Budtz-Jorgensen et al., 2001; Sheiham et al., 1999), since edentate individuals of various ages avoid hard foods (e.g. fruits, vegetables, but also meat), which typically are valuable nutrients-containing foods (Hutton et al., 2002). Clinical studies show that impaired oral health and loss of teeth is associated with malnutrition in aged people (Mojon et al., 1999; Nordenram et al., 2001). Indeed, having a higher number of natural teeth relates to better nutritional intake in senior (Sheiham and Steele, 2001) and aged adults (Suzuki et al., 2005). Furthermore the presence of (some) natural teeth is related to eating food of a normal (rather than mashed) consistency in the aged population (Nordenram et al., 1996). Within this scope, it is interesting to note that deterioration of (self-perceived) chewing ability in adults over 65 years of age is positively related to a decline in dietary variety (Kwon et al., 2006), which in turn is related to lower nutritional status in aged people (Bernstein et al., 2002). Clinicians improving nutritional status by restoring masticatory function with a dental prosthesis, should note that the type of denture (viz. with or without implants) can affect the outcome; better nutritional scores are achieved by implant-retained over-dentures compared to regular dentures in older adults (age range 65–75 years) (Morais et al., 2003), although dental treatment does not lead to improved nutritional status in aged adults living in a nursing home (Elmstahl et al., 1988). However, since institutionalized older persons have food intake scores that are comparable to an edentate community-dwelling population, *regardless of dental status* (Elmstahl et al., 1988; Sheiham et al., 2001), this could explain the latter findings. The clinical relevance of these results is clear: besides focusing on restoring and maintaining masticatory function in the elderly, the diet offered by an institution should be given professional attention as well.

Onset of disability and mortality are associated with a lower number of functional teeth (i.e. natural and prosthetic teeth) and edentulism in seniors (Hanada and Tada, 2001) and aged adults (Holm-Pedersen et al., 2008; Shimazaki et al., 2001). Disability is also negatively related to masticatory ability in aged adults (Takata et al., 2004a, 2004b). Perhaps, an explanation for these findings can be found in the fact that disability can negatively influence an aged person's denture use (Minakuchi et al., 2006), their ability to maintain a healthy oral environment (Avlund et al., 2001; Padilha et al., 2007) and is associated with raised dental treatment needs (Nordenram and Ljunggren, 2002), worse oral health (Mojon et al., 1999) and loss of teeth in seniors (Mollaoglu and Alpar, 2005; Miura et al., 1997). Vice versa, the ability to perform ADL improves (although not significantly) as a result of receiving professional oral care in aged adults (Yoneyama et al., 2002).

Besides their respective relations to mastication, outcomes such as nutrition, ADL and cognition are also related to each other. For example, cognitively impaired older persons are underweight (Stewart and Hirani, 2007) and elderly female patients with AD need more help with eating, they eat softer food, and are more often undernourished (Nordenram et al., 1996). In turn, malnutrition is related to loss of cognition in older persons (Ramos et al., 2005; Smith and Refsum, 2009). These interactions are beyond the scope of this review; however, they must be kept in mind.

In conclusion, clinical studies confirm the long-term relationship between mastication and cognition in older adults. There is a relation between cognition and masticatory *efficiency*; however, a relationship between cognition and masticatory *ability* is not, as yet, firmly established. The finding of a relationship between cognitive status and oral health also seems a robust finding throughout several studies. Furthermore, masticatory function is related to ADL. We argued that a relationship might be considered causal if the cause precedes the effect, a dose–response gradient is present, and the association is both specific and makes epidemiological sense. Perhaps most importantly, bias, chance and confounding influences must be ruled out as well. Based on the results of the clinical studies presented above, causality cannot be assumed. Although in some experimental studies cause preceded effect (i.e. receiving oral health care was associated with maintenance of cognitive function), this does not hold true for all studies. A dose response gradient is not observed, and although the association would make epidemiological sense, possible other confounding factors cannot be ruled out. More specifically, factors such as nutritional status and the ability to maintain good oral hygiene are most likely to play a mediating role in the relationship between mastication and cognition.

5. Discussion

The findings of the present review suggest a causal relationship between mastication and cognition in animals and healthy humans. There is additional support for a relationship between mastication and cognition in the elderly population, including those, perhaps even especially those, suffering from dementia.

As mentioned earlier, the requirements for assuming a causal relationship are: (1) the elimination of chance and bias, (2) a consistent association, (3) the cause must precede the effect, (4) a dose–response gradient must be present, and (5) the association must be specific (Spilker, 1991). The relationship between mastication and cognition has been tested against these criteria, and all of them have been met, at least in experimental studies. The elimination of influence of chance and bias (criterion 1) is assumed for all (peer reviewed) studies discussed here. Animal experimental studies robustly show that impaired mastication leads to impaired cognition (requirements 2 and 3), which aggravates when the condition lasts longer, and disappears when masticatory function is restored (4 and 5). Most human experimental studies confirm an increase of cognitive performance as a result of mastication (2–5). Contrary to the experimental studies, clinical studies, especially those with cross-sectional setups, cannot meet these criteria as easily, but still the finding of a relationship between mastication and cognition was reported, consistent and specific (2 and 5). However, causality cannot be assumed based on these studies, especially since confounding factors cannot be ruled out.

From the literature addressed here, the outline of an interaction between mastication, cognition, ADL, and nutrition emerges (see Fig. 1). It was shown that impaired mastication causes impaired cognition, malnutrition, and affected ADL. Furthermore, patients with loss of cognitive and/or physical abilities are more likely to have poor oral health and masticatory function, and are more likely to be malnourished, at least partly due to loss of masticatory function. It is likely that other relationships between these factors exist, however they are beyond the scope of this review.

Besides nutritional status and ADL, other possible variables that might influence both cognitive and masticatory function, could be age, social economical status (Sanders et al., 2006), the status of the

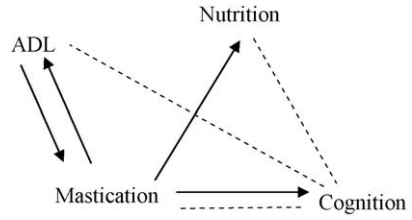

Fig. 1. The interplay of the various outcomes. Arrows indicate causal/longitudinally observed relationships; dotted lines indicate correlations; ADL = activities of daily living.

dentition, e.g. full dentures or natural teeth (Scherder et al., 2008), and the presence of pain (Scherder et al., 2003; Buhle and Wager, 2010), especially if the pain is in the orofacial region. Future studies will have to elucidate whether and how these factors play a role in the relationship between mastication and cognition. The study sample should then preferably be population wide, rather than a clinical subsample.

Several possible underlying biological mechanisms can be proposed. It is possible that diminished sensory input leads to reduced cell growth and development, as seen in animal studies (Yamamoto and Hirayama, 2001; Tsutsui et al., 2007). The cholinergic neurotransmitter system appears to be functionally impaired (Onozuka et al., 2002b), although the specific pathway of impairment is not yet known. The observed stress response is most likely caused by down regulation of certain genes, such as those coding for glucocorticoid receptors (Ichihashi et al., 2008). Down regulation is also observed for Fos protein, as a response to impaired mastication; perhaps the cholinergic disruption has a similar underlying regulatory mechanism. Finally, besides negative effects in response to disrupted mastication, positive effects of mastication could be explained in terms of exercise-related neurogenesis (Wu et al., 2008a; Xu et al., 2006; van Praag, 2009).

The clinical relevance of these results is compelling. In the general population, and in those nursing facilities caring for persons with dementia in particular, attention and priority should be given to prevention of loss of masticatory function and treatment of oral impairments to stabilize or even improve cognition. Oral care should be actively provided to older persons in nursing homes and should furthermore not be limited to individuals retaining some teeth but extended to edentate persons as well. One cannot rely on cognitively impaired older persons to recognize the need for oral care, indicating the necessity for professional dental health care to be available and to be administered on a regular basis, regardless of demand from the patient. The World Health Organization (WHO) recognized the importance of oral health care in 2006 and indicates a stringent need for research, training of caregivers, and development of policy regarding oral health care (World Health Organization, 2006). There should be general awareness of the importance and value of good oral health, not only in the scientific community, but in the general and clinical population as well.

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