Mastication and oral health in elderly persons with dementia

The relationship with cognition and quality of life
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1 General introduction  1
2 Mastication for the mind  15
3 Orofacial pain in dementia patients  51
4 Increased masticatory activity and quality of life  67
5 Digitalization of a mixing ability test  87
6 Oral mixing ability and cognition  101
7 A longitudinal randomized clinical trial  115
8 General discussion  137

Summary  153

Samenvatting  157

Dankwoord  161

Curriculum vitae  165

Outcomes  167
Dementia

Dementia is an umbrella term for a group of neurodegenerative conditions that are characterized by one or more of the following: loss of memory function, behavioral problems, mood changes, serious (disabling) loss of cognitive function, aphasia (i.e., inability to use and understand language), apraxia (i.e., inability to use and understand motor tasks), and/or agnosia (i.e., inability to use and understand objects). Some of the more common types of dementia are Alzheimer's disease (AD), vascular dementia (VaD), fronto-temporal dementia (FTD), and dementia with Lewy bodies (DLB). AD is the most prevalent type of dementia, and is diagnosed in about 60% of the cases; it is in the top ten (at number 6) of causes of death in the United States of America. VaD is present in about 30% of those diagnosed with ‘dementia’. Prevalence of other types of dementia is harder to quantify. For example, FTD mainly has high incidence numbers in persons younger than 65 years old but its prevalence is lower in the elderly, and DLB is diagnosed in about 4%, but percentages as high as 30% have also been reported. For both types of dementia, prevalence numbers are increasing, among others due to new criteria.

Despite some shared characteristics, there are also differences between these dementias, in both underlying pathophysiology and clinical presentation.

- AD patients have a neuropathology characterized by β-amyloid plaques and protein τ tangles in the temporal-parietal and frontal areas of the brain, and also in the hippocampus, entorhinal cortex, and amygdala. Furthermore, they have typical cell death in the hippocampus,
entorhinal cortex, locus coeruleus, and the nucleus basalis of Meynert. Behaviorally and clinically, loss of memory function is most apparent.

- VaD is caused by vascular problems, such as strokes (i.e., cerebrovascular accident, CVA; either cerebral hemorrhaging or infarctions) and presents itself with problems in executive functioning (such as planning and inhibition) rather than memory although any brain-region could be affected and thus, the clinical presentation can be very diverse.

- FTD patients have cellular damage in the frontal and/or temporal sides of the brain, resulting in personality changes and aphasia. FTD can be divided into three clinical syndromes: a ‘frontal’ variant, a ‘temporal’ variant (also known as semantic dementia), and progressive (non-fluent) aphasia.

- People who suffer from DLB have accumulations of \(\alpha\)-synuclein protein in the cortex, causing visual hallucinations and sleep disturbances. Patients can also show signs of Parkinsonism.

- Finally, mixed types (e.g., an AD patient who has had vascular incidents as well) are commonly observed.

Whether someone will develop dementia depends on several factors, such as genetic susceptibility, and also on other aspects, known as risk factors. Ageing is one of the main risk factors for dementia. This is reflected in the prevalence numbers: worldwide, the prevalence is 0.7–1.9% for persons aged 60–64 years, at 70–74 years this number is increased to 2.2–5.1%, at 80–84 years it is estimated at 7.3–16.4%, and within the group of >90 years old, reports indicate a prevalence of 26.4–79.5%. The prevalence is not equally spread around the globe: it is relatively high in Latin America, low in Asia, and Western Europe leans towards the higher numbers, especially for women. In 2010, about 35.6 million people suffered from dementia worldwide; this number will have almost doubled to 65.7 million in 2030, due to an ageing population.

Besides ageing, known risk factors are a low level of education and illiteracy. Other risk factors are functional dependence in activities of daily living (e.g., eating, walking, or dressing oneself), (cardio)vascular risk factors such as hypertension, and psychiatric disorders such as depression. A mentally and socially inactive lifestyle is a risk factor, as well as physical inactivity. Physical activity is known to attenuate the negative effects of stress, cardiovascular disease, and their interaction on cognition, and also enriches the environment. An enriched environment offers visual, social and somatosensory stimuli, promotes interaction, and has a positive effect on cognitive function.

Knowledge about the risk factors for a certain disease may guide research, and may offer chances for the development of new interventions. For example, regular, moderate intense, physical activity (e.g., brisk walking for 30 minutes, 5 times/week) is currently advised for persons of all ages, wanting to prevent (further progression
of) loss of cognition and dementia. One might suggest that mastication is a form of physical activity, because mastication increases heart rate and cerebral blood flow. Impaired mastication is also a risk factor for dementia, as will be discussed below.

Mastication

Experimental animal studies show that impairing masticatory activity through modified occlusion or diet leads to deficits in cognitive and neurobiological outcomes. Some authors even suggest a causal relationship: active mastication might have a positive, preventive action on loss of cognition, whereas disturbed mastication can cause physiological and behavioral deterioration in animals. In human studies, similar correlations have been reported. Having lost 50% or more of the natural dentition, especially at a younger age, has been identified as a risk factor for developing AD. A prolonged period of edentulism (>15 years) and tooth loss is related to an increased risk of lower global cognitive performance in healthy elderly. Edentulism is also associated with lower episodic memory in a healthy sample. Low self-reported dental status was correlated with an increased risk for dementia four years later, in community dwelling elderly persons. A negative relationship between higher cognitive functioning (executive function) and the presence of temporomandibular disorders, orofacial pain, and headaches was found in healthy elderly adults wearing a full dental prosthesis, as well as a positive relationship between mandibular performance (i.e., a domain consisting of maximum bite force and mandibular mobility) and episodic memory. Multiple tooth-loss and self-reported chewing difficulties were associated with impairment in global cognitive functioning in a sample comprising both community dwelling and institutionalized elderly persons. In elderly females suffering from dementia, self-reported masticatory function was found to be significantly lower than in matched females without dementia. In sum, these results show that in both animal studies and human studies, a lower masticatory status is associated with lower cognitive function.

There are a few possible underlying physiological mechanisms that might explain this association.

- **Nutrition** – Being able to maintain an adequate diet, in order to achieve a healthy nutritional status, might play a mediating role in the multifactorial relationship between mastication and cognition, amongst others by facilitating neurogenesis.

- **Enriched environment** – Having a better masticatory function is associated with having a larger variety of food-choices. A complex, enriched environment (such as eating a diverse diet with foods of both hard and soft consistency) can facilitate synaptogenesis. An enriched
environment facilitates recovery of spatial learning ability in aged mice after masticatory rehabilitation. The loss of sensory input through the periodontal receptors can cause an impoverished environment through stimulus deprivation, which is known to negatively affect cognition.

- **Stress** – Impaired mastication might cause stress, or, given that chewing can relieve stress in both humans and animals, it might offer a counteractive mechanism for stress, which is lost when mastication is reduced or hardly possible. Regions involved in memory and executive function, such as the hippocampus and prefrontal cortex, respectively, are known for their vulnerability to stress.

- **Blood flow** – The link between mastication and cognition could also have its foundation in the cerebral blood flow. Studies show that mastication increases middle cerebral arterial blood flow. Having proper masticatory function may restore cognition after cerebrovascular damage, and getting prosthodontic treatment improves brain perfusion, associated with better cognition.

Deserving special attention is the suffering from (orofacial) pain, as this might also be of influence on the association between masticatory activity and cognition. Pain in general is undertreated in elderly persons suffering from dementia. Loss of physical activity can be a sign of pain, but it can also be a cause of pain, thus creating a vicious circle. Pain assessment is not easy; a combination of both self-report and observation scales is recommended. Pain indicators are: the facial expression (grimace, rapid blinking); vocalization (including heavy breathing); certain body movements; and changes in behavior, viz., socially (withdrawing, acting aggressively), personally (not eating; wandering) and mentally (confusion, crying). Specific behaviors indicating orofacial pain might be: holding or rubbing the face, touching the sore area, careful (slow and/or small) mandibular movements, changes in appetite, avoiding some typical foods (hard, or cold), and/or resisting oral care. Given the complex interactions of physical activity with cognition, being aware of (orofacial) pain, and treating it adequately, is essential for general and mental health.

Besides these commonly suggested physiological mechanisms that might explain the relationship between mastication and cognition, some others are also mentioned. Inflammation, for example, has been suggested as a physiological mechanism explaining the correlation between oral health and Alzheimer’s disease, but the loss of teeth might also be indicative of an (early) adverse lifestyle. Others speculate that perhaps a genetic trait makes one prone to pathological ageing, and causes deterioration of both cognition and masticatory function. Which of these underlying mechanisms is appropriate for explaining the association between mastication and cognition is currently not known. Regardless of the underlying mechanism, however, dementia research should not focus solely on physical and
mental functions, such as mastication and cognition; it should also pay attention to the interaction of these measures of health with relevant patient-based outcomes such as quality of life.

Quality of Life (QoL)

The construct of Quality of Life (QoL) describes a person's well-being and it is considered an important outcome variable for patients suffering from dementia. It includes, amongst others, physical health, absence of pain, cognitive function, mental contentment, and leading a (socially) fulfilling life. QoL scores are related to oral health, through mechanisms of choice of food, (mal)nutrition, presence of orofacial pain, and also xerostomia (i.e., a dry mouth) which can limit speech abilities and denture use. QoL can be assessed with rating-scales or questionnaires, for self-rating or by proxies. Interestingly, ratings of QoL can differ between self-rating and a proxy rating. For example, self-ratings showed an association between lower QoL and loss of cognition and depression, whereas proxies associated increased dependency in activities in daily living with lower QoL. Some studies suggest that a rater's mood or health status can influence the patient's QoL score, although others dispute this finding. In this thesis, QoL was assessed with a proxy-based questionnaire, because this was also suitable for those unable to self-report, due to suffering from severe dementia.

Cognition

The Mini Mental State Examination (MMSE) is the most commonly used screening instrument, which measures global cognition through a brief interview that assesses memory, word naming, personal orientation, and visuo-constructive capacities. The common use makes it attractive for research, since it allows for easy comparison with other studies. The term Cognition is defined by the U.S. National Library of Medicine of the National Institutes of Health (NLM-NIH) as: 'Intellectual or mental process whereby an organism becomes aware of or obtains knowledge'. Cognition can be assessed with neuropsychological tests, such as short screening instruments or extensive collections of complementary tests, often referred to as a test battery. There are many screening tests available, reviewed by Cullen et al. In this paper, the authors identify six core domains for cognition: 1) attention/working memory, 2) learning and recall, 3) expressive language, 4) visual construction, 5) abstract reasoning, and 6) executive function. Executive function is an umbrella term, and although it is not (yet) clearly defined in literature, there is general consensus that it describes the ability to operate independently, encompassing higher cognitive functions such as set-shifting/cognitive flexibility, inhibition, divided attention, and goal-directed behavior. For clinical purposes, using more tests than just one screening instrument is recommended for investigating cognition. In this thesis,
both screening with the MMSE, as well as elaborate neuropsychological testing has been done, in order to obtain both comparable and thorough information. As the main aim was to study the effect of mastication on cognition and quality of life, masticatory performance needed to be qualified, and preferably quantified, as well.

Masticatory performance

Masticatory performance can be assessed subjectively through self-report, objectively through the assessment of ‘markers’, or through a combination of both. Subjective assessment of masticatory performance, e.g., with questionnaires, can be informative, but in elderly persons with (severe) dementia, self-report is most likely unreliable. Therefore, masticatory performance was assessed in this thesis with an objective method. For this purpose, a new mixing ability protocol using two-color chewing gum was created. In this test, participants chewed a piece of two-color gum for 20 seconds, after which it was retrieved and analyzed. Building on previous work, mandibular mobility was also assessed, which means measuring the maximal voluntary vertical and horizontal movements one can make with their mouth.

The methods described above for assessing QoL, cognition, and mastication were used to assess elderly persons with dementia, which were recruited in several Dutch organized care settings.

Psychogeriatric care facilities in The Netherlands

In The Netherlands, there are several types of organized care settings providing specialized psychogeriatric (PG) care, such as daycare facilities for community dwelling elderly, and residential settings with varying levels of care, e.g., low-medium care, with an open ward policy (in Dutch ‘verzorgingshuis’), or special care units, with closed wards (in Dutch ‘verpleeghuis’). Attending daycare has a positive effect on both the participant and his/her family members and is typically the first step of the ‘care-chain’. As the dementia progresses, residential care becomes inevitable, and the elderly person becomes institutionalized. In this thesis, the three types of organized PG care settings have been incorporated. This approach granted a relatively controlled environment, and created the opportunity for cluster matching.

GENERAL AIM

The main aim of this thesis was to investigate the effect of increased masticatory activity on quality of life and cognition in elderly persons with dementia, which was achieved through an oral health care intervention executed by the nursing staff of psychogeriatric care facilities, and through making changes in diet. The oral health
care intervention was done according to the Dutch ‘Oral health care Guideline for Older people in Long-term care Institutions’ (OGOLI) \(^{85,86}\).

OUTLINE

Below is an outline of the chapters of this thesis.

Chapter 1

Chapter 1 is the general introduction to this thesis.

Chapter 2

In chapter 2, the possible causal relationship between mastication and dementia was investigated in peer-reviewed reports. First, animal studies are discussed, followed by human studies, including both experimental and observational studies, performed in healthy and clinical samples. Causality is investigated for these associations according to predefined standards.

Chapter 3

As pain, and especially orofacial pain, can influence both mastication and cognition, it is important to be able to adequately recognize this pain in elderly persons suffering from dementia. Literature on this topic is reviewed in chapter 3.

Chapter 4

The work for this thesis is centered around the investigation of the implementation of an intervention to increase masticatory activity, through improving oral health care and changes in diet. The protocol for this randomized clinical trial (RCT), designed as a longitudinal matched-cluster randomized single-blind multicenter study, is presented in chapter 4. A detailed description of the methods and techniques is given.

Chapter 5

In order to measure whether masticatory function improves, tools for measuring performance are needed; tools that are suitable for the population and the scope of the study. Such a tool was not yet available, and so, a new technique was developed, using two-color chewing gum. This tool was tested for sensitivity for change, reliability, and validity, which is described in chapter 5.
Chapter 6

The baseline data from all participants in the RCT study are investigated with linear regression techniques for possible associations between masticatory performance and cognition, which is presented in chapter 6.

Chapter 7

The effects of the intervention in the RCT are investigated in chapter 7, using a mixed analysis of variance. The analysis was done prior to reaching the pre-established endpoint as described in chapter 4, due to concerns with regards to compliance to the planned intervention.

Chapter 8

In chapter 8, a general discussion of the thesis is provided. The implications of the results of this thesis and recommendations for the future are also given.

Summary

Finally, a summary of the thesis is provided, both in English and in Dutch.

REFERENCES

7. Zaccai J., McCracken C., Brayne C. – A systematic review of prevalence and
incidence studies of dementia with Lewy bodies. *Age Ageing.* 34(6); 561–566, 2005.


Mastication for the mind

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.

INTRODUCTION

The world population is ageing. 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. Given the fact that ageing is one of the risk factors for developing dementia, an increase in patients suffering from dementia is to be anticipated. There are several risk factors for developing dementias like Alzheimer’s disease (AD), which is one of the most common subtypes of dementia. These risk factors include ageing, illiteracy, a lower level of education, lower socioeconomic status, head trauma, genetic factors such as the apolipoprotein E4 (apoE) allele, cardiovascular risk factors such as being overweight, smoking, hypertension and diabetes mellitus, an inactive lifestyle and, perhaps surprisingly, loss of teeth. Loss of teeth has also been associated with malnutrition, mortality and disability, loss of cognitive function and prevalence of dementia.

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.

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.

AGE-RELATED CHANGES IN THE HUMAN DENTAL AND COGNITIVE DOMAIN

Age-related changes in the dental domain

Edentulism (i.e., not having any remaining teeth) is a common dental state amongst institutionalized older persons. Mentally healthy older persons living in a care facility are often in need of dental care, while neurodegenerative diseases such as dementia inhibit proper oral care and make it difficult to retain and control dentures. Furthermore, ageing coincides with a high prevalence of systemic diseases which can complicate dental treatment or cause additional problems such as bone necrosis. Medicine-induced xerostomia (dry mouth due to a lack of saliva) can lead to coronal and root caries. The consequences of diminished dental function and oral care for older persons are diverse; for example, an increased risk of infective endocarditis and fatal pneumonia. 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. Loss of masticatory function is furthermore associated with loss of physical fitness and functional status (ability to perform activities of daily living (ADL), and nutritional status. 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 and (2) masticatory ability, which is the self-assessed (also called subjective) masticatory function. 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) and number of teeth. Masticatory ability is usually measured by interviewing subjects, with or without the aid of questionnaires. For example, the question ‘Are you ordinarily able to chew or bite fresh carrots?’ can be used as an indicator of masticatory ability. 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. For example,
masticatory ability is related to the presence and amount of teeth 36, 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 37.

Normal human ageing is associated with diminished masticatory efficiency, such as loss of jaw muscle cross-sectional area and density 38 and loss of natural teeth 39, both more pronounced in women 38,39. Furthermore, changed swallowing patterns 40, and increased occurrence of residual debris in the mouth and throat 41 are age-related. There is a lengthening of chewing sequence by adding about 3 cycles for every decade of ageing 42. The chewing frequency (1.45 Hz for men and 1.77 Hz for women 42, generated by the central pattern generator which is located in the medulla and pons 43, remains stable throughout the lifespan 42,44. Bite force shows both gender-related variation 45 and age-related variety 45,46 and is highest in young men 47. Bite force is also related to number of teeth 47, occlusal support (i.e., type and size of the contact area of opposing teeth)48 and denture use 48,49. 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 34. 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 34.

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 31,50.

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) 51,52. 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 53-55 as is the white matter (pathways) connecting these areas 56. Another area that is both sensitive to ageing and functionally connected to the PFC 57, through the striatum, is the hippocampus (medial temporal lobe) 58. A dysfunction of the hippocampus causes impairment in episodic memory 59. Particularly, learning new information and retrieving information from memory becomes more difficult throughout the ageing process 60,61. Ageing may also impair the level of activity of the entire brain, called arousal, controlled by the Ascending Reticular Activating System (ARAS) 62. 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. 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).

MASTICATORY FUNCTION AND COGNITION: IS THE RELATIONSHIP CAUSAL?

To establish causality in any relationship, certain criteria need to be met. 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.

Animal experimental studies

Behavioral response to impaired mastication

Animal experimental studies, using the Senescence Accelerated Mouse (SAM), a murine model for ageing, specifically the P8 strain which is an accepted model for AD, 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 or completely removing them, it leads to impairment of learning and spatial memory. Besides by cutting or removing molars, mastication can also be impaired by offering animals only soft food, thus limiting the masticatory ability. The authors compared groups of 6-month-old SAMP8 mice to the senescence-resistant strain (SAMRt) 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 gave more correct responses than soft diet strain-matched individuals for both the Rt and P8 strain, indicating the negative influence of the soft diet. Support for the chronic deleterious effect of soft diet on learning also emerges from other animal studies.
Physical responses to impaired mastication and possible mechanisms

Impaired masticatory efficiency produces long-term physical changes which aggravate when the molarless condition persists for a longer period. Young specimens do not seem to suffer the negative effect of reduced mastication, whereas middle-aged and old animals do. 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. Several explanatory mechanisms possibly underly the relationship between impaired mastication and the responses described above 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, and reduces the pyramidal hippocampal cell count. 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. 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. Since a complex, enriched environment can facilitate synaptogenesis, it might be possible that the impoverished sensory input caused by a soft diet 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. 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. Higher plasma levels of corticosterone and lower levels of hippocampal glucocorticoid receptors 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, 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. Impaired mastication might cause stress, or, given that chewing is reported to relieve stress in humans and animals, 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. Hippocampal acetylcholine (ACh) is associated with spatial memory function in rodents. A disruption of the cholinergic system related to impaired learning was also found in rats. 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+. The molar crown-less condition lowered the hippocampal ACh concentration compared to control animals. No effect was found with the powder diet only group. The abovementioned and related studies not addressed here are summarized in Table 2.1.

Several comments with regard to these results can be made. First of all, some studies set out with young animals whereas others have worked with aged specimens, or both. 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. 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, 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, the average lifespan of the SAMP8 mouse is about 1 year. The Wistar rat can even live up to 3 years. 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, can be classified as middle-aged at best. This could explain the lack of results for a soft diet alone in that study. Indeed, in a similar investigation 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 and colleagues 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, others 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...
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<td>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.</td>
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<td>Powdered diet</td>
<td>0–21 weeks</td>
<td>BR: n/a</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: Number of BrdU positive cells (<em>i.e.</em>, generated within two hours 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.</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>Tsutsui et al.,</td>
<td>109</td>
<td>0–28 days</td>
<td>B6C3Fe-a/a mouse</td>
<td>Powdered diet</td>
<td>27–53 weeks</td>
<td>BR: 360 days group: 2nd and 3rd training day; soft diet group spatial learning ability decreased.</td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: Hippocampal (pyramidal) neuron loss in 360 days old soft diet group, compared to all other groups.</td>
</tr>
<tr>
<td>Kushida et al.,</td>
<td>38</td>
<td>0–28 days</td>
<td>Wistar Rat</td>
<td>Powdered diet</td>
<td>9 weeks</td>
<td>BR: Learning ability and memory decreased compared to age matched controls in step-through passive avoidance task.</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Mitome et al.,</td>
<td>54</td>
<td>0–28 days</td>
<td>C57BL/6 mouse</td>
<td>Extraction of all molars AND powdered diet</td>
<td>10–17 weeks</td>
<td>BR: n/a</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>

Table 2.1: Behavioral and physical responses to impaired mastication in animals.
<table>
<thead>
<tr>
<th>Author et al., Date</th>
<th>N</th>
<th>Age at onset</th>
<th>Animal</th>
<th>Intervention</th>
<th>Time span</th>
<th>Response</th>
</tr>
</thead>
</table>
| 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 powdered 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 | 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 | 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 | 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  | 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 | 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. |
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age at onset</th>
<th>Animal</th>
<th>Intervention</th>
<th>Time span</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ichihashi et al., 2007(2)</td>
<td>12</td>
<td>5–9 months</td>
<td>SAMP8 mouse</td>
<td>Adding a layer of resin on maxillary molars</td>
<td>14 days</td>
<td>BR: No effect compared to age matched controls.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: No effect compared to age matched controls.</td>
</tr>
<tr>
<td>Kubo et al., 2007(2)</td>
<td>20</td>
<td>5–9 months</td>
<td>SAMP8 mouse</td>
<td>Adding a layer of resin on maxillary molars</td>
<td>14 days</td>
<td>BR: No effect compared to age matched controls.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: No effect compared to age matched controls.</td>
</tr>
<tr>
<td>Onozuka et al., 1999(1)</td>
<td>20</td>
<td>9 months and up</td>
<td>SAMP8 mouse</td>
<td>Cutting of crowns of maxillary molars</td>
<td>14–28 days</td>
<td>BR: Spatial learning ability decreased compared to age matched controls; increasing impairment with duration.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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).</td>
</tr>
<tr>
<td>Onozuka et al., 2000(2)</td>
<td>34</td>
<td>9 months and up</td>
<td>SAMP8 mouse</td>
<td>Extraction of maxillary molars</td>
<td>17 days</td>
<td>BR: Spatial learning ability decreased in aged controls compared to young controls. Molarless condition aggravates aging effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Onozuka et al., 2000(3)</td>
<td>60</td>
<td>9 months and up</td>
<td>SAMP8 mouse</td>
<td>Extraction of maxillary molars</td>
<td>14–28 days</td>
<td>BR: Spatial learning ability decreased compared to age matched controls. Prolongation of molarless condition aggravates impairment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Watanabe et al., 2001(3)</td>
<td>35</td>
<td>9 months and up</td>
<td>SAMP8 mouse</td>
<td>Extraction of maxillary molars</td>
<td>17 days</td>
<td>BR: Spatial learning ability decreased in aged controls compared to young controls. Molarless condition aggravates aging effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Author</td>
<td>N</td>
<td>Age at onset</td>
<td>Animal Intervention</td>
<td>Time span</td>
<td>Response</td>
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<tr>
<td>Watanabe et al., 2001(3)</td>
<td>73</td>
<td>35</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Extraction of maxillary molars</td>
<td>17 days</td>
</tr>
<tr>
<td>Oonozuka et al., 2002b</td>
<td>61</td>
<td>61</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Extraction of maxillary molars</td>
<td>21 days</td>
</tr>
<tr>
<td>Oonozuka et al., 2002a</td>
<td>48</td>
<td>48</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Extraction of maxillary molars</td>
<td>10 days</td>
</tr>
<tr>
<td>Oonozuka et al., 2002a</td>
<td>30</td>
<td>30</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Extraction of maxillary molars</td>
<td>11 days</td>
</tr>
<tr>
<td>Watanabe et al., 2002(1)</td>
<td>69</td>
<td>20</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Cutting of crowns of maxillary molars</td>
<td>17 days</td>
</tr>
<tr>
<td>Watanabe et al., 2002(2)</td>
<td>69</td>
<td>55</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Cutting of crowns of maxillary molars</td>
<td>27 days</td>
</tr>
<tr>
<td>Watanabe et al., 2002(3)</td>
<td>69</td>
<td>21</td>
<td>SAMP8 mouse</td>
<td>9 months and up</td>
<td>Cutting of crowns of maxillary molars</td>
<td>27 days</td>
</tr>
</tbody>
</table>

Table 2.1: Behavioral and physical responses to impaired mastication in animals (continued).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age at onset</th>
<th>Animal</th>
<th>Intervention</th>
<th>Time span</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ichihashi et al., 2007</td>
<td>12</td>
<td>9 months</td>
<td>SAMP8 mouse</td>
<td>Adding a layer of resin on maxillary</td>
<td>14 days</td>
<td>BR: Spatial learning ability decreased in aged controls compared to young</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and up</td>
<td></td>
<td>molars</td>
<td></td>
<td>controls. Bite raised condition aggravates aging effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: Less GR immunoreactive cells in CA1 and DG and lower expression of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GRmRNA in CA1, CA3 and DG compared to age matched controls.</td>
</tr>
<tr>
<td>Kubo et al., 2007</td>
<td>20</td>
<td>9 months</td>
<td>SAMP8 mouse</td>
<td>Adding a layer of resin on maxillary</td>
<td>14 days</td>
<td>BR: Spatial learning ability decreased in aged controls compared to young</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and up</td>
<td></td>
<td>molars</td>
<td></td>
<td>controls. Bite raised condition aggravates aging effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR: Plasma corticosterone levels elevated and pyramidal cell density in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CA3 lower compared to age matched controls.</td>
</tr>
<tr>
<td>Ichihashi et al., 2008</td>
<td>10</td>
<td>9 months</td>
<td>SAMP8 mouse</td>
<td>Adding a layer of resin on maxillary</td>
<td>unknown</td>
<td>PR: Less GR-immunoreactive cells in CA1 and DG compared to age matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and up</td>
<td></td>
<td>molars</td>
<td></td>
<td>controls. Fewer GR-immunoreactive cells dorsal vs. ventral DG.</td>
</tr>
</tbody>
</table>

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 79: females; in case of surgery: controls undergo same procedure except no actual extraction/cutting/adding layer; anesthesia with pentobarbital sodium except 79; 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 swimming speed or visual ability (although not assessed in all studies). Behavioral testing if not otherwise specified: Morris mazes: 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 hours later. Performance= time until stepping through door. Ad 71: 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.
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.

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, 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.

Acute cardiovascular effects of mastication

Mastication has been shown to acutely lead to higher heart rates in young adults. Chewing a piece of gum for 20 minutes at 1.33 Hz increases heart rate and blood pressure in young adults. 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. Although maximal values are found after 10 minutes of chewing, as soon as 2 minutes after onset, heart rate and blood pressure changes are present; 10 minutes after ending the chewing task, the heart rate is still elevated, blood pressure (both systolic and diastolic) however, returns to resting levels. Since increased heart rate increases cerebral blood flow (CBF) in young adults, 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, in a group of adults with ages ranging from 18–40 years and as a result of clenching the jaws at maximal force in seniors. 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). The masticatory response is immediate, bilateral and ends immediately after the task ends. 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 seconds). The increase in blood volume is higher in senior participants when they are wearing their dental prosthesis, compared to not wearing a dental prosthesis. Increased CBF is often observed in older subjects during exercise, and many studies indicate the benefits of exercise, even leisure time activity, on the brain in both young adults and older adults, e.g., and increases of heart rate and blood pressure also occur in young adults.

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. Changes in regional rather than general CBF as a result of mastication have also been investigated. Chewing a piece of gum at 1Hz 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). The hyper-perfusion ends within 15 minutes of cessation of chewing; increased cerebral activation in the sensorimotor cortex only lasts 10 minutes after cessation of chewing in adults (age range 24–31 years). The above addressed and related studies are summarized in Table 2.2.

The results of the studies presented in Table 2.2 suggest an acute mastication-related activation of several brain areas such as the PFC, supplementary motor area, sensory-motor cortex, parietal cortex, insula, cerebellum, and the thalamus. 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. Since the hippocampus is known for its involvement in memory, 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 and mastication.
also augmented concentration levels and achievement\textsuperscript{120}. We could speculate that mastication amplifies brain-area-specific, task-induced activation.

Several studies had the subjects performing unusual \textit{(i.e., not resembling normal)} behavior, such as pushing the tongue forward or sideways inside the mouth or chewing on a rubber strip\textsuperscript{102,118}. 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 and colleagues (2003)\textsuperscript{121} 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\textsuperscript{121}. 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\textsuperscript{122}. 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)\textsuperscript{120}.

\textit{Acute cognitive effect of mastication}

Young, healthy volunteers immediately show improvement in self-rated attention\textsuperscript{120} and performance in cognitive tasks increases in adults (age range 18–46 years) when chewing on a piece of gum\textsuperscript{97,120,123-125}. 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\textsuperscript{120}. Chewing gum enhanced working memory and episodic long-term memory, and improved attention and processing speed in one out of four tests\textsuperscript{123}. Chewing during the first learning session improves learning, as shown in better delayed recall in a between-subjects study\textsuperscript{124}. Furthermore, mastication improves immediate and delayed word recall, and spatial and numeric working memory\textsuperscript{97}. 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\textsuperscript{97}. However, enhanced performance\textsuperscript{125-127} and improved attention and processing speed\textsuperscript{97,123} 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\textsuperscript{125}. The authors explain the discrepancies with the Wilkinson study\textsuperscript{97} 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\textsuperscript{128}.  

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Table 2.2: Brain areas that are activated during mastication, as measured in regional cerebral blood flow.

<p>| Study                        | N   | Age in years (range or mean) | Scanning technique | Protocol                                                                 | PFC | SMA | SMC | FTC | PC | Ins | Cing | Hippo | Amyg | Thy | Str | Caud | Cere | Prec |
|------------------------------|-----|------------------------------|--------------------|-------------------------------------------------------------|-----|-----|-----|-----|----|-----|------|-------|------|-----|-----|-----|------|------|------|
| Momose et al., 1997 ¹⁰⁴     | 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   | X    | X     | X    | X   | X   | X   | X    | X    |
| Sesay et al., 2000 ¹⁷⁷       | 7   | 24–57                        | Xe-CT              | S: during chewing and at rest 20 min after chewing.         |     |     | NS  | NS  | NS | X   | X    | X    | X    |     |     |     |     |     |
| Onozuka et al., 2002c ¹⁷⁸   | 17  | 20–31                        | fMRI               | S: during 4 cycles of; 32 s. chewing – 32 s. rest. Compare task vs. rest. | X   | X   | X   | X   | X  |     |      |     | X    | X    |     |     |     |     |
| Onozuka et al., 2003(1) ¹²¹  | 11  | 19–26                        | fMRI               | S: during 8 cycles of; 32 s. chewing 32 s. rest. Compare task vs. rest. | R   | R   | L   | R   | R  |     |      |     | R    | L    |     |     |     |     |
| Onozuka et al., 2003(2) ¹²¹  | 8   | 42–55                        | fMRI               | idem                                                        | R   | L   | L   | L   | I  |     |      |     | R    | L    |     |     |     |     |
| Onozuka et al., 2003(3) ¹²¹  | 13  | 65–73                        | fMRI               | idem                                                        | R   | R   | R   | L   | L  |     |      |     |     | R    | L    |     |     |     |     |
| Tamura et al., 2003 ¹⁷⁹      | 14  | Not given                    | fMRI               | S: during 5 cycles of; 25 s. chewing, 25 s. rest. Compare to 250 s. rest. |     |     |     |     | X  |     |      |      |     | X    |     |     |     |     |
| Takada &amp; Miyamoto 2004 ¹⁸⁰  | 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    |     |     |     |     |
| Sasaguri et al., 2004 (1) ¹¹⁹| 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    |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age in years (range or mean)</th>
<th>Scanning technique</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sasaguri et al., 2004 (2)</td>
<td>n=33</td>
<td>61–72</td>
<td>fMRI</td>
<td>idem</td>
</tr>
<tr>
<td>Shinagawa et al., 2004</td>
<td>n=6</td>
<td>24–31</td>
<td>fMRI</td>
<td>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</td>
</tr>
<tr>
<td>Kordass et al., 2007</td>
<td>n=13</td>
<td>24.6</td>
<td>fMRI</td>
<td>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</td>
</tr>
<tr>
<td>Hirano et al., 2008</td>
<td>n=18/n=13</td>
<td>24.5/24.8</td>
<td>fMRI</td>
<td>S: assessment at rest before chewing (2x), and after chewing 60 s. C: Working memory task, execute during rest and after chewing</td>
</tr>
</tbody>
</table>

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 excl.BRAIN AREAS: PFC=prefrontal cortex; PMA=premotor area; SMA=supplementary motor area; SMC=sensory-motor cortex; FTC=frontotemporal cortex; PC=parietal cortex; Ins=insula; Cing=cingulate cortex; Hippo=hippocampus; Amyg=amygdalae; Thal=thalamus; Striatium=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. *Note: no difference between rest and 20 min later.
A discussion unfolded in the literature in 2004\textsuperscript{129-131} 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\textsuperscript{124,127} and a re-examination study to control for all possible artifacts by the same authors\textsuperscript{126} 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\textsuperscript{127}. On the other hand, a third study\textsuperscript{132} 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\textsuperscript{132}. There is additional support for the suggestion that flavor plays a role in the effect of mastication on memory through arousal in young adults\textsuperscript{133,134} and younger middle-aged adults (age range 27–33 years)\textsuperscript{135} 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\textsuperscript{121} and the PFC is involved in cognitive function\textsuperscript{136}, 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.
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).

Cognition and masticatory efficiency
Cognition relates to maximal bite force and maximal mandibular excursions in full dental prosthesis wearing aged persons. Cognitively impaired aged older women show a lower bite force, a smaller occlusal contact area, lower number of teeth, and are more often edentulous than healthy age matched controls. Edentulism is related to worse cognitive performance in seniors and aged adults, while retention of some teeth relates to better cognitive functioning in aged nursing home residents. Loss of teeth is even recognized as a risk factor for developing AD in seniors and aged adults. Having only a few teeth increases the risk for developing dementia one decade later, in aged non-apolipoprotein E carriers. Furthermore, being edentulous and not using a denture is a risk factor for becoming mentally impaired over a 6-year period in aged adults.

Cognition and masticatory ability
One study compared the masticatory ability of aged females suffering from dementia to matched healthy women. 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%. Cognitive achievement of aged edentulous denture wearers could be predicted by complaints of pain in the face, head, and mandible, 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. The relationship between masticatory ability, rather than prosthetic status, with cognitive functioning has not been examined in that study.

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. Bad oral health, such as having periodontal disease, can lead to tooth loss in the older population, 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) deteriorate slower compared to a group not receiving oral care. The MMSE is a screening instrument for
global cognitive functioning. Several cross-sectional studies have also reported a negative relation between cognition and oral health (missing teeth and presence of periodontitis) in senior adults and in aged adults between cognition and dental treatment need, between cognition and caries incidence, and between cognition and use of dental healthcare. Declining cognition might lead to under-appreciation of oral health and need for care, leading to deterioration of the oral environment. 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. However, denture use and stability were lowered in the more severely impaired group, thus compromising masticatory function.

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, and adequate intake of certain nutrients seems to protect against mental decline in older adults, especially when combined with exercise. 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, since edentate individuals of various ages avoid hard foods (e.g., fruits, vegetables, but also meat), which typically are valuable nutrient-containing foods. Clinical studies show that impaired oral health and loss of teeth is associated with malnutrition in aged people. Indeed, having a higher number of natural teeth relates to better nutritional intake in senior and aged adults. Furthermore, the presence of (some) natural teeth is related to eating food of a normal (rather than mashed) consistency in the aged population. 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, which in turn is related to lower nutritional status in aged people. 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), although dental treatment does not lead to improved nutritional status in aged adults living in a nursing home. However, since institutionalized older persons have food intake scores that are com-
parable to an edentate community-dwelling population, regardless of dental status¹⁶¹, 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 seniors¹⁶³ and aged adults¹³,²⁸. Disability is also negatively related to masticatory ability in aged adults¹⁶⁴,¹⁶⁵. Perhaps, an explanation for these findings can be found in the fact that disability can negatively influence an aged person’s denture use¹⁶⁶, their ability to maintain a healthy oral environment¹⁶⁷,¹⁶⁸, and is associated with raised dental treatment needs¹⁴¹, worse oral health¹⁵⁵ and loss of teeth in seniors¹⁶⁹,¹⁷⁰. Vice versa, the ability to perform ADL improves (although not significantly) as a result of receiving professional oral care in aged adults²⁶.

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 underweight¹⁴⁰ and elderly female patients with AD need more help with eating, they eat softer food, and are more often undernourished¹³⁹. In turn, malnutrition is related to loss of cognition in older persons¹⁴⁹,¹⁵⁰. 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.
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) 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. 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 Figure 2.1). 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, the status of the dentition, e.g., full dentures or natural teeth, and the presence of pain, 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. The cholinergic neurotransmitter system appears to be functionally impaired, although the specific pathway of impairment is not yet known. The observed stress response is most likely caused by down-regulation of
Figure 2.1: The interplay of the various outcomes. Arrows indicate causal/longitudinally observed relationships; dotted lines indicate correlations; ADL=activities of daily living.

certain genes, such as those coding for glucocorticoid receptors $^{83}$. 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 $^{152,174,175}$.

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 $^{176}$. 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.
REFERENCES


48. Ikebe K., Nokubi T., Morii K., Kashiwagi J., Furuya M. – Association of bite
force with ageing and occlusal support in older adults. J. Dent. 33(2); 131–137, 2005.


63. Velanova K., Lustig C., Jacoby L.L., Buckner R.L. – Evidence for frontally me-


77. Kushida S., Kimoto K., Hori N., Toyoda M., Karasawa N., Yamamoto T.,


effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats. Behav. Brain Res. 83(1–2); 239–242, 1997.


92. Rowlatt C., Chesterman F.C., Sheriff M.U. – Lifespan, age changes and tumour incidence in an ageing C57BL mouse colony. Lab Anim. 10(10); 419–442, 1976.


Exercise and mental health: many reasons to move.

Brain-derived neurotrophic factor levels and cognitive function.

Chewing-side preference is involved in differential cortical activation patterns during tongue movements after bilateral gum-chewing: a functional magnetic resonance imaging study.


179. Tamura T., Kanayama T., Yoshida S., Kawasaki T. – Functional magnetic

CHAPTER 3

Orofacial pain in dementia patients

ABSTRACT

This article presents a comprehensive review of the literature on the diagnosis of pain in the orofacial region of patients suffering from a cognitive impairment or a dementia. This review was based on a literature search yielding 74 papers most of which dealt with the assessment of pain in general in nonverbal individuals, for which several observational tools have been developed. Unfortunately, none of these tools have been designed for the specific assessment of orofacial or dental pain. Thus, none of them can be recommended for use in the dental setting. There is hardly any information available in the literature on how to assess orofacial and/or dental pain in patients with a cognitive impairment or a dementia. Given the expected increase in the incidence of dementia over the upcoming decades, it is of the utmost importance that dentists can use well-tested tools that can help them in the diagnosis of orofacial and dental pain in this vulnerable patient population. Such a tool should incorporate specific orofacial/dental pain indicators, such as the patient holding/rubbing the painful orofacial area, limiting his/her mandibular movements, modifying his/her oral behavior, and being uncooperative/resistant to oral care.

INTRODUCTION

Dementia is an acquired, organic, mental disorder that is characterized by a loss of intellectual abilities that is of sufficient severity to interfere with daily life activities. It is not a disease but rather a group of symptoms that may accompany certain diseases or conditions. The most common subtype of dementia is Alzheimer’s disease (about 54%), followed by vascular dementia (16%). The remaining 30% includes other subtypes of dementia, e.g., frontotemporal dementia. In Alzheimer’s disease, the most prominent clinical symptoms include memory disturbances, aphasia (i.e., a defect or loss of the power of expression by, e.g., speech, or of language comprehension), apraxia (i.e., loss of ability to carry out familiar, purposeful movements in the absence of paralysis or other motor or sensory impairments), and visual agnosia (i.e., loss of the power to recognize the import of visual stimuli). Vascular dementia is mainly characterized by deterioration in both cognitive and motor functions, e.g., gait disturbances. Frontotemporal dementia is primarily characterized by behavioral disturbances.

Age is the highest risk factor for dementia. More specifically, the higher the age, the higher the prevalence of dementia: in older persons of 60–65 years of age, the prevalence is approx. 1%; in older persons of 85 years of age and older, 10–35%. Such a prevalence implies that the chance that a dentist will encounter a person with dementia is considerable. The dental care for this vulnerable patient population is complicated by several factors, among which a decline in communication and resistance to care. Moreover, orofacial dyspraxia has been described in a patient with frontotemporal lobar degeneration, while the severity of Alzheimer’s disease may be associated with failing the ideomotor (i.e., aroused by an idea or thought) face apraxia test. Ideomotor apraxia may compromise the patient’s own contribution to oral hygiene, e.g., brushing one’s teeth.

When professionals and family members were asked about the target outcomes for long-term oral health care in patients with dementia, a three-round Delphi study showed that the patients being free from oral pain was the number one target outcome. In another study using structured interviews, hospital dentists as well as patients’ relatives rated freedom of oral pain as the most important target outcome as well. In general, pain is often underdiagnosed and undertreated in patients with dementia. In part, this undertreatment may be due to concerns related to the increased risk of medication-induced adverse events in the elderly. However, results from several studies indicate that older patients with dementia are prescribed fewer analgesics (e.g., acetaminophen, opiates) and non-steroidal anti-inflammatory drugs (NSAIDs) than older persons without dementia, whereas they suffer from the same painful condition, e.g., hip fracture surgery. Undertreatment of pain in dementia is more alarming considering possible neuropathology-related pain alterations, e.g., an increase in pain experience. Within this scope, it is not surprising that pain with a dental etiology is also underdetected and under-
treated in persons with dementia, as is evident from a study of observed discrepancies between the presence of possible pain-causing conditions, e.g., fractured or broken teeth as assessed by a dentist, and the presence of possible dental-related pain, as assessed by a geriatrician as part of a general physical examination. However, the details of the pain-assessment method were not elaborated, which makes an unequivocal interpretation of this report impossible.

Reliable assessment of orofacial pain in dementia is not only clinically relevant for the pain as such. Orofacial pain is one of the clinical symptoms of a temporomandibular disorder, which is characterized, among others, by a reduction in chewing ability. In turn, impaired chewing may result in chronic malnutrition, while malnutrition, for example expressed in vitamin D deficiency, is associated with poorer physical activity. In Alzheimer's disease, a decrease in the level of functionality hampers energy consumption, which reduces appetite, thus creating a vicious circle in nutrition. Reliable pain-assessment with subsequent adequate pain treatment may interrupt this vicious circle in dementia.

The literature lacks a focused overview regarding the diagnosis of pain in the orofacial region of patients suffering from dementia. Therefore, the aim of this article was to assess the literature on this topic by using PubMed of the U.S. National Library of Medicine (NLM) and the National Institutes of Health. The following query was used: ("facial pain"[MeSH Terms] OR "facial"[All Fields] AND "pain"[All Fields]) OR "facial pain"[All Fields] OR ("orofacial"[All Fields] AND "pain"[All Fields]) OR "orofacial pain"[All Fields]) OR ("toothache"[MeSH Terms] OR "toothache"[All Fields] OR "dental"[All Fields] AND "pain"[All Fields]) OR "dental pain"[All Fields]) OR TMD[All Fields]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields]). No limits were used to restrict the output of the search. The query yielded six papers that were published between 1969 and 2009 of which 25 papers were omitted for various reasons (mainly because they dealt with non-related topics). The remaining 44 papers were supplemented with 30 papers that did not show up in the above-described searches but were nevertheless considered applicable by using the reference lists of the 44 articles and the authors’ personal collections as sources.

PAIN IN DEMENTIA

Dementia influences both the reporting and experience of pain. In the central nervous system, pain is processed by the medial and lateral pain systems. The lateral pain system is mainly involved in the sensory-discriminative aspects of pain, whereas the medial pain system plays a role in, among others, the cognitive-evaluative and motivational-affective aspects of pain. There is ample evidence that cerebrovascular disease, which is characteristic not only for vascular dementia but also for Alzheimer's disease, affects the white brain matter. White matter lesions dis-
connect brain areas, and consequently may cause a de-afferentiation pain, also paraphrased as ‘central pain’ \(^{21,24}\). In other words, two of the most prevalent subtypes of dementia, Alzheimer’s disease and vascular dementia, may coincide with an *increase* in (central) pain experience \(^{11}\). These findings enhance the risk for undertreatment of pain in this population, emphasizing the need for reliable pain-assessment.

**ASSESSMENT OF PAIN IN GENERAL IN DEMENTIA**

During the last decade, several comprehensive reviews of pain-assessment tools for use in persons with dementia have been published \(^{9,11,25-28}\). In communicative patients, a first step in pain-assessment could take place by self-report, using simple verbal descriptor scales, numerical scales (0 to 10), visual colored analogue scales (pain thermometers), or facial pain scales \(^{11,29}\). It has been suggested that for pain-assessment in persons with mild to moderate cognitive impairment, it is advisable to have a variety of such instruments available, so that the best tool can be selected for each individual patient \(^{28}\). For those who can no longer reliably communicate about pain, observations of specific behaviors are indicated, like vocalizations, facial expressions, and body movements. For the presence of pain, but not for pain severity, such observations can be used accurately \(^{11,30}\). They can be made either directly by health professionals or indirectly through reports by family members or nursing staff.

An accurate estimation of pain in nonverbal individuals provides great challenges for the future \(^{25}\). Even if physiological pain measurements are developed (e.g., registrations of brain activity or determinations of pain-related blood chemicals), the question remains how nonverbal individuals experience pain. For a proper assessment of pain experience, it is extremely important to know the person in pain well \(^{26}\). Changes in behavior that may signal pain can best be recognized by those who care for a person with dementia on a daily basis. Indeed, the challenge for the observer of pain-related behavior lies in the interpretation of the individual’s personal pain expressions \(^{11}\). This means that observational methods for pain-assessment work best in the hands of caregivers who are involved in the long-term care for the individual with dementia. Further, the nursing staff should be knowledgeable about pain and common pain conditions \(^{31}\). However, Smith \(^{26}\) has realistically noted that such a situation will hardly ever be realized due to, among others, high staff turnover rates in most care facilities. Thus, reliable and valid tools that also work in the hands of caregivers who do not know the observed individual that well are also needed.

A host of observational pain-assessment methods for nonverbal patients have been described in the literature. Smith \(^{26}\) provided a detailed review of several pain-assessment tools, including their psychometric properties. She has concluded that each instrument has its strengths and limitations, and that all of them would benefit
from additional testing. Herr et al.²⁷ systematically searched the literature for pain-assessment tools that were developed for or tested in nonverbal older adults. To be included in their review, tools had to fulfill a set of clearly described criteria, such as having undergone at least one psychometric assessment. Thus, the authors included 10 instruments and have provided a detailed overview of these instruments’ psychometric properties²⁷. An update of this overview can be found at http://prc.coh.org/PAIN-NOA.htm. The authors concluded that, unfortunately, none of the observation-based tools for pain-assessment in nonverbal individuals can be recommended for broad adoption in clinical practice²⁷. Until a strong, valid tool emerges, pain-assessment in nonverbal patients can be approached in several steps: (1) anticipate the presence of pain with or following disease, injury, or surgery; (2) establish baseline behavior so as to enable the observation of pain-related behavior; (3) look for less obvious indicators of pain, like agitation or aggression; and (4) in case of doubt, administer analgesics and observe possible changes in behavior, which may then be due to pain relief²⁷,³².

ASSESSMENT OF OROFACIAL PAIN IN DEMENTIA

As for the assessment of pain in general in communicative patients with dementia, also the assessment of orofacial pain in such patients could still take place by a variety of self-report instruments (see above). The vast majority of the articles that were reviewed, however, have dealt with instruments for the assessment of pain in nonverbal persons. Surprisingly, while orofacial pain undoubtedly comprises an important part of all pains in individuals with dementia, none of the tools found in the literature were specifically developed for orofacial pain-assessment. At best, dental problems and/or orofacial/dental pain were part of an assessment tool with a broader application (see below)³³. Therefore, all instruments that were found with the current search were scrutinized with respect to their possible qualities to assess orofacial and dental pains.

Of the 10 instruments that were selected by Herr et al.²⁷, five surfaced with the present search approach, viz., ADD, DS-DAT, Doloplus 2, PACSLAC, and PAINAD. Since these tools were found with a strategy that focused on orofacial and/or dental pains, the authors’ a priori expectation was that they would, at least in part, focus on these conditions. Therefore, these five instruments will be reviewed first. The Assessment of Discomfort in Dementia (ADD) protocol was designed to assess not only physical pain but also affective discomfort³⁴,³⁵. Semistructured interviews with experienced nurses of long-term facilities for older persons with dementia were used to collect signs and symptoms of pain and discomfort. Unfortunately, apart from a possible decrease in appetite (which is not specific for orofacial pain; see below), it remains unclear whether orofacial behavior is being observed as part of the ADD protocol. Reliability and validity have not been sufficiently
tested ²⁷, which so far hampers a widespread application of this tool. Further, the comprehensive nature of the ADD protocol makes it too complex for routine use in long-term care facilities for nonverbal individuals, let alone that the instrument could be used in a dental setting.

The Discomfort Scale for Dementia of the Alzheimer Type (DS-DAT) was developed for the assessment of affective discomfort and pain in patients with advanced dementia who lost their cognitive capacities and verbal communication abilities ³⁶. The system uses frequency, intensity, and duration scores for behavioral indicators like noisy breathing, negative vocalization, certain facial expressions (e.g., content, sad, or frightened), and body language (relaxed or tense). The scoring method is generally considered complex, time consuming, and mainly applicable in research settings. The instrument's psychometric properties warrant further study, especially regarding its validity in patients with pain-related conditions ²⁷. The fact that observations of the jaw (‘a slack unclenched jaw’ is one of the indicators for a content facial expression) are part of the system, does not make this instrument applicable for the specific assessment of orofacial and/or dental pain. This applicability remains to be studied.

Another paper dealt with the (Norwegian version of) the Doloplus ³⁷, an originally French instrument that has been translated in several languages but still awaits extensive testing of its psychometric properties in English-language settings ²⁷. While facial expressions of pain are part of the Doloplus ２ (as they are of all observational instruments examined), it is unclear whether orofacial behavioral observations are part of this pain-assessment tool. For example, indicators like ‘protective body postures adopted at rest’, ‘protection of sore areas’, and ‘changes in mobility’ can be observed in the body as a whole, but also specifically in the orofacial area. If the latter is the case, the instrument may be useful in dental settings.

The Pain-assessment Scale for Seniors With Severe Dementia (PACSLAC) is a 60-item observational tool for pain behaviors ³⁸. This originally Canadian-English instrument has been translated in several languages, including Dutch ³⁹, and has been used clinically ⁴⁰ as well as with video acquisition systems ⁴¹. The instrument is in need of more psychometric testing to confirm its reliability and validity ²⁷. Some of the constituent items are related to the orofacial area; most of them concern facial expressions, notably teeth clenching and opening the mouth. Also, it is unclear whether any of the activities or body movements observed (e.g., refusing to move, moving slow, resistant to care, guarding sore area) include the orofacial area. Changes in appetite, another possible ‘orofacial pain indicator’, may be nonspecific, as noted below. Consequently, the PACSLAC cannot yet be recommended for use in the dental setting.

The Pain-assessment in Advanced Dementia Scale (PAINAD) was developed as an easy-to-use and clinically relevant tool for the assessment of pain in advanced dementia. This originally American-English tool ⁴²-⁴⁴, that was translated in several target languages (e.g., German) ⁴⁵,⁴⁶, relies on the observation of five behavioral in-
dicators of pain in nonverbal individuals: breathing, vocalization, facial expression, body language, and consolability. The tool is not comprehensive, which adds to its easy-to-use character, but compromises its ability to detect more subtle changes in pain. Further, both its reliability and its validity require more testing. Finally, although it is stated in the description of the indicator ‘body language’ that “the jaw may be clenched”, again no specific orofacial indicators are included in this instrument. Thus, the dental application of the PAINAD cannot yet be recommended.

Zwakhalen et al. evaluated the psychometric properties of the Dutch translation of three of the above-discussed instruments, viz., the Doloplus 2, the PACSLAC, and the PAINAD. They concluded that despite the common call for more reliability and validity testing, these aspects are generally acceptable for these three pain-assessment tools. Surprisingly, nurses preferred the PACSLAC not only over the rather difficult-to-use Doloplus 2 but also over easy-to-use the PAINAD. Nurses qualified the latter as being too concise. In another comparison study, the PAINAD was compared with the Abbey Pain Scale, an Australian tool that attempts to measure acute and chronic pain in late-stage dementia, again, with insufficient psychometric data available, and unfortunately without a specific focus on orofacial and/or dental pain. The authors concluded that neither of these tools met their standards, especially because the motivational-affective aspects of pain cannot be assessed properly. Importantly, in none of these comparison studies was attention given to orofacial/dental pain.

Besides the five pain-assessment instruments that were also selected by Herr et al., there are at least a couple of other tools for general (i.e., non-dental) application. Apparently, there is a large need for pain-assessment tools that can be used reliably and validly in nonverbal individuals. In one article, the authors suggested a trial of analgesics as part of the pain-assessment procedure, whenever a non-pharmacological approach turned out to be inadequate. As for the above-discussed instruments, also the so-called Mobilization-Observation-Intensity-Dementia Pain Scale (MOBID) and the Certified Nursing Assistant Pain-assessment Tool (CPAT) for nursing home residents with dementia lack a specific focus on orofacial and dental pains. Where the CPAT is a purely observational tool, the MOBID contains observations of pain behaviors during, among others, caregiver-imposed movements (mobilizations). Interestingly, tooth brushing/mouth care was originally among the imposed activities included in the protocol. Unfortunately, after initial testing, the item was removed from the instrument, because it seemed to assess a nonpain construct (the authors suggest ‘surprise’ or ‘confusion’). The authors also noted a difficulty to rate pain in relation to mouth care (disliking this activity was difficult to distinguish from pain behavior) as well as possible differences in the test procedure between patients with and without removable dentures. The resulting instrument thus lacks a focus on the orofacial area, as do all the other pain-assessment tools discussed above.

There are several studies that used the so-called Facial Action Coding System.
(FACS) as a tool to assess pain in nonverbal individuals. FACS is a comprehensive system that uses explicit, anatomy-based criteria to distinguish discrete facial actions, typically on video recordings. The usefulness of the system has been shown in studies on musculoskeletal pain among seniors undergoing rehabilitation after knee surgery, as well as in cognitively impaired and demented patients following experimental pain stimuli. From these studies, it can be concluded that even though augmented facial expressions are not reflective of the presence or intensity of nociception, FACS has the potential to serve as a pain-assessment tool in nonverbal patients. Unfortunately, in none of these studies, was the (evoked) pain present in the orofacial area; rather, it was present in the arms and legs. Thus, the application of FACS in orofacial or dental pains remains to be assessed.

DENTAL PROBLEMS IN DEMENTIA PATIENTS

Three articles have focused on dental problems in patients with dementia, although without a (specific) focus on pain. In the first article, a review by Ghezzi and Ship, the gradual inability to perform oral self-care with the progression of dementia was highlighted because this aspect has major consequences for oral health. Among others, poorer gingival health, increased coronal and root caries, and more mucosal pathologies were described in comparison with gender- and age-matched healthy controls. While the authors did not address the difficulty of pain-assessment in dementia, they did state that “routine dental care must be performed to eliminate potential sources of pain (...).” The authors advocated, in their own words, “aggressive preventive measures (...),” to maintain the dignity and quality of life of a person with dementia.

The second article addressed denture use by institutionalized elderly people with various degrees of dementia. It was found that especially the individual’s ability to dress/undress oneself and to rinse his/her mouth were major indicators for non-use of dentures (either complete or partial), both factors having clinically relevant odds ratios larger than two (viz., 2.3 and 6.1, respectively). Unfortunately, pain in relation to use/non-use of dentures by persons with dementia was not assessed.

In the third article, the dental approach of patients with Alzheimer’s disease was discussed, preceded by an update on the medical aspects of the disorder. The authors proposed the use of a brief checklist for an accurate assessment of risk factors that may influence the diagnosis and treatment of oral problems in individuals with dementia. Unfortunately, pain is not part of this screening tool, although the authors did state that Alzheimer’s disease interferes with the patient’s ability to communicate, among others, dental pain symptoms.

Clearly, the absence of (specific) attention for orofacial/dental pain in these three articles suggests that future studies should take this important clinical symptom
into consideration. The present review found only one review article with a specific focus on pain in dementia from the dentist’s point of view, and one research paper describing an instrument that was specifically designed to assess oral health aspects (including dental pain) of the cognitively impaired and individuals with dementia living in residential care facilities. As part of a comprehensive review, Lapeer rightfully stated that in the absence of language skills, behavioral observations are critical to pain-assessment, even though they must be taken at ‘face value’, i.e., the determination of pain behavior is very difficult in nonverbal cases. The author concluded that oral health care professionals must favor the side of treatment rather than ignore a potentially painful condition. However, except by providing information on the assessment of pain in nonverbal individuals in general, the author does not clarify how orofacial/dental pain can be diagnosed in such cases.

Also to be discussed in this section is the above-mentioned research paper by Chalmers et al. Using the Brief Oral Health Status Examination (BOHSE) as their starting point, the authors developed a simplified screening tool, the so-called Oral Health Assessment Tool (OHAT), which could be administered by a range of residential care staff. Importantly, while three out of the ten BOHSE categories were omitted, Chalmers et al. added a category for the assessment of behavioral problems and pain related to oral and dental problems. Hence, the OHAT consists of eight categories that can all be scored on a three-point scale, with 0 = healthy, 1 = oral changes (for dental pain defined as ‘verbal and/or behavioral signs of pain such as pulling at face, chewing lips, not eating, aggression’), and 2 = unhealthy (for dental pain defined as ‘physical pain signs [swelling of cheek or gum, broken teeth, ulcers], as well as verbal and/or behavioral signs [pulling at face, not eating, aggression]’). While the intraobserver and interobserver agreement of the dental pain category were both found to be substantial (kappa statistics), the correlation of this category with dental examination findings was low and non-significant. In other words: dental pain can be assessed reliably using the OHAT, but the validity is reason for concern. This may be due to the nonspecific character of part of the scale definitions (e.g., not eating, aggression). Another issue that negatively influences the psychometric properties of this dental pain category of the OHAT is the fact that a distinct subgroup of participating care staff indicated that they were not able to complete the dental pain category, among others due to an inadequate understanding of the 3-point scale definitions. In conclusion, even though it is promising that dental pain was added to this screening tool for the cognitively impaired and individuals with dementia living in residential care facilities, the moderate psychometric characteristics and the nonspecific assessment of dental pain prevent a broad application of this tool in the dental setting.
This review provides a focus on the diagnosis of pain in the orofacial region of patients suffering from dementia. There are only a handful of papers that actually have dealt with this topic, and in many of the papers, orofacial and/or dental pain only played an indirect role. It should be noted that nonverbal individuals with dementia are typically not being seen by dentists in community practices but rather by geriatric dentists affiliated to specialized residential facilities. Nevertheless, orofacial pain in dementia patients is a largely understudied topic that, given the growing population of persons affected by cognitive impairments or dementias with, possibly, alterations in pain experience, needs more attention from researchers in the near future.

When comparing the instruments for pain-assessment in nonverbal persons they selected after a systematic search of the literature, Herr et al. used the American Geriatrics Society (AGS) guidelines, a comprehensive framework for the organization of behavioral pain indicators, as their reference. The AGS guidelines distinguish six main types of behavioral pain indicators: (1) facial expressions (e.g., grimacing, closed or tightened eyes, rapid blinking); (2) verbalizations, vocalizations (e.g., noisy breathing, moaning, calling out); (3) body movements (e.g., guarding, restricted movement, mobility changes); (4) changes in interpersonal interactions (e.g., withdrawn, resisting care, aggressive); (5) changes in activity patterns or routines (e.g., refusing food, changes in rest pattern, increased wandering); and (6) mental status changes (e.g., increased confusion, distress, crying or tears). Unfortunately, most of these behavioral pain indicators have a general nature, i.e., they are not helpful in the specific assessment of pain in the orofacial area in nonverbal individuals.

However, some indicators from the AGS categories, ‘body movement’ and ‘changes in activity patterns or routines’, may have some differential diagnostic merits. As indicated above, the ‘body movements’ category includes indicators like rigid, tense body posture, guarding, restricted movement, and mobility changes. For example, for orofacial pain with a musculoskeletal origin, it is known that patients hold/rub the painful orofacial area and restrict their mandibular movements as to prevent the pain from getting worse, and to promote healing. The ‘changes in activity patterns or routines’ category includes, among others, indicators like refusing food and appetite changes. According to Dworkin, diet modifications can indeed be considered a result of pain. Clearly, these indicators might point towards an orofacial/dental origin of the pain, although they may also be positive in case of other, nonorofacial pains. Considering all the above, it may be possible to create an instrument capable of assessing orofacial/dental pain in nonverbal individuals.

From the above review of the literature, suggestions can be gathered as to how to compose a reliable and valid instrument for the assessment of orofacial and/or dental pain in persons with dementia, using relevant items from pain-assessment...
tools that were developed for general use. Importantly, specific orofacial/dental pain indicators must be used, like ‘the patient...’ (1) ‘...holds/rubs the orofacial area’, (2) ‘...limits his/her mandibular movements’, (3) ‘...modified his/her oral (e.g., eating) behavior’, and/or (4) ‘...is uncooperative or resistant to oral care’. Further, the instrument must be easy-to-use in a dental setting and should not require extensive training of the staff. Finally, a plan for implementation should be part of the study that includes the development and psychometric testing of the pain-assessment tool, as to achieve broad acceptance in an efficient and timely manner.

In conclusion, there is hardly any information available on how to assess orofacial and/or dental pain in patients with a cognitive impairment or a dementia. Nevertheless, suggestions can be gathered from the literature on how to develop a reliable and valid instrument for the assessment of orofacial pain in such cases. Given the expected increase in the incidence of dementia over the upcoming decades due to the increase of the ageing population, in combination with the fact that people tend to keep their own, natural dentition until old age, it is of the utmost importance that dentists can use a well-tested tool that can help them in the diagnosis of orofacial and dental pain in this vulnerable patient population. A proper diagnosis will prevent unnecessary suffering as well as unnecessary treatments, and will thus lead to a higher quality of life.
REFERENCES


Increased masticatory activity and quality of life

ABSTRACT

Worldwide, millions of people are suffering from dementia and this number is rising. An index of quality of life (QoL) can describe the impact a disease or treatment has on a person’s well-being. QoL comprises many variables, including physical health and function, and mental health and function. QoL is related to masticatory ability and physical activity. Animal studies show that disruption of mastication due to loss of teeth or a soft diet leads to memory loss and learning problems. Since these are common complaints in dementia, it is hypothesized that improvement of masticatory function and normalization of diet consistency can increase QoL in elderly persons suffering from dementia. Therefore, the goal of the present study is to examine whether an increase in masticatory activity, achieved by increased food consistency and enhancement of masticatory function through improved oral health care has a positive effect on QoL, including cognition, mood, activities of daily living (ADL), and circadian rhythm in persons with dementia.

The described study is a prospective longitudinal matched cluster randomized single-blind multicenter study. Participants are elderly persons living in the Netherlands, suffering from dementia and receiving psychogeriatric care. An intervention group will receive improved oral health care and a diet of increased consistency. A control group receives care as usual. Participants will be assessed four times; outcome variables besides QoL are cognition, mood, independence, rest-activity rhythm, blood pressure, and masticatory function.

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This research protocol investigates the effect of an intervention executed by daily caregivers. The intervention will increase masticatory activity, which is achieved by three different actions, (providing oral health care, increasing food consistency, or a combination of both). There is a certain amount of variety in the nature of the interventions due to local differences in nursing homes. This might be a scientific weakness in the study design; however, a practical implementation of any findings will be subject to the same factors, making this study design clinically relevant.

BACKGROUND

Dementia is an umbrella term for a heterogeneous group of neurodegenerative disorders, characterized by functionally disabling, progressive cognitive deterioration \(^1\). The most prevalent subtypes of dementia are Alzheimer’s disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and vascular dementia (VaD) \(^1\). These dementias can present differently; some domains that are affected in one type of dementia are preserved in others \(^2\). The diagnosis ‘dementia’ should therefore always be based on deficits in more than one cognitive domain \(^2,3\).

Worldwide, almost 36 million people are suffering from dementia and this number is expected to rise to 115.4 million in 2050 \(^4\). This rise is mainly due to an increase in population of persons aged 60 and over \(^5\), as aging is one of the main risk factors for dementia \(^6\). Genetic factors play a role as well; the apolipoprotein E (ApoE) \(\varepsilon4\) allele is a risk factor for several types of dementia such as AD \(^7-10\); especially when occurring along with depression \(^11\). Other risk factors for dementia are female gender, illiteracy/low education, head trauma, lower socioeconomic status (SES) \(^6\), diabetes, depression \(^7\), vascular disorders (e.g., hypertension), environmental stress, and an inactive life style \(^12\).

Quality of life (QoL) is an term used to describe a person’s well-being and more specifically, the impact a certain disease or treatment for this disease has on a person’s life \(^13\). QoL comprises many variables, including physical health (e.g., absence of pain and nausea), physical function (e.g., being independent in the activities of daily living (ADL)), mental health (e.g., absence of fear, agitation and mood disorders), and mental function (e.g., good cognitive function). Having a meaningful pastime and social interactions is another component that is typically included in QoL indexes \(^14,15\). Using questionnaires to interview caregivers such as relatives or nurses can provide some information regarding a person’s QoL. However, since the observation by such proxies can be different than the patient observation and is influenced by the mood and cognition of the caregiver him/herself \(^13\), using additional methods to assess QoL is preferred. For example, sleep disorders influence a person’s QoL \(^16\), and the sleep pattern and circadian rhythm can easily and objectively be tracked with actigraphy. Similarly, cognition can be measured using neuropsychological tasks. Loss of mental function is one of the more noticeable
symptoms of dementia, and the diagnosis ‘dementia’ is usually based on cognitive testing. A thorough cognitive screening should therefore also be included when studying QoL in dementia.

As there is no cure for dementia, interventions are aimed at improving the clinical consequences. For example, interventions targeting life style factors, such as increasing physical activity, have been found to improve cognitive measures in healthy elderly. Physical activity interventions targeting elderly persons suffering from dementia may improve cognitive function, mood, and QoL.

Besides exercise interventions, improvement or supplementing the diet can positively influence cognition or reduce the risk of developing cognitive impairments. A ‘good’ diet would comprise fruits, nuts, and vegetables; foods that are typically harder to chew. These foods become more difficult to eat for aging persons, most notably when tooth loss is present. Loss of masticatory function is also associated with increased disability and mortality. Being able to chew properly, therefore, is of utmost importance for elderly persons to maintain a healthy diet and preserve cognition. This is especially the case when they are at risk for, or suffering from, dementia. Unfortunately, many older persons living in a nursing home are completely edentulous, and if they have remaining teeth, they are often in need of dental care. Offering both oral health care and an improved diet to elderly persons with dementia will most likely improve their health situation and thus, their QoL.

In sum, QoL is a very relevant outcome variable when assessing the results of interventions aimed at elderly persons suffering from dementia. Related mental and physical outcomes such as cognition and independence should be assessed as well to study the effects comprehensively. The study described in this protocol investigates the effect of an intervention aimed at increasing masticatory activity through improving oral health care and increased food consistency, on QoL, including cognition, mood, independence, rest-activity rhythm, and blood pressure in older people with dementia, receiving institutionalized care.

METHODS AND DESIGN

Study design

The study has a prospective longitudinal matched cluster randomized single-blind multicenter design. Assignment to either the intervention group or the control group will take place through matched cluster randomization, on a care unit level (i.e., not on an individual level). Participants in the study will be followed for 24 weeks and will be assessed at regular intervals, viz. at baseline, six weeks, twelve weeks, and 24 weeks after baseline. A care organization enrolls two care units, in order to provide matching groups within a single care setting. One group will be
a control group and receive care as usual; the other group will be an intervention
group. Participants are blind to the intervention. Since receiving training and alter-
ing the daily nursing care is part of the intervention, care-givers such as the nursing
staff cannot be blind for the intervention. The examiners will be blinded.

Participants

Participants are elderly persons, aged 65 years and older, diagnosed with dementia
and receiving professional psychogeriatric care in a Dutch nursing home or daycare
facility. If possible, the subtype of the dementia disorder (e.g., Alzheimer’s disease,
vascular dementia, dementia with Lewy bodies, or frontotemporal dementia) will be
noted. Exclusion criteria are: a history of psychiatric disorders, including depression,
(history of) alcoholism, cerebral traumata, hydrocephalus, and brain tumors. This
information will be obtained from the medical records. Another exclusion criteria
will be a score on the Mini Mental State Examination (MMSE⁹, a short instrument
which assesses global cognition, awareness, and memory), of 25 or higher at baseline.
Such a score is contraindicative of dementia ³⁰.

Participants are recruited through psychogeriatric care organizations. After a
care organization agrees to participate in the study, all clients and their legal repre-
sentatives are contacted and invited to participate in the study. They are thoroughly
informed about the study, upon which written consent is obtained. Participation is
always voluntary.

Sample size

To calculate the number of participants needed, a power analysis is performed. The
primary outcome variable (QoL) is used to calculate the power and a linear time
effect is assumed for both intervention and control conditions. A difference on total
score of 10 points after 24 weeks is considered clinically relevant. This equals to
a difference of 2.5 points per 6 weeks. After running simulations with a known
total variance of 300 and a mean score of 80 (pilot data), a sample size of 200
participants (spread over 10 care organizations and 10 participants per care unit) is
needed. Allowing for 10% dropout, this means (200 × 10/9 =) 224 participants need
to be included in the study.

Covariates

Participants’ characteristics that might be of influence are taken into account. These
covariates are age, gender, educational level, and ApoE4 status.

The highest educational level is classified by the Verhage scale ³¹; a seven point
rating scale. A score of 1 equals a level of less than six years of elementary school;
score 2 stands for completed elementary school; a score of 3 indicates more than six
years of elementary schools and less than three years of secondary education; score 4 is indicative of elementary school and three years secondary education; score 5 stands for elementary school and four years of secondary education; score 6 represents pre-university education and/or higher vocational education; and a score of 7 stands for a finished training at a university or technical college.

Genetic susceptibility for dementia as indicated by ApoE genotype, is assessed by collecting buccal cells. Two Catch-all TM collection swabs (Epicentre, Madison, Wisconsin, USA) per participant are used.

Confounding factors

Possible confounding variables are comorbid disorders and medication usage.

Comorbid disorders such as diabetes and depression are taken into account. The diagnosis is retrieved from the medical status and classified according to the Dutch translation of the Long-Term Care Facility Resident Assessment Instrument (RAI) $^{32}$. There are eight categories; endocrine/metabolic/nutritional; cardiovascular; locomotor system; neurology; sensory; psychiatric/mood; respiratory; other (e.g., allergies, anemia, cancer, and renal failure).

Medication usage is tracked by checking the current medical list provided by the local pharmacist at every assessment interval. Coding is done according to the Dutch Pharmacotherapeutic Compass $^{33}$.

Intervention

The intended goal of the intervention is to increase masticatory activity and ultimately, QoL. Therefore, the basic conditions to enable mastication have to be met; one has to have a healthy mouth and must be given food that requires chewing. This results in an intervention aimed at improving oral health care and increasing food consistency.

Oral health care comprises brushing the teeth at least once a day, for at least one minute per jaw. This is a minimum requirement, brushing the teeth twice daily is recommended, in combination with the use of toothpicks and dental floss. Clinical lessons are offered to train the nursing staff in providing this oral health care. Instructions on how to care for a dental prosthesis is also topic of these lessons. The specific skills needed for providing oral health care are also practiced. This is in concordance with the 2007 ‘Guideline oral health care in (residential) care homes for elderly people’ $^{34}$.

Increasing food consistency is achieved by: a) evaluation of the need for pureed foods and b) offering food of tougher consistency. Due to apraxia (i.e., inability to perform tasks or movements) or dysphagia (i.e., difficulty in swallowing), some participants are not able to chew and swallow food of normal consistency; hence, their food needs to be pureed. However, some participants might be given pureed
foods without medical need, for example out of convenience for the nursing staff. A qualified speech therapist can diagnose swallowing disorders and therefore the need for pureed food. Participants who are given pureed food without medical need will be reintroduced to more solid foods. All participants able to masticate normally are offered food of tougher consistency, such as apples, bread including its crust, crunchy cookies, raw vegetables and salads.

OUTCOME VARIABLES

Quality of Life

The primary outcome variable is QoL, assessed with the Qualidem questionnaire. The Qualidem is considered the preferred instrument for rating QoL for elderly persons with dementia and is appropriate for large and small-scale settings. A proxy is asked to rate observable behaviors on a 4-point Likert scale (i.e., ‘never’, ‘rarely’, ‘sometimes’, and ‘often’). Statements are for example: ‘is cheerful’, ‘refuses food’, ‘smiles’, or ‘wants to stay in bed’. For each statement, 0, 1, 2 or 3 points are awarded. The most positive outcome is given the highest point value (e.g., ‘smiles often’ is given 3 points, ‘refuses food often’ is given 0 points). A higher score suggests a higher QoL. The Qualidem score can be divided into several subscales. Not all subscales are appropriate for participants with severe dementia, so only the four subscales recommended for this group will be included; ‘care relationship’ (0–21 points), ‘positive affect’ (0–18 points), ‘restless tense behavior’ (0–9 points), and ‘social isolation’ (0–9 points). The maximal score is 57 points.

As described earlier, QoL comprises many aspects of life. In order to assess this multicomponent aspect of QoL, the following secondary outcome variables are included.

Cognition

Cognition, especially memory function and executive function, is investigated using a pen-and-paper-based neuropsychological assessment. Trained examiners, blind for the intervention, will visit the participants at the care unit. First, the participant is screened with the MMSE. Based on the MMSE score, a set of neuropsychological tests will be conducted. If a participant is not able to give a single adequate response on any of the MMSE questions (i.e., MMSE score is zero) no further cognitive testing will take place. Participants scoring 1–4 on the MMSE will take the first four tests described below, and participants scoring 5 or higher on the MMSE will perform these tests and three additional tests (also described below). All these tasks are complementary as they assess different cognitive skills.


Category Fluency

Category fluency is assessed in two separate instances, by asking the participant to name either as many animals or as many professions as possible in one minute. Time is measured with a stopwatch, and all responses are recorded. Identical responses are counted only once (e.g., horse, horse; doctor, doctor), responses assigning gender (e.g., lion, lioness; steward, stewardess) are counted as two correct responses. These rules are explained to the participant before starting. Faulty responses are ignored (i.e., not counted nor subtracted). If the participant starts a random conversation or remains quiet, a gentle reminder (‘can you name any other animals/professions?’) is given. The obtained score is the amount of correct responses.

Memory and attention

Memory and attention are assessed by verbally presenting sequences of numbers to the participant, who has to repeat them. The sequences start out with a length of two digits, and after three items, one extra digit is added. The task is cut off when two out of three responses are incorrect. Only correct responses are counted; faulty responses are ignored. The participant is allowed to make corrections. Maximal score is two.

Working memory

Working memory is assessed with a digit span backwards task, which is virtually the same as above; only this time the participant has to give the response in the reverse order. New sequences of digits are used. The task is cut off when two out of three responses are incorrect. Only correct responses are counted; faulty responses are ignored. The participant is allowed to make corrections. Maximal score is two.

Visuo-spatial function

In order to assess visuospatial function, incomplete line drawings are shown, while the participant has to indicate what the images represent. The drawings are of increasing difficulty, showing animals or everyday items or situations (e.g., a fish, a book, or a man carrying something heavy). After five incorrect responses, the task is cut off. In case of incomplete responses (e.g., ‘a man’ instead of ‘a man carrying something heavy’), the examiner asks the participant to elaborate: ‘please describe everything you see’. Only correct responses are counted; faulty responses are ignored. The participant is allowed to make corrections. Maximal score is two.

If a participant scores five points or higher on the MMSE, three tests are added:
**Verbal long term memory**

To assess verbal long term memory, the examiner reads out loud a list of eight everyday words (such as ‘pencil’ or ‘bird’), which the participant must repeat from memory after each presentation; this is repeated five times. Points are awarded for correct responses; the maximal score is 40. After approximately 10 minutes, a delayed free recall and recognition condition will be administered. During the recognition condition, the participant has to indicate whether a word does or does not belong to the original list. Sixteen words are now read out loud, the eight original words and eight new words. Maximal score for free recall is 8, maximal score for recognition is 16.

**Nonverbal episodic memory**

A visual memory task is used to measure nonverbal episodic memory. A card with eight red squares printed on it is placed between the examiner and the participant. The examiner taps the squares in a certain order which the participant is asked to repeat. The sequences start with a length of two squares and after two trials the sequences are lengthened with square. The task is cut off when both responses of a certain length are incorrect. Only correct responses are counted; faulty responses are ignored. The participant is allowed to make corrections. Maximal score is 14.

**Nonverbal working memory**

By using virtually the task same as above, nonverbal working memory is assessed. This time the participant is asked to give the response in the reverse order, the printed squares are colored green and new sequences are used. The task is cut off when both responses of a certain length are incorrect. Only correct responses are counted; faulty responses are ignored. The participant is allowed to make corrections. Maximal score is 14.

**Assessment of mood**

Mood is assessed with two questionnaires regarding observable behaviors, measuring either depression or agitation. Both questionnaires will be filled out by a proxy, typically a member of the permanent nursing staff.

**Depression**

The presence or absence of depression is qualified using the Cornell Scale for Depression in Dementia (CSDD; Dutch version (CSDD-D; Nineteen statements about the participant are scored on a Likert scale: a = not able to judge; 0 = absent; 1 = slightly or variably present; and 2 = severe. Maximal score is 38 points; a higher score indicates the presence of more depressed behaviors. Statements refer
to behaviors such as suicidal tendencies and facial expressions of sadness or fear, but also to weight loss or sleep disturbances. A score below 8 is considered to be within the normal range and a score of 8 and higher is indicative of depression.⁴³,⁴⁵

**Agitation**

The amount of agitated behaviors is scored using the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI).⁴⁶ A total of 29 observable behaviors are scored on a 7-point Likert scale. Items are behaviors such as spitting, (verbal) aggression, biting, screaming, complaining, and others. The behaviors can be observed never (1), less than once a week (2), once or twice a month (3), several times per week (4), once or twice per day (5), several times per day (6), or several times per hour (7). Minimal score is 29; maximal score is 203. A higher score is indicative of more agitated behaviors.

**Assessment of independence**

The ability to perform activities of daily living is assessed with the Katz index of Independence in Activities of Daily Living.⁴⁷ This index rates five activities and the ability to perform them unaided. They are: dressing, using the toilet, eating, moving around, and taking a shower or bath. A sixth question regards whether the participant is incontinent. A score of 1 indicates independence, score 2 stands for ‘needs some help’, and a score of 3 is given when someone is completely dependent (or, completely incontinent). Minimal score is 6; maximal score is 18.

**Assessment of the rest-activity rhythm**

The rest-activity rhythm is a circadian rhythm that reflects the sleep-wake rhythm in an indirect way. The rest-activity rhythm is measured during a week (7×24 hours), using an Actiwatch activity monitor (Cambridge Neurotechnology Ltd., Cambridge, United Kingdom). The Actiwatch is a small device that is worn on the wrist. It is placed on the dominant arm, unless this leads to agitation (e.g., due to presence of a wristwatch or bracelet). The Actiwatch is taken off only during showering since it is not waterproof. The Actiwatch records the motions of the arm, which are a proxy for overall activity.⁴⁸ The recorded data are analyzed for the following variables:

**Interdaily stability (IS)**

The interdaily stability is a measure for the degree of similarity of activity patterns within the measured period. A stable rhythm is characterized by a higher IS score; scores are between zero and 1.
Intradaily variability (IV)
The intradaily variability is the difference in activity levels in periods throughout the day. A normal activity pattern shows low IV; a sinusoid pattern results in a score of zero, a score of 2 is obtained for noise, and higher scores can arise obtained due to peaks in activity.

Relative amplitude (RA)
The relative amplitude is calculated by dividing the difference between the means of the ten most active hours (M10) and the five least active hours (L5) by the sum of these means within a day/night cycle.

\[ RA = \frac{M_{10} - L_{5}}{M_{10} + L_{5}} \]

A larger RA is associated with a more pronounced wake/sleep cycle. A more detailed description of these variables and their analysis is available elsewhere.\(^48\)

Assessment of blood pressure

Blood pressure is measured in millimeters of mercury (mmHg) with a blood pressure monitoring device (SpaceLabs Medical Inc., Redmond, Washington, United States of America). The participant is sitting down quietly, unless they are bedridden in which case they are lying down. Systolic blood pressure and diastolic blood pressure are noted, as well as heart rate. Hypertension is defined as systolic blood pressure higher than 160 mmHg and/or diastolic blood pressure over 95 mmHg.\(^49\)

Assessment of masticatory function

Mastication can be assessed in several ways. Most notably is the distinction between subjective, self-rated masticatory ability and the objective outcome masticatory efficiency (also described as masticatory performance).\(^50,51\) In the present study, masticatory ability is not assessed, since the cognitively impaired participants are not likely to be able to reliably answer questions about their chewing capacity. Participants’ masticatory efficiency is assessed using several techniques. First of all, the dental status is recorded: is the participant dentate, is he/she wearing a partial or full prosthesis, etc. If possible, the dental records are used for obtaining this information, otherwise, nursing staff is interviewed, or a visual inspection is performed. Secondly, several assessments are taken:

Occluding units
The number of pairs of upper and lower teeth that touch each other when the mouth is closed (i.e., occluding units) are measured using dental modeling wax (Alminax;
Müller & Weygandt, Büdingen, Germany). The wax is solid at room temperature and becomes soft when immersed in warm water. The participant bites down on a plate of softened wax and then it is allowed to harden again. Determination of the number of occluding units is done by visual inspection. In complete dentitions, 8 teeth are present in each quadrant (two incisors, one canine, two premolars, and three molars). Thus, the maximal score is 16 occluding units (i.e., 32 teeth).

Maximal mandibular excursions
Active, voluntary, mandibular mobility assessed as the distance between the upper and lower incisal edges, in millimeters, and is measured with a flexible plastic ruler (Dental Union, Nieuwegein, The Netherlands). First, the participant is asked to open his/her mouth as wide as possible without experiencing any pain. Next, the participant is encouraged to open his/her mouth as far as possible, even if this is painful, thus enabling the assessment of the maximal mouth opening. During the maximal opening, the participant is continuously encouraged. Maximal protrusion (i.e., outward forward movement of the mandible) is assessed by asking the participant to push the lower jaw forward as far as possible. Laterotrusion (i.e., outward movement of the jaw to the side) to the left and right are also measured. After every mandibular excursion, the participant is asked whether this is painful and if so, where the pain is located and what the intensity of the pain is. Pain location is recorded as joint area, pre-auricular, cheek area, floor of the mouth, temporal area, and other. Pain intensity is recorded on a 5-point Likert scale: 0 = no pain, 1 = tenderness, 2 = mild pain, 3 = moderate pain, and 4 = severe pain. Overjet (i.e., the antero-posterior distance between the upper and lower incisors), overbite (i.e., the vertical overlap of the upper and lower incisors), and midline deviation (i.e., the horizontal distance between the upper and lower dental arch midlines) are recorded while the participant rests in occlusion. The vertical maximal opening is corrected for overbite, the protrusion is corrected for the overjet, and the laterotrusions are corrected for the midline deviation.

Maximal voluntary bite force (MVBF)
The maximal voluntary bite force (MVBF) is measured with the VU University Bite Force Gauge (VU-BFG). The VU-BFG is a hand-held device which uses a load cell to measure maximal voluntary bite force in kilograms. The VU-BFG can be used centrally between the incisors or unilaterally between the (pre-) molars. For this study, the VU-BFG will be used between the incisors. The participant is instructed to bite as long and hard as possible and is encouraged continuously during the sampling. If the sampling fails (e.g., due to losing the prosthesis), a second attempt will be made after a rest period. Maximal sampling time is 20 seconds, and sampling takes place at a frequency of 50 Hz. All bite force samples are logged; the highest (i.e., peak) value is used as MVBF.
**Mixing ability**

In order to quantify actual masticatory performance, a mixing ability test in which the participant has to orally knead two viscoelastic colored materials is used. A four-gram sample made of blue and pink chewing gum (Bubblicious *® Ultimate Original and Twisted Tornado; Cadbury, London, United Kingdom) is given to the participant, with the instruction to chew naturally. The sample resembles a piece of candy due to its general appearance (bicolor capsule-shaped sample in a cellophane wrapper) and smell (sugary and sweet) which makes it easier for the participant to accept it as test food. A casting mold ensures consistent production of samples. Several protocols use a fixed number of chewing cycles, e.g., . However, participants suffering from dementia may find it hard to count and chew at the same time. An observer cannot accurately distinguish individual chewing cycles either, due to for example swallowing in between chewing motions, movements of the head while chewing (e.g., looking around), presence of a tremor, or obscuring of the jaw due to facial features such as sagging skin or beard (pilot data, not shown). Using a fixed amount of chewing cycles is therefore not possible in this population. Since in healthy people the average chewing frequency is stable at approximately hertz ( for women and Hz for men; , the assumption is made that this is also the case in persons suffering from dementia. This was confirmed in a pilot study (data not shown) and therefore a standard chewing time of seconds will be used. A stopwatch is used to measure time. After digital optical analysis, a mixing ability score is obtained.

**STATISTICAL ANALYSIS**

The data from this prospective longitudinal matched cluster randomized single-blind multicenter study will be analysed using a linear mixed model. The fixed effects are ‘condition’ and ‘time’; the linear ‘condition x time’ interaction is the effect parameter of interest and ‘care unit’ and ‘participant (within the care unit)’ are the random effects (both intercepts and slopes). An intention to treat analysis will be performed.

The baseline (cross-sectional) data will also be analysed for Pearson’s and/or Spearman’s coefficients, to establish correlations between the primary outcome variable QoL and the secondary outcome variables (viz. cognition, mood, independence, rest-activity rhythm, blood pressure, and masticatory function). Additionally, linear regression analyses will be performed to study the independent contribution of the various secondary outcome variables to QoL.

A baseline comparison will be performed to make sure that the intervention group and control group are similar with regards to variables that are not of primary interest (i.e., the covariates and confounders) and the outcome variables. Any
difference between the groups afterwards is then likely due to the intervention. If there are differences between the groups prior to the intervention, the baseline scores will be incorporated as covariates in the analysis.

ETHICAL CONSIDERATIONS

This study is approved by the Medical Ethical Committee of the VU University Medical Centre (METc VUmc; ref: 2010–342) according to the Declaration of Helsinki (2008). The research has been included in the general assessment and registration form (ABR form) (ref: NL33230.029.10) and in the Netherlands National Trial Register (NTR) (ref: NTR1561).

DISCUSSION

The described study is a prospective longitudinal matched cluster randomized single-blind multicenter study, investigating the effect of an intervention aimed at increasing masticatory activity by increasing and improving oral health care and the consistency of the diet. Participants in this study are elderly people suffering from dementia and receiving institutionalized care. The intervention is performed by daily nursing staff.

Strengths of this design are the direct clinical applicability of results; a transfer to the clinic does not need to be made since all work is done in a clinical setting. The intervention is performed by the nursing staff, allowing immediate assimilation into daily care. By taking baseline measurements and also repeated follow-up assessments, a thorough insight into the effect of the intervention is obtained. Chance findings are less likely to occur, and the effect over time can be made clear. The broad spectrum of data collection allows for a further widening of the research scope. Besides QoL, important variables such as cognition, mood, independence, and the rest-activity rhythm are assessed. Also, the research methods are varied; both qualitative and quantitative measures are used. By combining these two research methods, we obtain both quantitative, objective data about ‘how’ the intervention is effecting the outcome variables and qualitative, more subjective data, which is descriptive and can provide insight into the ‘why’ an intervention does or does not have an effect. Quantitative data can provide insight in effect sizes and underlying mechanisms, is not subject to interpretation and not dependent on a proxy’s mood and cognition (e.g., ¹³). Nonparametric testing, used for qualitative data, is stricter and therefore if results are found, they tend to be more robust. The heterogeneity of the research population is (partly) eliminated by matching and cluster randomizing the care units.
There are of course also some aspects of the study design that might prove to be shortcomings. The Consolidated Standards of Reporting Trials (CONSORT) guidelines\(^5^6\) include the practice of blinding of participants, the nursing staff, and the assessors. However, since the nursing staff in this protocol plays a vital role in providing the altered care as the intervention agents, they cannot be blinded. A placebo treatment which resembles oral health care in such a way that the nursing staff would not notice the difference without actually being effective is, to our knowledge, not available. The same holds true for the participants; there is no placebo treatment available and therefore, participants in the control group receive ‘care as usual’. This ‘care as usual’ for dependent elderly could, and one might even argue, should, include oral health care, but it has been shown that this is often unfortunately not the case (e.g., \(^2^6\),\(^2^8\),\(^5^7\),\(^6^0\)). In contrast to the nursing staff and the participants, the trained examiners are blinded for the participants’ allocation in either the intervention or control group.

There will also be a certain amount of variety in the nature of interventions due to local differences in nursing homes. For example, the presence of a dentist or dental hygienist and/ or the possibility to cook rather than order meals, will shape the specific details of the local intervention. This flexibility might be perceived as a weakness in the study design, because the intervention is not uniform across the several care facilities; however, a practical implementation of any findings would be subject to the same factors, making the study design clinically relevant. Furthermore, the use of matched cluster randomization, with one care organization always providing both an intervention and control group, is a good way to control for this variation. In the CONSORT guidelines, this design is described as stratification by center and is considered appropriate to control for differences such as can occur in multicenter studies\(^5^6\).

Effects in the increased food consistency group cannot be attributed to mastication per se, but can also be considered as an effect of the changed diet, enhancing for example, vitamin intake. Similarly, any effects of oral health care cannot purely be attributed to increased mastication; for example lowered incidence of oral pain or inflammation might also have effects on QoL. Despite these limitations, we argue that the outcomes of this study will point the direction for further research into these areas and will provide important insights in the topic of gerodontology in particular and dementia care in general.
LIST OF ABBREVIATIONS

AD: Alzheimer’s disease; ADL: Activities of Daily Living; ApoE: Apolipoprotein E; CMAI: Cohen-Mansfield Agitation Inventory; CONSORT: Consolidated Standards of Reporting Trials; CSDD-D: Cornell Scale for Depression in Dementia; DLB: Dementia with Lewy Bodies; FTD: Frontotemporal Dementia; IS: Interdaily stability; IV: Intradaily variability; L5: 5 least active hours; M10: 10 most active hours; mmHg: millimeters of mercury; MMSE: Mini Mental State Examination; MVBF: Maximal Voluntary Bite Force; QoL: Quality of Life; RA: Relative Amplitude; RAI: Resident Assessment Instrument; SES: Socioeconomic Status; VaD: Vascular Dementia; VU-BFG: VU University Bite Force Gauge

REFERENCES


REFERENCES • 83


59. Willumsen T., Karlsen L., Naess R., Bjorntvedt S. – Are the barriers to good oral hygiene in nursing homes within the nurses or the patients? *Gerodontology.* 29(2); e748–e755, 2012.

CHAPTER 5

Digitalization of a mixing ability test

ABSTRACT

Many techniques are available to assess masticatory performance, but not all are appropriate for every population. A proxy suitable for elderly persons suffering from dementia was lacking, and a two-color chewing gum mixing ability test was investigated for this purpose. A fully automated digital analysis algorithm was applied to a mixing ability test using two-colored gum samples in a stepwise increased number of chewing cycles protocol (Experiment 1: n=14; 7 males, 19–63 years), a test-retest assessment (Experiment 2: n=10; 4 males, 20–49 years), and compared to an established wax cubes mixing ability test (Experiment 3: n=13; 0 males, 21–31 years). Data was analyzed with repeated measures ANOVA (Exp.1), the calculation of the intraclass correlation coefficient (ICC) (Exp. 2), and Spearman’s rho correlation coefficient (Exp. 3). The method was sensitive to increasing numbers of chewing cycles ($F(5,65)= 57.270$, $p= 0.000$), and reliable in the test-retest (ICC value of 0.714, $p= 0.004$). There was no significant correlation between the two-colored gum test and the wax cubes test. The two-colored gum mixing ability test was able to adequately assess masticatory function and is recommended for use in a population of elderly persons with dementia.

Proper masticatory function is essential for a healthy nutritional status. This is especially important for older persons suffering from dementia, since they are prone to malnutrition. Malnutrition in older persons is associated with comorbid disorders, loss of independence, and lower cognitive function. Subjective assessment of masticatory performance by, e.g., questionnaires can be informative but is unreliable in older persons with dementia because of a decline in communicative abilities. Objective, laboratory-derived methods are therefore needed. Some proxies for masticatory function are more suitable for clinical populations than others. For example, assessment of mixing ability is preferred over comminution ability (i.e., the ability to pulverize a solid material) in dentally compromised populations. Wax mixing ability correlates well to comminution scores. Wax mixing tests are safe and suitable for healthy persons, however, older persons suffering from dementia might swallow such inedible item as dementia is associated with eating disorders. There is also a general loss of taste perception in aging. Intense flavors such as higher concentrations of sugar are generally preferred by seniors. Therefore, using a visually attractive, sweet-smelling and tasting two-color gum sample as part of a mixing ability test seems an appropriate way to assess masticatory function in elderly people suffering from dementia.

Both visual and digital assessments of two-colored gum samples have been studied; the latter method is recommended. Typically, the digital analysis involves some manual steps. Completely computerizing the assessment would improve the technique. In some studies, the individual pixel intensity levels are measured, and their standard deviation is taken as a mixing-index. However, the local intensity differences within the sample are then lost. A spatial frequency analysis has therefore been suggested, and in this paper, such an analysis protocol will be proposed.

The goal for this study was to completely digitalize the analysis of a two-colored gum sample, while analyzing the spatial heterogeneity. This protocol is studied in several experiments, which are: a stepwise increased number of chewing cycles experiment, a test-retest study, and a comparison with an established mixing ability test, using wax cubes.
HYPOTHESES

We hypothesized that:

1. The digital analysis will have good sensitivity for change, i.e., it will be able to distinguish between the two-colored gum samples for every stepwise increase in the number of chewing cycles.
2. The method has good reliability, i.e., there will be similarity between the test-retest samples from the same subject.
3. The method has good validity, i.e., there will be a correlation between the two-colored gum score and the score on the established wax cube mixing test.

METHODS

Participants

All participants were healthy adults with normal dentition and masticatory function, and familiar with chewing gum. The method was pilot tested on the target population and extensive data collection was done as part of a larger study.¹⁸

Mixing ability tests

Two different mixing ability protocols were used. A two-colored gum method (all experiments), and a wax cube technique (Experiment 3).

Two-color gum

Commercially available soft pink and blue chewing gum¹ was used to make two-color gum samples of 12x12x28 mm (see Figure 5.1). The two parts were manually stuck together with a drop of dissolved sugar.

Participants were instructed to chew naturally, for either a specific amount of cycles (Experiment 1: 5–10–15–20–25–30 successive cycles), or 20 seconds (Experiments 2 and 3). Between 10–20 chewing cycles are recommended.¹³ However, counting chewing cycles whilst chewing is impossible for cognitive impaired persons (pilot data, not shown) who are the intended target group for this protocol. Since the average chewing frequency is stable and approximately 1.35 Hz, chewing for 20 seconds was used as an alternative. After chewing, the sample was retrieved.

¹ Bubblicious, Ultimate Original and Twisted Tornado, Cadbury Nederland BV, Breda, Netherlands.
placed between two clear cellophane sheets and squeezed with a flattening device consisting of two connected hard acrylic glass plates with an embedded \(80 \times 80 \times 1\) mm frame. Subsequently, the sample was placed under a glass plate, and both sides were photographed with a digital camera\(^2\) with a 12.2 megapixel sensor, fixed focal length lens\(^3\), under standard tungsten lighting. The digital images were analyzed with Mathematica\(^4\). The first step of the analysis software script was cropping out the sample from the background. The image was downsized to 10% creating a picture of approximately 100\(\times\)100 pixels. The image data were split up into the Red, Green and Blue channels\(^7,16\). Only data from the Red channel was used for the further analyses as this showed the highest contrast.

A spatial heterogeneity algorithm assessed the local differences between the intensity levels of pixels and their parallel and perpendicular neighbors. Every pixel has an intensity level between zero (black) and one (white). For each pixel, the difference between its intensity level and its neighbors’ intensity level was calculated. Unmixed or barely mixed samples will mostly have minor differences, as there are predominantly pure pink or pure blue sections. Only at the intersection of the two colors, there will be major differences in pixel intensity levels. The actual value of these major differences will decrease as mixing increases, since the sample becomes more homogenous. The values of the top 1.0% major differences were taken and their mean was calculated. This outcome variable is called ‘DiffPix’. DiffPix is a number between 0 and 1; a higher number indicates larger differences in pixel

\(^2\) Canon 450D, Canon Inc. Tokyo Japan.
\(^3\) Canon EF 50mm F\(\text{1.8}\) II, Canon Inc., Tokyo, Japan.
\(^4\) Wolfram Research of Champaign, Illinois, USA.
Figure 5.2: Two matched samples. Chewed samples from two matched female participants aged 88 with a MMSE score of 9 (i.e., severe dementia $^{25}$) but with different temporomandibular profiles. Top left and right image (i.e., front and back of same sample): DiffPix score= 0.168. Subject had natural dentition in the mandible and a partial prosthesis in the maxilla. Maximal voluntary mouth opening was 52 mm. Total horizontal mandibular mobility (summed protrusion, laterotrusion to the left and right) was 38 mm. Bottom left and right image (i.e., front and back of same sample): DiffPix score= 0.231. Subject wore a complete denture. Maximal voluntary mouth opening was 33 mm. Total horizontal mandibular mobility (summed protrusion, laterotrusion to the left and right) was 12 mm. Neither participant reported pain during mandibular excursions.

intensity and thus, less mixing. See Figure 5.2 for an illustration of two samples chewed by matched, cognitive impaired older persons.

**Wax cubes**

A preheated ($37^\circ$ celsius) red-and-green semi checkered paraffin wax cube (12 mm cube, 1.5g) $^{17}$ was chewed for 10 strokes. After a practice trial, three test trials were performed. Analysis was performed as described in detail previously $^{17}$. Briefly it encompassed the following: Digital images were made using a color charge-coupled device camera$^{5}$ of both sides of the (unflattened) sample under standardized light-emitting diode (LED) lighting conditions. Using a digital image analyzer$^{6}$ they were

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$^{5}$ XC-003, Sony Co., Tokyo, Japan
$^{6}$ Luzex-FS, Nireco Co., Tokyo, Japan
assessed for the following variables: the total projection area (AH), the ratio of area above 50 µm in thickness to the total projection area (TR), the maximum length and breadth (ML and MB) which are combined in the ratio LB. Unmixed red and green areas (RA and GA) and the remaining mixed area were measured separately, and ratio of the mixed area to the total area was calculated (creating the parameter MIX). A measure for sample flatness (FF) was derived from ML and AH. A Mixing Ability Index (MAI) was then calculated per sample, using these parameters with a function derived from a discriminant analysis ¹⁷:

\[
MAI = (0.1360 \times MIX) + (0.2950 \times TR) + (0.003584 \times LB) - (0.002032 \times FF) + (0.0007950 \times AH) - 12.62
\]

A final mean MAI from the three samples was taken as the outcome variable. A higher MAI is indicative of better mixing.

Experimental procedure

The following experiments were performed:

**Experiment 1: stepwise increase of number of chewing cycles**
To establish the samples responsiveness, 14 participants (7 male, 7 female, age range 19–63 years) chewed a series of two-colored gum samples, in stepwise increased number of chewing cycles, starting at 5 times followed by 10, 15, 20, 25, and 30 times. In between steps, the participants rested as needed. The initiative to proceed to the next sample was taken by the participant.

**Experiment 2: Test-retest**
To assess the reliability, 10 participants (4 males, 6 females, age range 20–49 years; 7 participants also participated in Experiment 1) chewed a piece of two-colored gum habitually for 20 seconds. One hour later, they chewed a second piece of two-colored gum for 20 seconds.

**Experiment 3: inter-validation**
In the validation experiment, 13 females (age range 21–31 years) participated. First, they chewed three wax cubes, one after the other, for 10 strokes each. After a 60 seconds rest period, they chewed 2 consecutive samples of the two-colored gum for 20 seconds each. A final mean DiffPix from the samples was taken as the outcome variable.
Data analysis

Normality was investigated with the Kolmogorov-Smirnov test. The ability to distinguish between the samples for every stepwise increase in number of chewing cycles was investigated with a repeated measures ANOVA, corrected with post-hoc Bonferroni. Similarity between the test-retest samples from Experiment 2 was assessed using the intraclass correlation coefficient (ICC) in a two-way mixed-effect model, with absolute agreement. An ICC < 0.4 was considered poor, an ICC between 0.4 and 0.75 was considered fair-to-good, and an ICC > 0.75 was considered excellent\(^2\). To assess the correlation between the two mixing ability tests Spearman’s rho was calculated. IBM SPSS Statistics 19 was used. The significance level was set at \(p<0.05\).

RESULTS

Experiment 1

In Figure 5.3, the means and standard deviations of the DiffPix values for each of the successive chewing cycles is presented. There was an overall effect of chewing cycles on DiffPix (\(F(5,65)= 57.270, \ p = 0.000\), partial \(\eta^2 = 0.815\)). The contrasts are presented in Table 5.1.

Experiment 2

The results from Experiment 2 are presented in Figure 5.4. Comparison of the DiffPix scores for test and retest samples showed a fair-to-good reliability, with an ICC value of 0.714 (\(p = 0.004\)).

Experiment 3

The results from Experiment 3 are presented in Figure 5.5. A correlation coefficient \(r_s = 0.429, \ p = 0.144\) was found between the two mixing ability tests.
Table 5.1: Contrasts of mixing scores for different number of chewing cycles.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Mean group difference</th>
<th>St.Error</th>
<th>p-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–10</td>
<td>-.017</td>
<td>0.007</td>
<td>0.368</td>
<td>-.040 to 0.007</td>
</tr>
<tr>
<td>10–15</td>
<td>-.018</td>
<td>0.006</td>
<td>0.244</td>
<td>-.041 to 0.005</td>
</tr>
<tr>
<td>15–20</td>
<td>-.029</td>
<td>0.006</td>
<td>0.006*</td>
<td>-.050 to -.007</td>
</tr>
<tr>
<td>10–20</td>
<td>-.047</td>
<td>0.005</td>
<td>0.000*</td>
<td>-.066 to -.027</td>
</tr>
<tr>
<td>20–25</td>
<td>-.002</td>
<td>0.006</td>
<td>1.000</td>
<td>-.022 to 0.018</td>
</tr>
<tr>
<td>25–30</td>
<td>-.018</td>
<td>0.005</td>
<td>0.078</td>
<td>-.038 to 0.001</td>
</tr>
<tr>
<td>20–30</td>
<td>-.020</td>
<td>0.004</td>
<td>0.009*</td>
<td>-.036 to -.004</td>
</tr>
</tbody>
</table>

Post-hoc analysis of contrasts for Experiment 1, adjusted for multiple corrections with Bonferroni. Contrasted are all consecutive steps with a 5 chewing cycles difference, and two contrasts of a 10 chewing cycles difference (10 vs. 20 and 20 vs. 30). The significant contrasts are indicated with a * and also represented in Figure 5.3.

Figure 5.3: Means and standard deviations for the DiffPix values of the two-colored gum samples for the successive chewing cycles. Post-hoc analysis of the successive steps (5 chewing cycles stepwise increased), and contrasting samples chewed for 10 versus 20 and 20 versus 30 chewing cycles showed that a sample chewed 15 times had a significantly higher DiffPix score than a sample chewed 20 times. Diffpix score for a sample chewed 20 times was also significantly decreased from a sample chewed 10 times and higher than a sample chewed 30 times. No other significant differences were found between successive steps.
Figure 5.4: Within-subject DiffPix scores for test-retest sampling of the two-colored gum samples.

Figure 5.5: Within-subject mixing ability scores for the wax cubes test (Mixing Ability Index, MAI) and two-colored gum test (DiffPix). Note that better mixing ability would lead to higher MAI and lower DiffPix scores.
DISCUSSION

In older persons, impaired cognition is positively related to chewing difficulties \(^{21}\); therefore, it is important to assess masticatory performance in this population. In the current study, a bicolor chewing gum sample and a digital analysis algorithm were investigated. The method is designed for older persons with dementia, and pilot testing showed its acceptability.

A new outcome variable (DiffPix) assessed the spatial heterogeneity in the digital image. It was shown that overall DiffPix was responsive for the change in number of chewing cycles, and that differences of 10 chewing cycles were detectable, as well as a difference between 15 and 20 chewing cycles. Using the same samples, the ‘individual pixel intensity method’ was applied. MixingIndex was calculated (i.e., the sum of the standard deviation for the Red and Blue channel \(^7\)\(^{16}\)) and a repeated ANOVA was done. The assumption of sphericity was violated, \(\chi^2(14) = 31.027\), \(p = 0.006\), \(\varepsilon = 0.422\) so the Greenhouse-Geisser correction was used. An overall effect of chewing cycles on MixingIndex was found \((F(2.111, 27.441) = 82.333, p = 0.000\), partial \(\eta^2 = 0.864\)\). Post-hoc analysis showed that a sample chewed 15 times (15x) was significantly different from a 10x sample \((-0.043 (95\% CI, -0.070 to -0.016) p = 0.001\)\), and a 20x sample \((0.045 (95\% CI, 0.017 to 0.074) p = 0.001\)\). A 20x sample was also significantly different from 10x \((-0.088 (95\% CI, -0.114 to -0.062) p = 0.000\)\) and 30x \((0.27 (95\% CI, 0.003 to 0.052), p = 0.023\)\). This is different from the current results, as one extra contrast (10 vs.15) was significant. Combining MixingIndex and DiffPix in an algorithm should be included in future studies.

Using a fixed amount of cycles proved impossible in pilot experiments. Participants with dementia could not simultaneously count and chew. In addition, observers could not distinguish chewing cycles due to, e.g., movements of the head or obscuring facial features. In persons with impaired masticatory function (e.g., edentate seniors), the masticatory frequency is lowered \(^3\). The clinical effects are profound: time-pressed nursing staff force dependence \(^{22}\), resulting in unnecessary loss of autonomy \(^{23}\), and mistaking slow eating for refusal behavior leads to malnutrition and/or dehydration \(^{22}\). Assessing masticatory performance within a specified timeframe is a practical and clinically relevant alternative for a predetermined number of chewing cycles.

The two-colored gum protocol was also subjected to repeated sampling, and according to the ICC score, it showed fair-to-good (almost excellent) reliability. Validation of the two-colored gum sample and digital technique was attempted by comparing it to the mixing ability on wax cubes. Unexpectedly, we did not find a significant correlation.

The sample consisted of 13 young, healthy, dentate participants. Although a similar study reported a correlation in a sample of 11 young dentate subjects \(^6\), it is possible that the current sample might have been too small. The correlation coefficient \(r = 0.429\) indicates a moderate correlation between the two methods. A
$r$, of 0.429 is significant in a sample size of $n \geq 22^{24}$. A larger and more diverse sample might have led to the finding of a significant correlation, as in retrospect, it seems that the current study may have been underpowered.

Mastication includes the formation of a safe bolus $^{3,5}$. The wax cubes were judged on color mixing and bolus shape. The two-colored gum samples were flattened to increase and facilitate the digital assessment quality $^{14}$. Although flattening the bolus does not influence the assessment $^{14}$, incorporation of bolus size and shape in one method but not the other might have influenced the results.

CONCLUSION

The two-colored gum protocol is sensitive and reliable. Validity should be established, for example in a larger sample and with a comminution test as gold standard. Nevertheless, the current protocol is suitable to assess mixing ability as a proxy for masticatory performance. Using common household materials might allow others to use and adapt this method. This could even include clinicians such as dentists and health care workers, especially since a free trial version of the software is downloadable, and the script is available upon email-request to the corresponding author.
REFERENCES

16. Van Der Bilt A., Speksnijder C.M., de Liz P.R., Abbink J.H. – Digital image


Oral mixing ability and cognition

ABSTRACT

Masticatory status has been associated with cognitive ability in both animals and humans. It is hypothesized that there is also a positive correlation between masticatory performance and cognition in elderly persons suffering from dementia. Older persons suffering from dementia (n=114) were studied in a cross-sectional design. As self-report on masticatory function is unreliable in this population, masticatory performance was assessed objectively with a two-color gum mixing ability test. Cognition was assessed with a multi-domain neuropsychological test battery. Significant relationships were observed between masticatory performance and global cognition, and between masticatory performance and verbal fluency. Hierarchical regression analysis showed that the correlation with global cognition is influenced by scores for dependency in activities of daily living. The association between verbal fluency and masticatory performance was not significantly affected by secondary variables. An unexpected limitation of the study was the high drop-out rate of 50% for the mixing ability test. Nevertheless, the clinical implications of these findings are profound: care professionals should endeavor to maintain and stimulate mastication in older persons with dementia.
Worldwide, there are millions of people suffering from dementia, with incidence expected to increase in years to come. Dementia is an umbrella term for a group of neurodegenerative conditions; the most common types are Alzheimer’s disease (AD) and vascular dementia (VaD). Ageing is one of the main risk factors for dementia. Other risk factors are dependence in activities of daily living (ADL; e.g., eating, walking, or dressing oneself) and (cardio)vascular risk factors such as hypertension. A risk factor that has received relatively little attention is loss of natural dentition. In both animal and human studies, lower masticatory function is associated with lower cognition. Since loss of cognition is one of most impacting symptoms of dementia it is clinically important to investigate their relationship and search for possible underlying mechanisms. Cognition is commonly assessed with a short screening instrument, for example in combination with self-reported masticatory function. In elderly persons with (severe) dementia, however, self-report is most likely unreliable. Objective assessment of function, e.g., with a mixing ability test, is preferred. Such assessment has not yet been done, especially not in combination with elaborate neuropsychological testing, in elderly persons suffering from dementia. Therefore, the goal of the present study is to examine the relationship between mastication and cognition, using an objective mixing ability test and an extensive neuropsychological test battery in a sample of elderly persons suffering from dementia. It is hypothesized that a positive correlation between masticatory performance and cognition exists in older persons suffering from dementia.

Data was collected as part of a larger study, see. This study was approved by the Medical Ethical Committee of the VU University Medical Centre (METC VUmc; ref: 2010–342; Netherlands National Trial Register ref: NTR1561). Data collection took about 30 minutes for dental assessments and between 10–120 minutes for neuropsychological testing, based on the participants’ Mini Mental State Examination (MMSE) score, a short questionnaire which appeals to memory, word naming, orientation in time and space, and visuo-constructive capacities. Participants were Dutch elderly persons (≥65 years) with dementia, receiving psychogeriatric care. Participants and their legal representatives provided written informed consent. Figure 6.1 presents a flowchart of the sample, and Table 6.1 describes the sample, split into two subsamples based on mixing ability performance. Predefined exclusion criteria for the mixing ability assessment were presence of swallowing disorders or inability to chew (due to, e.g., facial paralysis from a cardiovascular accident). The study conforms to STROBE Guidelines.
Original Sample 
(n=122)

Fit inclusion 
criteria (n=114)

Included: 
performance 
Mixing Ability test 
(n=58)

Excluded: non-
performance 
Mixing Ability test 
(n=56)

Excluded for: 
MMSE >24 (n=4); 
head trauma (n=2); 
refusal (n=2)

Figure 6.1: Flowchart of the participants in the study. The original sample comprised 122 participants, 8 of which were excluded, for example based on Mini Mental State Examination (=MMSE) score. The remaining sample (n=114) was split up into two groups, based on the (in-)ability to participate in the mixing ability test (performers and non-performers). The characteristics of the two groups, included in Table 6.1, were comparable. The data from the performers was further analyzed.

Outcome measures

The primary outcome measures were masticatory performance and cognition. Masticatory performance was assessed with a mixing ability test using two-color chewing gum, which participants chewed for 20 seconds. Then, the spatial heterogeneity was assessed with a Mathematica¹ algorithm – expressed as a DiffPix score between zero and one; a lower score indicates better mixing¹³. A trained examiner assessed cognitive function with a battery of neuropsychological tests. Two cognitive functions were of particular interest in the current study: global cognition, which was assessed with the MMSE, and verbal fluency, which was assessed with a category fluency task. This task appeals to earlier learned knowledge, as participants are required to name as many animals, or, on a separate instance, professions, during one minute. See ¹¹ for more details on the neuropsychological tasks.

Secondary outcome variables were participants’ demographics, independence, physical and mental health status, and the status of their masticatory system. Information regarding age, gender, educational level, medication use, and comorbid disorders was obtained from the medical records. Educational level was classified using the Verhage index¹⁴, which ranges from 1–7. The Katz Index of Independence

¹ Wolfram Research of Champaign, Illinois, USA.
Table 6.1: Participants’ characteristics for two subsamples, based on capacity to perform the mixing ability test (‘performers’ versus ‘non-performers’).

<table>
<thead>
<tr>
<th></th>
<th>Performers ((\text{n}_{\text{total}}=58))</th>
<th>Non-performers ((\text{n}_{\text{total}}=56))</th>
<th>(t/U) value</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>(\text{Mean} \pm \text{SD} / \text{Median})</td>
<td>(\text{Mean} \pm \text{SD} / \text{Median})</td>
<td>(\text{Observed Range/Ratio})</td>
<td>(\text{Observed Range/Ratio})</td>
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<tr>
<td>Demographics</td>
<td></td>
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<td></td>
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<tr>
<td>Age(^a)</td>
<td>58</td>
<td>56</td>
<td>–.1</td>
<td>0.96</td>
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<tr>
<td>Gender (m/f)(^b)</td>
<td>(n/a)</td>
<td>(n/a)</td>
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<td>Education(^c)</td>
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<td>35</td>
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<tr>
<td>Independence</td>
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<td></td>
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<td></td>
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<tr>
<td>ADL(^c)</td>
<td>37</td>
<td>39</td>
<td>485.5</td>
<td>0.01*</td>
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<tr>
<td>Physical Health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity (^c)</td>
<td>55</td>
<td>51</td>
<td>1,255.0</td>
<td>0.34</td>
</tr>
<tr>
<td>CVA(^b) (y/n)</td>
<td>(n/a)</td>
<td>(n/a)</td>
<td>1,280.5</td>
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</tr>
<tr>
<td>Medication(^c)</td>
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<td>35</td>
<td>495.0</td>
<td>0.86</td>
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<td>Mood</td>
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<tr>
<td>Depression (^b) (y/n)</td>
<td>(n/a)</td>
<td>(19/16)</td>
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<td>Agitation(^c)</td>
<td>37</td>
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<td>741.0</td>
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<td>Dentition score (^c,d)</td>
<td>55</td>
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<td>893.0</td>
<td>0.53</td>
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<tr>
<td>Mobility(^b)</td>
<td>37</td>
<td>10</td>
<td>431.0</td>
<td>0.48</td>
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<tr>
<td>Pain (^c,d)</td>
<td>36</td>
<td>12</td>
<td>221.0</td>
<td>0.82</td>
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<td></td>
<td>Performers (n=58)</td>
<td>Non-performers (n=56)</td>
<td>t/U value</td>
<td>p</td>
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<tr>
<td></td>
<td>n</td>
<td>Mean ±SD/ Median</td>
<td>Observed Range/ Ratio</td>
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<td>Cognition</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Global cognition&lt;sup&gt;c&lt;/sup&gt;</td>
<td>56</td>
<td>10 ±7.0</td>
<td>0–24</td>
<td>37</td>
</tr>
<tr>
<td>Verbal fluency&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51</td>
<td>8.0 ±7.2</td>
<td>0–25</td>
<td>32</td>
</tr>
<tr>
<td>Verbal short term memory&lt;sup&gt;c&lt;/sup&gt;</td>
<td>48</td>
<td>8.7 ±3.9</td>
<td>0–16</td>
<td>32</td>
</tr>
<tr>
<td>Verbal working memory&lt;sup&gt;c&lt;/sup&gt;</td>
<td>47</td>
<td>3.7 ±2.9</td>
<td>0–11</td>
<td>29</td>
</tr>
<tr>
<td>Visuospatial function&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51</td>
<td>3.9 ±3.1</td>
<td>0–11</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>If MMSE &gt; 5</td>
<td>41</td>
<td></td>
<td></td>
<td>22</td>
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<td></td>
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<tr>
<td>Verbal long-term memory</td>
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<td></td>
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<tr>
<td>imprinting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36</td>
<td>14.3 ±7.0</td>
<td>0–30</td>
<td>17</td>
</tr>
<tr>
<td>free recall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35</td>
<td>0.6 ±2.5</td>
<td>0–12</td>
<td>16</td>
</tr>
<tr>
<td>recognition&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34</td>
<td>9.8 ±2.4</td>
<td>4–15</td>
<td>16</td>
</tr>
<tr>
<td>Visuospatial short term memory&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35</td>
<td>4.7 ±1.8</td>
<td>0–9</td>
<td>16</td>
</tr>
<tr>
<td>Visuospatial working memory&lt;sup&gt;c&lt;/sup&gt;</td>
<td>34</td>
<td>2.9 ±2.2</td>
<td>0–8</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Analysis was based on independent t-tests. <sup>b</sup>: Analysis was based on Chi square tests. <sup>c</sup>: Analysis was based on Mann-Whitney U test. <sup>d</sup>: Both dental arches natural dentition; <sup>e</sup>: One arch dentate, other arch partial prosthesis; <sup>f</sup>: One arch dentate, other arch full prosthesis; <sup>g</sup>: Both arches partial prosthesis; <sup>h</sup>: One partial and one full prosthesis; <sup>i</sup>: Two full prostheses; <sup>j</sup>: One arch edentate, other dentate; <sup>k</sup>: One arch edentate and other a partial prosthesis; <sup>l</sup>: One arch edentate, other full prosthesis. Mobility: summed score in millimeters for maximal voluntary mouth opening, moving the jaw forwards (protrusion) and sideways (laterotrusion to the left and right), corrected for overjet and overbite. <sup>m</sup>: Scores are 0=no pain, 1=moderate pain; <sup>n</sup>: Mild pain; <sup>o</sup>: Severe pain. <sup>p</sup>: Standard deviation; <sup>q</sup>: Observed range; <sup>r</sup>: Minimal and maximal observed values; <sup>s</sup>: Male/female; <sup>t</sup>: ADL= Activities of Daily Living (a higher score indicates more dependence in performing activities of daily living); <sup>u</sup>: Cerebral Vascular Accident; <sup>v</sup>: Yes/no.
in Activities of Daily Living \(^{15}\) was filled out by a proxy (i.e., daily nursing staff); total score ranges from 6–18. Comorbid disorders were classified according to the Dutch Long-Term Care Facility Resident Assessment Instrument (RAI) \(^{16}\); total score ranges from 0–8. Medication use was indexed according to the Dutch Pharmacotherapeutic Compass 2011 \(^{17}\); total score ranges from 0–20. Possible depression was measured with a proxy-questionnaire \(^{18}\); the results were dichotomized \(^{11}\). Agitated behaviors were scored with a proxy questionnaire \(^{19}\); total score ranges from 29–203. The type of dentition was classified based on the combined dentition in the mandible and maxilla. The highest score (10) was given to fully dentate participants and the lowest score (1) was awarded to completely edentate participants (see Table 6.1 for details). A trained examiner obtained information regarding dentition through visual inspection, medical records, and proxy report. The examiner also assessed mobility of the temporomandibular joint \(^{20}\), which was summed into a mobility score. Possible presence of pain during 4 mandibular excursions was recorded on a Likert scale. The scores were summed into a total pain score, ranging from 0–16.

Statistical analysis

Normality was established with the Kolmogorov-Smirnov test. Two subsamples were created based on participation in the mixing ability test, and compared using independent-t tests, if data were continuous and normally distributed. If this was not the case, nonparametric tests were used, viz., Mann-Whitney U tests, and for dichotomous variables Chi square tests.

Only the subsample \((n=58)\) that performed the mixing ability test (‘performers’) was further analyzed. Associations between the main outcome variable ‘mixing ability’ (‘DiffPix’) and the predictors (i.e., the cognitive functions) were calculated using single linear regressions. If the association between a predictor and mixing ability was at least near significance \((p<0.10)\), it was further investigated with hierarchical regression. Included as covariates were variables that were either significantly different between the subsamples (i.e., ADL), showed a correlation with mixing ability (i.e., educational level, \(r=-0.354, p=0.043\), and dentition, \(r=-0.515, p=0.00\), or were indicated as possible confounder in literature (i.e., age and gender \(^{2}\)). Each eligible covariate was separately added to the single regression model. If the subsequent change in B-coefficient of the predictor was \(>10\%\), the covariate was regarded a confounder of the association between the predictor and the outcome measure. The covariate causing the largest effect was selected and added to the model, and the remaining covariates were then analyzed in Model 3, and so on. A predefined condition was that the number of included covariates should be investigated in at least a tenfold of the number of cases (i.e., for each covariate \(n=10\) cases). Adherence to the assumptions for hierarchical regression was checked, i.e., linearity, independence of observations, normality, equal variance (homoscedasticity), and
Table 6.2: Single linear regression analysis between mixing ability and cognition*.

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>n</th>
<th>$R^2$</th>
<th>$B$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>56</td>
<td>0.163</td>
<td>–6.1</td>
<td>0.00**</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>51</td>
<td>0.173</td>
<td>–6.1</td>
<td>0.00**</td>
</tr>
<tr>
<td>Verbal short term memory</td>
<td>48</td>
<td>0.015</td>
<td>–4.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>47</td>
<td>0.007</td>
<td>–3</td>
<td>0.58</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>51</td>
<td>0.072</td>
<td>–5.8</td>
<td>0.06</td>
</tr>
<tr>
<td>If MMSE &gt; 5</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Verbal long-term memory
- imprinting 36 0.031 –2.3 0.31
- free recall 35 0.005 –5 0.67
- recognition 34 0.007 5.9 0.63
- Visuospatial short term memory 35 0.000 0.5 0.96
- Visuospatial working memory 34 0.037 –2.8 0.26

* assessed with two-color chewing gum and neuropsychological tests, respectively. $R^2$ = explained variance; $B$ = unstandardized regression coefficient. *$p<0.05$; **$p<0.01$.

Ruling out multicollinearity and influential cases. Due to the clinical presentation of dementia and the nature of the investigations (which included participating in neuropsychological tests and interviews), not all participants were able to complete the assessments. Therefore, data was missing. Likewise, not all background information was available. Finally, not all proxy assessments were filled out properly (e.g., incomplete or contradicting reports). The number of valid cases is reported for every variable.

RESULTS

About half of the participant group ($n=58$) performed the mixing ability test. They had an overall DiffPix score of $0.249 \pm 0.032$ (mean $\pm$ SD). Most participants were able to participate in (some of) the neuropsychological assessments (see Table 6.1). Performers had higher verbal short term memory scores and were more independent in ADL. Outcomes on the other tasks were not significantly different.

Single regression analyses showed significant associations between mixing ability and global cognition, and between mixing ability and verbal fluency (see Table 6.2). The association between mixing ability and visuospatial function was near significant. However, because the data violated most of the assumptions for linear models, visuospatial function was not further investigated with hierarchical regression analyses.

The association between mixing ability and global cognition, and mixing ability and verbal fluency were initially very significant (Table 6.2) but due to missing
Table 6.3: Hierarchical regression models, for oral mixing ability* with global cognition, and verbal fluency.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Variables</th>
<th>B</th>
<th>β</th>
<th>p_{association}</th>
<th>R^2</th>
<th>p_{model}</th>
<th>p_{change}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>33</td>
<td>DiffPix</td>
<td>-0.67</td>
<td>-0.41</td>
<td>0.02*</td>
<td>0.167</td>
<td>0.02*</td>
<td>n/a</td>
</tr>
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<td>Model 2</td>
<td>33</td>
<td>DiffPix</td>
<td>-7.17</td>
<td>-0.26</td>
<td>0.11</td>
<td>0.337</td>
<td>0.00**</td>
<td>0.01**</td>
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<tr>
<td>Model 3</td>
<td>33</td>
<td>DiffPix</td>
<td>-4.93</td>
<td>-0.29</td>
<td>0.08</td>
<td>0.358</td>
<td>0.00**</td>
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<tr>
<td><strong>Verbal fluency</strong></td>
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<tr>
<td>Model 1</td>
<td>30</td>
<td>DiffPix</td>
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<td>-0.33</td>
<td>0.08</td>
<td>0.109</td>
<td>0.11</td>
<td>n/a</td>
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<td>DiffPix</td>
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<td>0.182</td>
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</tr>
<tr>
<td>Model 3</td>
<td>30</td>
<td>DiffPix</td>
<td>-7.77</td>
<td>-0.28</td>
<td>0.20</td>
<td>0.233</td>
<td>0.07</td>
<td>0.20</td>
</tr>
</tbody>
</table>

|                |    |           |     |     |                 |       |           |            |

* assessed with two-color chewing gum (‘DiffPix’); B=unstandardized regression coefficient; p_{association} = significance level of the individual association between the dependent variable (global cognition or verbal fluency) and the independent variable (DiffPix, ADL, or Dentition), B=unstandardized coefficient; β=standardized coefficient; R^2=explained variance; p_{model}= overall significance level of the model; p_{change}= significance level of the change, resulting from adding a variable to the next model. DiffPix= mixing ability score; ADL = activities of daily living; Dentition= dentition score ; *p<0.05; **p<0.01.

values for the covariates, these associations are lost in the first steps of the hierarchical models. Adding ADL and/or dentition causes a change in B coefficient >10%, indicating these covariates are confounders (see Table 6.3).

**DISCUSSION**

About 50% of the participants did not successfully participate in the mixing ability test. To our knowledge, this was the first study using a mixing ability test, as a proxy for masticatory performance in elderly persons with dementia. It was not possible to predict a drop-out rate; future studies should be aware of the possibility of high drop-out. The non-performing subsample was more dependent in ADL than the performing subsample. In the hierarchical regression analysis, ADL was found to
influence the association between global cognition and masticatory performance. In community dwelling seniors, masticatory performance was positively related to ADL performance. This could indicate that the non-performers subsample would have had worse masticatory performance, had they performed the test.

Global cognition and verbal fluency were positively associated with masticatory performance in elderly persons suffering from dementia. Hierarchical regression analysis showed that the correlation between global cognition and masticatory performance was influenced by independence in activities of daily living and type of dentition. Due to missing values, the strong associations found in the single regressions (Table 6.2) became weaker in the hierarchical regression (global cognition), or disappeared (verbal fluency). Other cognitive functions did not significantly associate with masticatory performance. In a study with independent healthy seniors, participants were matched for age, gender, educational level, and MMSE score. A natural teeth group scored significantly better than an edentulous group on four out of one/two neuropsychological tests, and almost significantly better on two more tests. This also means that performance by the natural teeth group was not different from the edentulous group on the other six out of 12 tests.

It would seem that the present study is in agreement with this report – some cognitive functions associate with mastication, others might not. As for the underlying mechanism, we can only speculate (see also 6); nutrition might play a mediating role in a multifactorial relationship. Global cognition and verbal fluency are also sensitive to cerebrovascular pathology. High and moderate (but not low) intensity mastication increases the middle cerebral artery blood-flow velocity. This suggests that the underlying mechanism between mastication and cognition could also have its foundation in the cerebral blood flow. It would be most interesting to investigate the effect of oral rehabilitation and dietary interventions to stimulate vigorous chewing in order to engage this mechanism and perhaps rehabilitate cognition in older persons with dementia.

In the present study, more than half of the participants used a full denture, while a few were edentulous. High numbers of edentulism and discontinuation of denture use in psychogeriatric long-term care residents are confirmed in literature. Edentulism was negatively associated with global cognitive function in cognitively healthy elderly, implying that retention of teeth might be needed for preservation of cognition. Dentition type was found to influence the association between global cognition and masticatory performance in the present study as well. In a large elderly sample, a cognitively impaired group had fewer teeth and more trouble chewing hard food than a cognitively healthy group. The association between cognitive impairment and tooth loss could be explained by confounders, but the association with chewing difficulties could not. The authors speculated that a well-fitting and functioning dental prosthesis can accommodate for negative effects of tooth loss, but difficulties with chewing might cause cognitive impairment.
present results support the suggestion that maintenance of masticatory performance might be beneficial for cognition.

We also found a correlation between verbal fluency and masticatory performance, in concurrence with literature. In a subsample of healthy community dwelling seniors wearing full dentures, performance in an executive functioning domain, including verbal fluency, correlated with masticatory ability ²⁹. In institutionalized elderly persons, typically only global cognition is assessed. To our knowledge, this is the first time that cognition in this population has been extensively addressed. Therefore, the current findings with regards to verbal fluency cannot directly be compared to other studies.

There are a few limitations to the current study. First, there were missing values. This was due to non-performance in the mixing ability test, but also due to the nature of dementia, incomplete proxy reports, or incomplete participants’ files. This limited the number of cases available for analysis, which was especially of influence in the hierarchical regressions. Second, some participants were excluded from the mixing ability test by a proxy, e.g., out of fear for agitation, exhaustion, or choking due to misunderstanding the task. Possibly, this caused severe cases to be excluded, thus limiting this study to a cooperative and cognitively better subsample. However, as the groups did not differ on 9 out of 10 neuropsychological tasks (i.e., only on verbal short term memory) and not on agitation and depression scores, this might have only played a minor role, if at all. Third, several dementia subtypes show specific neuropsychological profiles ³⁰. In the current study, all dementia types were pooled. It is possible that this clouded the data.

In conclusion, to our knowledge, this was the first time that the correlation between mastication and cognition has been investigated in psychogeriatric nursing home residents, using extensive neuropsychological testing and objective measures for masticatory performance. Correlations were found between mastication and global cognition, and mastication and verbal fluency, which concurs with other studies regarding subjective assessments and healthy elderly persons. No correlation was found between other neuropsychological tasks and masticatory performance. These results suggest that clinicians should be aware of possible negative effects of loss of general and masticatory function and should strive to maintain function as long as possible in order to facilitate active mastication, and, possibly, cognition.
REFERENCES


A longitudinal randomized clinical trial

Masticatory function and oral health are important for maintaining cognition and quality of life (QoL), especially in elderly persons suffering from dementia. A randomized clinical trial was conducted to investigate the effect of increased masticatory activity through oral health care and adaptations in diet on cognition and QoL in elderly persons suffering from dementia. One hundred and four Dutch participants were included in the analysis. Data collection included screening global cognition, applying the Qualidem proxy questionnaire, and assessment of masticatory performance with a two-color chewing gum mixing ability test. An oral health care intervention was implemented according to national guidelines, by providing clinical lessons, and supervision. Dietary changes were designed with the staff and managers. An unplanned closing (ad hoc terminalis) data analysis was done with a mixed repeated measures ANOVA. There was a statistically significant interaction between the intervention and time on the QoL subscale ‘restless tense behavior’. Significant main effects of time were noted for global cognition, and for the QoL subscales ‘positive affect’ and ‘social isolation’. No other effects were found. During the execution of the trial, concern grew about the actual adherence to the intervention. Efforts to increase awareness and adherence were to no avail. Comparable trials reported similar results. It was therefore decided to discontinue the trial. Alternative methods to implement oral health care in nursing homes are proposed, such as a “Denticure”.

INTRODUCTION

Background

Around the globe, millions of elderly persons are suffering from dementia, and it is expected that this number will increase in the near future. Dementia is an umbrella term for a group of psychogeriatric neurodegenerative conditions; the most prevalent subtypes of dementia are Alzheimer's disease (AD; about 60% of the cases) and vascular dementia (VaD; about 30%). The expected rise in dementia incidence is mostly due to aging of the population, since age is one of the main risk factors for dementia. One of the most prominent symptoms is the loss of cognitive function, which is also a main part of the diagnosis.

Increasing physical activity improves cognition, quality of life (QoL), and mood in older persons with dementia. Many studies indicate the benefits of exercise as a protective factor, and perhaps even as a treatment for deterioration of cognition. The most likely explanatory mechanism behind this effect is the increased cerebral blood flow, which is often observed during exercise. Mastication also induces higher heart rates and increases cerebral blood flow.

In senior persons, this increase is larger when wearing their dental prosthesis, compared to not wearing it. Interestingly, rehabilitating masticatory function through the application of dental prostheses leads to both improved masticatory ability and improved cognitive function, and persons who have received prosthodontic treatment show brain perfusion associated with positive cognitive outcomes.

Although habitual mastication is not the same as intensive physical activity, it is likely that at least some of the positive effects of mastication on cognition, which will be discussed in more detail below, can be explained by exercise effects, such as increased cerebral blood flow.

A relationship between masticatory and cognitive performance has been reported for both animals and humans. Experimental animal studies show that impairing masticatory activity through modified occlusion or diet leads to deficits in spatial memory and loss of neurons in several cerebral regions. In human studies, multiple tooth loss and lower self-reported masticatory function is associated with impaired global cognitive functioning in both community dwelling individuals and institutionalized elderly persons.

Lower masticatory function is also related to lower QoL. The concept of QoL describes a person's well-being, and comprises many variables, including physical health and function (e.g., absence of pain, independence in activities of daily life) mental health and function (e.g., absence of depression, cognitive performance), and having meaningful experiences such as maintenance of dignity and enjoyable mealtimes. All these aspects are interrelated, with presence of pain also playing an important role. Suffering from pain in the head and neck region (e.g., temporomandibular disorders (TMD), is associated with lower QoL. QoL is also
adversely affected by oral health problems such as a dry mouth. Furthermore, better oral health is associated with a lower risk for (amongst others) pneumonia, cardiovascular problems such as endocarditis, and stroke and diabetes. Oral health and available oral health care is often not adequate in the senior population, particularly in nursing home residents. An intervention aimed at improving oral health care in nursing homes might thus positively influence cognition and QoL in residential elderly. It is possible that, as a result of such an intervention, masticatory function also improves, which in turn could lead to increased masticatory activity. For example, having better masticatory function was positively related to both preservation of cognition and eating a more diversified diet (mostly hard and healthy foods, such as beans and other vegetables) in cognitively healthy elderly. As masticatory activity could be considered a form of physical activity, and since exercise interventions are shown to act protective against cognitive decline and dementia, stimulating masticatory activity with a diet intervention, aimed at offering foods of increased consistency, may have additive beneficial effects on cognition and QoL.

Objectives and Hypotheses

The objective of this randomized clinical trial (RCT) was to investigate the effects of increased masticatory activity, achieved by improved oral health care and a diet of increased consistency, on cognition and QoL, in elderly persons with dementia. We hypothesized that increased masticatory activity would have a positive influence on these outcomes.

METHODS

The detailed protocol for this RCT is reported elsewhere; briefly, it encompasses the following:

Participants

Participants were Dutch persons, aged 65 years and older, suffering from dementia and receiving institutionalized psychogeriatric care. Participants were recruited in nursing homes, and approached by the nursing home manager. The entire residential population was contacted at the start of the project, and new residents were invited upon admittance to the nursing home. Figure 7.1 presents a flowchart of the sample.

From the initially included 122 participants, 104 were included in the longitudinal analysis. Participants’ dropout was either due to participant’s relocation or mortality. Missing values for (some parts of) the assessments occurred for a few
Figure 7.1: Flowchart of participants. Seven nursing homes provided 122 participants for the original sample. 104 participants were included in the longitudinal investigation; 28 in the control group and 76 in the intervention group. Each nursing home had agreed to provide an equal number of control and intervention units. One nursing home (NH2) was unable to keep the groups separate, due to interchanging staff, causing all participants in that nursing home to be included in the intervention group. One nursing home (NH3) was unable to recruit participants from the control unit. NH=nursing home; SCU=special care unit; SHA= shared housing arrangement; DC= daycare facility.
participants, sometimes temporarily. This happened for example if the participant was hospitalized. On a few occasions, a proxy requested the participant’s exclusion from parts of the assessment, out of worry for too much arousal or exhaustion. The specific participant numbers included in an analysis are provided for each variable, in the corresponding tables.

Nursing home 1 started first, after which nursing home 2 started, and so on. After a baseline assessment (T₀), a 6-week follow up assessment was conducted (T₁). Another 6 weeks later (i.e., 12 weeks since baseline) a second follow up assessment took place (T₂). Finally, 24 weeks after baseline, a third follow up assessment (T₃) was conducted. Dates defining the periods of recruitment and follow-up vary per nursing home. Baseline data are reported in Table 7.1.

Interventions

There were two intervention routes, aimed at increasing the masticatory activity: (A) improving oral health care, and (B) increasing the diet’s consistency. All nursing homes implemented route A – improving oral health care, and four nursing homes (NH₂, NH₄, NH₅, NH₆) implemented route B – increasing the diet’s consistency on top of route A. For analysis purposes, all routes have been combined into a single ‘experimental’ group. The experimental group was compared to a control group, who were receiving care as usual.

**Route A: Improved oral health care** was organized by offering clinical lessons to the daily nursing staff, which included a theoretical and a practical part. These lessons provided oral care instructions according to the 2007 Dutch ’Oral health care Guideline for Older people in Long-term care Institutions‘ (OGOLI)⁴⁴.⁴⁵. This guideline defines oral care for dentate, and edentate individuals, as well as for prosthesis wearers. At each assessment, and if needed in between, (intensive) counseling was offered. In two nursing homes (NH₁ and NH₅), the local dental hygienist supervised the daily implementation. Two other nursing homes (NH₂ and NH₃) had a residential dentist (i.e., visiting the nursing home and treating patients once a week) who was involved in the project. Two nursing homes (NH₄ and NH₆) had no professional oral health care workers, but had an active and enthusiastic team of nursing staff with designated persons implementing the intervention.

**Route B: Increasing the diet’s consistency**, to contain more solid foods, was done depending on the local possibilities. Two nursing homes (NH₁ and NH₃) could not adapt the daily meals. The manager from NH₁ did organize a Christmas dinner for residents and staff, with a special focus on chew-engaging foods. Some institutions were able to do their own shopping and cooking, one on a daily basis (NH₅), another (NH₂) only sporadically (as they were dependent on volunteers to do the actual cooking). The nursing staff from NH₄ and NH₆ were dependent on organized food preparation centers for the hot meals, and could therefore only change the diet’s consistency by requesting it to be ‘not pureed’. They made addi-
<table>
<thead>
<tr>
<th>Covariates</th>
<th>Variable</th>
<th>Control group (n total=28)</th>
<th></th>
<th>Intervention group (n total=76)</th>
<th></th>
<th>Value test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Mean±SD/Median</td>
<td>Range/ Ratio</td>
<td>n</td>
<td>Mean±SD/Median</td>
<td>Range/ Ratio</td>
</tr>
<tr>
<td>Demographics</td>
<td>Age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28</td>
<td>86.29±5.45</td>
<td>77–97</td>
<td>76</td>
<td>85.04±5.91</td>
<td>67–97</td>
</tr>
<tr>
<td></td>
<td>Gender (m/f)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28</td>
<td>Female</td>
<td>3/25</td>
<td>76</td>
<td>Female</td>
<td>10/66</td>
</tr>
<tr>
<td></td>
<td>Educational level&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
<td>2</td>
<td>2–6</td>
<td>52</td>
<td>4</td>
<td>2–7</td>
</tr>
<tr>
<td>Independence</td>
<td>ADL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17</td>
<td>16</td>
<td>8–18</td>
<td>49</td>
<td>15</td>
<td>8–18</td>
</tr>
<tr>
<td>Physical Health</td>
<td>Hypertension (y/n)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22</td>
<td>No</td>
<td>1/21</td>
<td>57</td>
<td>No</td>
<td>6/51</td>
</tr>
<tr>
<td></td>
<td>Comorbidity score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28</td>
<td>2</td>
<td>0–5</td>
<td>68</td>
<td>3</td>
<td>0–5</td>
</tr>
<tr>
<td></td>
<td>Medication score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21</td>
<td>4</td>
<td>1–8</td>
<td>34</td>
<td>3.5</td>
<td>0–7</td>
</tr>
<tr>
<td>Mood</td>
<td>Depression (y/n)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17</td>
<td>Yes</td>
<td>10/7</td>
<td>45</td>
<td>Yes</td>
<td>26/19</td>
</tr>
<tr>
<td></td>
<td>Agitation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>41.5</td>
<td>29–118</td>
<td>50</td>
<td>44</td>
<td>29–96</td>
</tr>
<tr>
<td>Masticatory system</td>
<td>Dentition&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
<td>5</td>
<td>1–10</td>
<td>59</td>
<td>5</td>
<td>1–10</td>
</tr>
<tr>
<td></td>
<td>Mobility&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>13</td>
<td>58.79±19.35</td>
<td>23.5–82.0</td>
<td>31</td>
<td>56.53±15.43</td>
<td>27–90</td>
</tr>
<tr>
<td>Pain at excursion&lt;sup&gt;b,g&lt;/sup&gt;</td>
<td>11</td>
<td>0</td>
<td>0–3</td>
<td>34</td>
<td>0</td>
<td>0–4</td>
<td>170.0</td>
</tr>
<tr>
<td>Outcome variables</td>
<td>Global cognition</td>
<td>MMSE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24</td>
<td>10</td>
<td>61</td>
<td>9</td>
<td>0–24</td>
</tr>
<tr>
<td></td>
<td>Care relationship&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>14.5</td>
<td>8–21</td>
<td>49</td>
<td>13</td>
<td>7–21</td>
</tr>
<tr>
<td></td>
<td>Positive affect&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>13</td>
<td>9–18</td>
<td>49</td>
<td>14</td>
<td>4–18</td>
</tr>
<tr>
<td></td>
<td>Restless tense&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>4.5</td>
<td>0–9</td>
<td>50</td>
<td>5</td>
<td>0–9</td>
</tr>
<tr>
<td></td>
<td>Social Isolation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td>6</td>
<td>3–9</td>
<td>49</td>
<td>7</td>
<td>1–9</td>
</tr>
<tr>
<td></td>
<td>Masticatory performance</td>
<td>Mixing ability&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17</td>
<td>0.25±0.04</td>
<td>0.20–0.32</td>
<td>32</td>
<td>0.27±0.04</td>
</tr>
</tbody>
</table>

<sup>a</sup> quantitative value with normal distribution; mean ± sd and t-test reported; <sup>b</sup> = Mann Whitney U test; <sup>c</sup> = Dichotomous variable with expected cell frequencies < 5; Fisher’s exact test, two sided significance reported; <sup>d</sup> = Dichotomous variable; <sup>e</sup> = chi square test; <sup>f</sup> = Denition score; 10 = both dental arches natural dentition; 9 = one arch dentate, other arch partial prosthesis; 8 = one arch dentate, other arch partial prosthesis; 7 = both arches partial prosthesis; 6 = one partial and one full prosthesis; 5 = two full prostheses; 4 = one arch edentate, other dentate; 3 = one arch edentate and other a partial prosthesis; 2 = one arch edentate, other full prosthesis; 1 = completely edentate; <sup>g</sup> = Mobility: summed score in millimeters for maximal voluntary mouth opening, moving the jaw forwards (=protrusion) and sideways (=laterotrusion to the left and right), corrected for overjet and overbite; <sup>h</sup> = Scores are 0 = no pain; 1 = sensitive; 2 = mild pain; 3 = moderate pain; 4 = severe pain. SD = standard deviation; m/f = male female; y/n = yes/no; ADL = independence in Activities of Daily Living (a higher score indicates more dependence); QoL = Quality of Life (a higher score indicates a better quality of life); MMSE+ = Mini Mental State Examination; na = not applicable; *p ≤ 0.05.
tional changes to the diet’s consistency by supplementing lunch with hard fruits such as apples. The changes in diet were listed in a notebook.

The oral health care intervention was implemented according to the aforementioned guideline, in an effort to standardize the procedures. The diet intervention was heterogeneous, without means of standardizing, as described.

Adherence to the intervention was formally and informally checked. A dental hygienist performed plaque checks at baseline and on several follow-up occasions, in NH1, NH2, and NH5. Each nursing home had a dated tick-off list mounted to the wall of every bathroom, to track whether oral care was provided (marked with an ‘X’) or not (marked with an ‘o’). The supervising researcher made surprise visits to the nursing homes to interview the members of the daily nursing staff, and performed visual inspection of bathrooms for the presence of toothbrush and toothpaste, or soap. As part of the clinical lessons, nursing staff was informed that a denture should not be cleaned with toothpaste, but with a common household soap. This is a product that is not typically found in a bathroom, and its presence on the sink, next to the toothbrush, was taken as an indicator of adherence. Attendance to clinical lessons was also noted.

Outcomes

A geriatric assessment should include, amongst others, measures for functional capacity such as cognition, and nonmedical outcomes such as QoL. Therefore, the current set of outcome variables set is multidimensional. The Mini Mental State Examination (MMSE), which assesses memory, orientation in time and place, episodic memory, naming, and visuo-constructive capacities was used to measure global cognition. QoL was assessed with the Qualidem questionnaire, which is recommended for persons residing in a special care unit (SCU) nursing home and is also appropriate for assessing QoL in persons residing in shared housing arrangements (SHA). Only the four subscales that are appropriate for a severe dementia group were used: care relationship, positive affect, restless tense behavior, and social isolation. Finally, a mixing ability test was used to measure masticatory performance, as it was expected that increased masticatory activity would also improve masticatory performance. The mixing ability test uses a fully automated computer algorithm. Blinded, trained external examiners conducted all the assessments. The examiners were calibrated, both periodically and at random.

Sample size

In the protocol for this RCT, the sample size was calculated with a power analysis based on the outcome variable QoL. The estimated sample size was \( n = 224 \); the current sample comprises 104 participants (see also Figure 7.1). However, it was decided that the trial should be discontinued, after which an unplanned (ad hoc)
closing (*terminalis*) analysis would be appropriate. This decision was made because of serious concerns with regard to adherence to the intervention.

**Design**

The trial was designed as a prospective longitudinal matched cluster randomized single-blind multicenter study. Nursing homes enrolled at least two similar care units (*matched clusters*); typically a unit was an entire geriatric ward. One unit would be the control group, and the other unit the intervention group. Ideally, the allocation of clusters to either the control group or the intervention group would be done at random (*cluster randomized*). However, in the majority of the cases, the nursing home manager was forced to assign *a priori* a care unit to either the control condition or the experimental condition. This was for example due to rapid staff turnover in one unit, or the presence of team members who were enthusiastic to be part of the project. There was no allocation concealment since the study was single blind. As the primary goal of the intervention was changing the daily care, it was impossible to keep the nursing staff blind. They had to either provide care as usual, or attend clinical lessons and change their daily routine. Equally, participants might have been aware of increased oral care, or different foods being added to their daily routine. A placebo condition was not possible, as it was not clear whether this should be for example, a pleasant condition (social interaction) or a mild stressful interaction (perhaps mild grooming such as cutting nails, or brushing hair), and, in the latter case, whether this would be ethically acceptable. Therefore, ‘care as usual’ was taken as the control condition.

**Statistical methods**

Normality was investigated with the Kolmogorov-Smirnov test. Baseline comparisons were made between the control and intervention group, using independent t-tests if the data were quantitative and normally distributed. If this was not the case, nonparametric tests were used, *viz.*, Mann-Whitney U tests, and for dichotomous variables Chi square tests, unless the expected cell frequencies were <5, in which case Fisher’s exact test was used. Differences found between the groups at baseline were included as covariates in the subsequent analyses. An intention-to-treat analysis was done, meaning that data from all nursing homes that had agreed to implement the intervention were included, whether or not the implementation was successfully done. Missing values occurred due to the nature of dementia and the type of assessment (requiring a participant’s active participation).

In the study design, a mixed linear model analysis (also known as multilevel linear model) which is able to analyze unbalanced datasets, with (large amounts of) missing data \(^{53,54}\) was planned. The initial step in analyzing such a dataset for longitudinal assessments is a repeated measures ANOVA \(^55\). Therefore, a mixed-design
### Table 7.2: Results for the Mixed Analysis of Variance.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>nC</th>
<th>nI</th>
<th>Effect of time</th>
<th>Effect of group</th>
<th>Interaction effect</th>
<th>Partial η²</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F     p</td>
<td>F   p</td>
<td>F     p</td>
<td>Df(i,e)</td>
<td></td>
</tr>
<tr>
<td>Global Cognition</td>
<td>17</td>
<td>39</td>
<td>3.693 0.019*</td>
<td>0.265 0.609</td>
<td>0.416 0.709</td>
<td>(2.54, 137.26)</td>
<td>0.008</td>
</tr>
<tr>
<td>Qol-Care Relationship</td>
<td>13</td>
<td>13</td>
<td>0.995 0.400</td>
<td>1.312 0.263</td>
<td>0.617 0.606</td>
<td>(3,72)</td>
<td>0.025</td>
</tr>
<tr>
<td>Qol-Positive Affect</td>
<td>13</td>
<td>12</td>
<td>3.790 0.014*</td>
<td>0.069 0.795</td>
<td>0.292 0.831</td>
<td>(3,69)</td>
<td>0.013</td>
</tr>
<tr>
<td>QoL-Restless Tense</td>
<td>13</td>
<td>13</td>
<td>0.588 0.625</td>
<td>1.363 0.255</td>
<td>3.203 0.028*</td>
<td>(3,72)</td>
<td>0.118</td>
</tr>
<tr>
<td>QoL-Social Isolation</td>
<td>13</td>
<td>13</td>
<td>3.288 0.025*</td>
<td>0.019 0.892</td>
<td>0.999 0.398</td>
<td>(3,72)</td>
<td>0.040</td>
</tr>
<tr>
<td>Masticatory performance</td>
<td>8</td>
<td>17</td>
<td>0.446 0.721</td>
<td>1.285 0.269</td>
<td>1.898 0.138</td>
<td>(3,69)</td>
<td>0.076</td>
</tr>
</tbody>
</table>

*quantitative value with normal distribution; mean ± standard deviation and t-test reported; nC = n control group; nI = n intervention group; Df(i,e) = Degrees of freedom (interaction, error); *p ≤ 0.05.

ANOVA (2*4) was used for the current analysis. Time and group were the independent variables, time (4 levels) was the within-subjects factor and group (2 levels, intervention vs. control) was the between-subjects factor. It was checked whether the assumptions for ANOVA were met. In case of a significant interaction of time and intervention, the differences between the groups were further investigated for each time-point, with univariate (one way) ANOVA. In case of a significant main effect, this was further investigated with post-hoc pairwise comparisons.

The partial η² was used as a measure of estimated effect size; partial η² = 0.01: small effect; partial η² =0.06: moderate effect; partial η² =0.14: large effect.

**RESULTS**

**Participants**

The characteristics of the participants are shown in Table 7.1. Both demographic and clinical characteristics are provided. The groups were not different at baseline assessment. For each variable, the number of participants for which the data were available is presented.
Outcomes

The main effects for time, intervention, and the interaction effects from the mixed ANOVA are presented in Table 7.2.

For the QoL subscale ‘restless tense behavior’, a statistically significant interaction between the intervention and time was found (F (3, 72) = 3.203, p = 0.028, partial $\eta^2 = 0.118$). Further analysis of the between-group differences showed that the intervention group had significantly lower scores than the control group at 12 weeks and 24 weeks after baseline (F(1, 24) = 4.744, p = 0.039, partial $\eta^2 = 0.165$, and F(1, 24) = 4.240, p = 0.050, partial $\eta^2 = 0.150$, respectively).

For three outcomes variables, a main effect of time (i.e., independent of group) was found. There was a negative main effect of time on global cognition (F (2.54, 137.26) = 3.693, p = 0.019; partial $\eta^2 = 0.064$). The post-hoc pairwise comparisons showed that this was due to a significant (p = 0.032) decline in MMSE score between the 6-week and 24-week assessments.

There was a negative main effect of time on the QoL subscale ‘positive affect’ (F (3, 69) = 3.790, p = 0.014; partial $\eta^2 = 0.141$). The post-hoc pairwise comparisons showed that this was due to a significant (p = 0.048) decline in score between the baseline assessment and the 24 weeks follow up assessment.

There was a positive main effect of time on the QoL subscale ‘social isolation’ (F (3, 72) = 3.288, p = 0.025; partial $\eta^2 = 0.120$). The post-hoc pairwise comparisons showed no significant contrasts, due to the Bonferroni adjustment for multiple comparisons. However, the main effect was most likely the result from a difference between scores from the 6-week and 24-week assessment, as this is the contrast closest to significance (p = 0.089) . The scores for the outcome variables and the main and interaction effects are shown in Figure 7.2 (A-F).

DISCUSSION

The current investigation was an ad hoc terminalis analysis; i.e., both the trial’s discontinuation as well as the subsequent analysis were deviations from the original study protocol. The main reason to perform an early analysis with participant recruitment at its halfway mark, was the fact that serious concerns with regards to implementation success of the intervention arose during the site visits. After preliminary inspection of the adherence checks (i.e., the attendance to the clinical lessons, the tick-off lists, and the plaque scores), it was felt that the trial should be discontinued, after which an final analysis would be performed on the outcome variables. There were several indicators that suggested that adherence to the planned intervention was suboptimal.

First of all, attendance to clinical lessons was low, temporary workforce staff was
Figure 7.2: A-F: Outcomes and main/interaction effects. Bar graphs of the median scores (for F; mean) of the outcome variables for both groups, plotted against assessment moment (0, 6, 12, and 24 weeks). Error bars indicate 25–75 percentiles (for F; standard deviations). In case of an interaction effect, the significant between-group differences are indicated with diamond-ended lines (F). Significant main effects of time are indicated with arrows. Dotted arrows indicate an insignificant post-hoc pairwise comparison from a significant main effect. Note: a lower score for masticatory performance indicates better performance.
never enrolled, and managers rarely attended. This was most unfortunate because management support and active leadership is related to intervention success ⁵⁷.

Secondly, although spontaneous and unstructured, the interviews with the daily nursing staff consistently revealed recurring difficulties. Often mentioned was a lack of time, to offer oral health care, to adapt the diet, or to assist to eat foods with a harder consistency. A lack of money, to buy toothbrushes, toothpaste or harder foods was also reported regularly.

Third, the plaque checks that were performed by the dental hygienist at some of the locations indicated that there was no improvement at any time, and the tick-off lists, if filled out, also indicated low levels of oral care (data not shown). Other aspects that were cause of concern were: major changes in staff (nursing staff, dentists, dieticians, and management); the crossover of nursing staff in a particular nursing home, contaminating the control group, and a sometimes indifferent or perhaps reluctant attitude of nursing staff towards oral health care and mastication. A final decision was made to discontinue the study, based on the findings of these adherence checks. Comparable outcomes from oral health care interventions emerging in literature ⁵⁸,⁵⁹ supported this decision further.

Subsequent data analysis showed one (moderate) interaction effect; a negative effect of the intervention on the QoL ‘restless tense behavior’ subscale. This result could indicate that being submitted to oral health care, when done irregularly by inexperienced or reluctant staff, is unsettling. There was a negative main effect of time on ‘global cognition’, which is fitting with the clinical presentation of dementia ⁶⁰. There was also a negative main effect of time on ‘positive affect’; the participants where less often happy, content, or cheerful. Mood disturbances such as depression are also often part of the disorder ⁶¹, thus, these results are not surprising. The positive main effect of time on ‘social isolation’ indicates that social interaction with others was less often rejected, and participants called out fewer times. The most influential contrast, albeit nonsignificant, was between the 6-weeks and 24-weeks assessment. It might be possible that when the intervention started, participants initially became resistant and uncooperative, and later on, they either grew accustomed to the new routine, or perhaps, as the intervention was not successfully implemented, their initial resistance subsided and their behavior returned to baseline levels.

The implementation of the OGOLI guideline ⁴⁴ has also been longitudinally studied in an intensively supervised and counseled program ⁵⁸,⁵⁹ in The Netherlands and Belgium. Results were disappointing; the plaque levels remained high in both intervention and control group ⁵⁸,⁵⁹. In another study, it was found that even though training nursing staff improved denture hygiene, oral health remained poor in almost half of the residents ⁶². Although nurses’ attitudes towards oral health care may improve following training, this is not enough to produce a clinically significant effect ⁶³-⁶⁵. A key aspect of the OGOLI guideline is the use of a designated nurse who is specifically trained in and dedicated to oral health care ⁴⁵.
study, however, no such local coordinator was made available for any of the nursing homes, despite efforts made by the research team. This could explain the lack of implementation success, because the presence of a local oral care professional can improve nurses’ attitude towards oral care. In fact, the introduction of a designated oral health coordinator had a positive effect on the oral health of institutionalized elderly, with intervention success being more influenced by charisma and engagement of the coordinator, than by clinical lessons. Designating daily oral care providers and supplying them with practical and educational tools can be effective in improving oral health in residents suffering from dementia. In one of these studies, oral care training was supplemented by counseling on managing adverse behaviors, a strategy that others found to be effective as well. Clearly, this is a promising addition; studies confirm that resistant behavior play a major role in the oral health of dependent residents. Based on these clinical and literature findings, it is recommended to commit dedicated oral health nurses to providing the daily oral care. These oral health nurses, the name ‘Denticure’ might be appropriate and may help in establishing its unique position, should receive specialized training in both offering oral health care to elderly persons with dementia, and perhaps more importantly, in dealing successfully with resistant behaviors. If a nursing home decides to employ a Denticure, this person can become a recognizable part of the daily routine, and facilitate communication between nursing staff and dental professionals. Since the Denticure is expected to fully focus on performing oral care, (s)he can be held accountable for this task. Trying to assimilate oral health care into the daily nursing staff’s tasks, ‘since it only takes two minutes’, means failing to appreciate both the importance and challenges of oral health care. The coming cohorts of nursing home residents are likely to offer new oral care challenges, such as oral implant supported dentures, further stressing the need for a specialized, daily oral health care professional, such as the Denticure.
REFERENCES


27. Lexomboon D., Trulsson M., Wardh I., Parker M.G. – Chewing Ability and


55. Krueger C., Tian L. – A comparison of the general linear mixed model and re-


REFERENCES • 135


72. Willumsen T., Karlsen L., Naess R., Bjorntvedt S. – Are the barriers to good oral hygiene in nursing homes within the nurses or the patients? *Gerodontology*. 29(2); e748–e755, 2012.


The main aim of this thesis was to study the relationship between mastication, cognition, and quality of life (QoL) in elderly persons with dementia. In a clinical setting, an experimental approach (randomized clinical trial; RCT) was used to examine the effect of increased masticatory activity on cognition and QoL. Supplemental research was done by reviewing the existing literature. In this general discussion, the outcomes of the RCT will be reflected upon, including how this relates to the literature, and what conclusions can be drawn for the future.

**RELATIONSHIP BETWEEN MASTICATION AND COGNITION**

In the literature, there is a body of evidence emerging that there is, in fact, a relationship between mastication and cognition. This literature is discussed in chapter 2. The results from the cross-sectional analysis from the baseline data of the RCT, as discussed in chapter 6, agree with these findings; correlations between global cognition and masticatory performance, and between verbal fluency and masticatory performance were found. Masticatory performance was assessed with an objective mixing ability test, which was developed for this purpose, and which is discussed in chapter 5. With this test, the correlation between mastication and cognition was objectively studied for the first time, in elderly persons with dementia, rather than through self-report, as was done by, e.g., Miura et al. ¹. Furthermore, cognition was extensively assessed, instead of only globally screened. The fact that only two cognitive functions showed a correlation means that other cognitive functions — i.e., (working) memory and attention, visuospatial (working) memory and function, and verbal long-term memory — did not correlate. Others have also found that mastication influences some, but not all, cognitive functions. For example, chewing
a piece of gum might improve sustained attention but not memory, or chewing a piece of gum improved (working) memory but not attention. In healthy elderly persons, better masticatory function related positively to recall and recognition of sentences, recall of test session, and prospective memory, but not to face recognition, recall and recognition of actions, attention, and tests for executive function. Clearly, there is still more work to be done, to investigate how mastication might be related to exactly which cognitive functions.

**RELATIONSHIP BETWEEN QUALITY OF LIFE AND MASTICATION**

Besides cognition, mastication is also related to QoL. QoL is a patient-based, nonmedical appraisal of the burden presented to individuals suffering from dementia. An important part of QoL is being contented, having fulfilling encounters and maintenance of dignity. QoL can be influenced by masticatory function and oral health; for example being able to eat healthy foods without help or the need for mashing creates enjoyable mealtimes which improves QoL, whereas suffering from a dry mouth hinders denture use, and thus, speech and social interaction, which lowers a person's QoL. Pain of course can play an important role. Painful conditions such as pain in the skull, jaw, or neck (e.g., Temporomandibular Disorders) are known to lower a person's QoL. Assessment of the longitudinal data suggested that the implementation of the intervention might have negatively influenced QoL, as restless and tense behaviors increased in the intervention group. As discussed in chapter 7, however, the intervention was not implemented successfully, with oral care being performed more or less haphazardly, and this might have led to apprehension with the participants.

**PAIN**

One interesting finding of the RCT was that relatively little orofacial pain was reported. In the cross-sectional analysis, pain during mandibular excursions was rarely found, as almost 90% of the participants indicated to have ‘no pain’, and the maximal summed pain score was 4 out of a possible maximal score of 16. However, as mentioned in chapter 1, in elderly persons with (severe) dementia, self-report is most likely unreliable. Since there are no observation scales specifically aimed at assessing orofacial pain, as discussed in chapter 3, presence of pain during these mandibular excursions was not measured in another way, besides self-report. Given the voluntary nature of the excursions it was assumed that no major painful condition arose during the assessments.

However, since pain tends to be underdiagnosed and undertreated in elderly
persons suffering from dementia, it seems likely that there were, in fact, undiagnosed orofacial painful conditions that influenced the mandibular excursions and masticatory performance. Common oral conditions in elderly persons are, amongst others: dental caries, (advanced) gingivitis (i.e., inflammation of the gums; bleeding gums), periodontitis (i.e., inflammation of the supportive tissue around the teeth), xerostomia (dry mouth), and candidiasis, which can present as: pseudomembranous candidiasis [in Dutch, spruw]; denture stomatitis; and/or angular cheilitis (fissures at mouth corners). These conditions are uncomfortable, if not painful. For example, even if it is asymptomatic in most patients, denture stomatitis can be painful and/or can give a burning sensation in the mouth. Similarly, pseudomembranous candidiasis is often clinically not relevant, but in some patients, it can cause discomfort and changes in taste; angular cheilitis is most uncomfortable when one has to open the mouth, for example during mandibular excursions.

One case in particular was exemplary in how attention for oral health care and possible presence of pain can improve and impact quality of life (QoL).

One nursing home resident, (let’s call her Ms. Daisy), showed typical behavior. She was always in a bad mood, quickly agitated, would never smile or make pleasant conversation, and spent her time sitting alone in her wheelchair, leaning with her arm at the dining table, resting her chin in her hand, covering her mouth a bit. She would lament and wail, sometimes softly, sometimes she cried out loud. ‘Oh, Ms. Daisy, hush!’ That’s what the nursing staff called at her, if she was being too loud or disturbing other residents. On ‘good’ days, she would sit there, alone at the dinner table, quietly whimpering. On ‘bad’ days, she would be returned to her room, maybe given some tranquilizing medicine.

When the project started in her nursing home, the resident dental hygienist was allowed to take the time to visit and inspect every participant’s mouth. Ms. Daisy turned out the have a serious case of oral candidiasis, and most likely felt discomfort, pain, experienced altered taste. She was perhaps even aware of this, as her general behavior of avoiding contact and covering her mouth changed immensely when her candidiasis was treated; she smiled, laughed, even hugged members of the staff. She no longer felt inhibited to engage in social interactions, had a good mood, and was pleasant to be around. This reflected positively on the staff and other residents, who in turn became more pleasant and relaxed.

Clearly, the behavior indicated (orofacial) pain, as described in chapter 3, such as calling out (vocalization), the sloughed posture (body movements), her behavior (withdrawn; aggressive; sad), holding her face, and resisting oral care. Awareness of (oro-) facial pain would have improved her QoL, and that of those around her, a lot sooner.
Randomization, allocation concealment, and blinding

In chapter 4, the proposed method for data collection is described. There are a few critical comments that can be made. For example, the design was intended as a longitudinal matched cluster randomized single-blind multicenter design. In one participating center, due to crossover of nursing staff, the control group was contaminated, and the cluster match was lost. This happened early in the project, and therefore it was decided to include the control group in the intervention group. The nursing staff of the new intervention group was briefed and trained accordingly. Complete randomization and allocation concealment is preferred, to prevent selection bias. However, sometimes a certain ward was thought to be better suited for participation in the intervention group than others, for example due to presence of a stable team of nursing staff rather than one including many temporary workers. This might have created a selection bias. The study was designed to be single blind, and indeed, the trained examiners were blind for the intervention. It is possible that, due to the nature of the dementia, participants were also blind for, or perhaps unaware of, the intervention. However, some data were provided by proxies (such as the QoL ratings), and these proxies were members of the nursing staff, who regularly interacted with the participant; never for example a family member. These members of the nursing staff were sometimes the same persons that were also performing the intervention. Non-blinded examiners tend to rate more positively, thus creating ascertainment bias.²⁰ It is possible that inadvertently, bias was introduced; future studies should be aware of this limitation and make an effort to avoid this.

Missing values

An unexpected finding was the amount of missing values. It was estimated (chapter 3) that there would be about 10% dropout due participant’s relocation and mortality. However, the return rates that could reasonably be expected for the proxy questionnaires were not taken into consideration in these calculations.

The initial response rate of the current study is normal to high; in survey studies, return rates on questionnaires are commonly about 60%²¹ to 70%²² in community samples, and lower (e.g., 42%)²³ in proxy questionnaires. In the current RCT, proxy-assessed activity of daily living (ADL) baseline scores were obtained for 66.6% (chapter 6; n=76/114). Similarly, 64.4% of the proxies returned completed QoL questionnaires for baselines assessments (chapter 7; n=67/104). For the longitudinal repeated assessments, however, results were worse; after 24 weeks, for only 25% of the participants, complete case data on QoL were available (chapter 7; n=26/104).

If we view these results in the light of the design, with multiple assessments, we might understand the response rates better by considering the following. If for a
single survey, the response rate is 65%, then repeating the survey 4 times would lead to an expected response rate of \( (0.65)^4 = 0.18 \), i.e., a response rate of about 20%, which is in line with the current findings of 25% response rates for complete cases.

Efforts to increase response rates were made from the beginning, as personal contact was established and maintained, the questionnaires were hand-delivered, and follow-up inquiries were made – actions that are known to improve response rates.\(^{21}\) The questionnaires were comprehensive, but as length of the questionnaires is not of influence on response rates,\(^{21,22}\) it is not likely that this was of influence on the results. Generic looking questionnaires were used, which should have been no problem, because adding a feel of authority to the presentation of the questionnaire by printing logo’s and adding signatures does not improve response rates.\(^{24}\) As an alternative, internet-based surveys might seem appropriate, but they are found to be less effective in generating a response than paper surveys.\(^{25}\)

It is understandable, but nevertheless most unfortunate, that such low response rates were obtained, and future studies should take these response rates into consideration when performing power calculations. Besides missing values due to the response rates on the questionnaires, low responses were obtained with the neuropsychological tests and the assessment of the masticatory performance.

The response rates for the neuropsychological tests were slightly better compared to the proxy response rates. Global cognition, for example, was successfully assessed with the Mini Mental State Examination (MMSE,\(^{26}\) in about 80% (chapter 6, \(n=93/114\)). Repeated response rates for global cognition were relatively high, 54% (\(n=56/104\)). This is probably due to the external trained examiners, who always aimed for 100% response, and only a participant’s (mental or physical) inability to participate, rather than a rater’s unwillingness to participate, influenced these response rates.

However, less than 50% of the participants were successfully examined with the full test battery, which was applied to those participants who scored higher than 5 of the MMSE (see chapter 3). In fact, a score of MMSE <9, indicating severe dementia,\(^9\) was obtained for more than half the sample. In Figure 8.1, a frequency distribution of the MMSE scores is given for the sample from chapter 6, and in Figure 8.2, the same data is presented in a pie chart, clearly illustrating the severity of the dementia in the sample.

The advanced dementia level of the sample was one of the reasons that participants attending daycare, with generally less severe dementia, were actively recruited in the later stages of the trial. In future trials, it would be worthwhile to actively include, from the beginning, care organizations with residents with less severe dementia, such as low-medium care wards (‘verzorgingshuis’) and daycare facilities. A bottom cut-off score for global cognition at baseline for participation might be considered, although global cognition did not appear to influence, for example, the ability to participate in the mixing ability test, as described in chapter 6, and the overall participation rates for the neuropsychological tests are not disappointing.
Figure 8.1: Distribution of global cognition of the participants in the cross-sectional study, assessed with the Mini Mental State Examination (MMSE). Participants are classified into a Severe/Moderate/Mild category (MMSE: 0–9; 10–19 and >20, respectively).

Figure 8.2: Pie chart of participants’ distribution according to Dementia Severity. Note that over half of the participants suffered from severe dementia according to Schiffczyk et al., (2010).
Masticatory performance was assessed with a combination of techniques (chapter 4). Mandibular excursion assessments were successfully performed in about 40% of the cases (i.e., chapter 6: 42.3% ($n=44/104$) and chapter 7: 41.2% ($n=47/114$)). Due to the severity of the dementia, participants often did not understand the verbal instructions at first explanation, however, using non-verbal communication, offering a demonstration and mimicking the desired motions, successful assessment was often still achieved. It was found that maximal mouth opening was easier modeled and assessed than protrusion and laterotrusions. Only complete assessments have been included in the analyses; it might be worthwhile to reconsider this in future papers, and only focus on maximal mouth opening, because limited maximal mouth opening alone is considered a clinical sign in studies on temporomandibular disorders.

The mixing ability test with two-color chewing gum, which was developed for this thesis, was found to be adequately responsive and reliable (chapter 5), although validity needs to be further established. The mixing ability test was used to assess the association between masticatory performance and cognition in a cross-sectional study of the clinical sample (chapter 6) and was taken as a measure of intervention success in chapter 7. The rationale behind this was that if the intervention increased oral health and thereby masticatory activity, masticatory performance would improve as well. Similar assumptions and assessments have been made, for example, when using a timed walk or a “Timed Up and Go” task to investigate the effect of a walking intervention.

A correlation between masticatory performance and cognitive measures was found, in a subsample of persons participating in the mixing ability test (chapter 6). About half of the participants did not perform the mixing ability test. There were several reasons for ‘nonperformance’. First of all, some participants were excluded based on predefined criteria, such as facial paralysis. Others were eligible to participate, but were withdrawn by an intervening proxy. For example, a member of the nursing staff would indicate that a participant should not perform the mixing ability test. This was done without a medical imperative, i.e., there was no physical or ethical reason that called for exclusion. Instead, the advice was given, for example, out of fear for agitation or exhaustion. Whether or not this fear was based on a thorough risk assessment was never debated; the trained examiners were instructed to respect the proxies’ instructions, and thus excluded the participant from the test. This may have led to a selection bias, which could be reflected in the higher dependency scores for ADL of the group of ‘nonperformers’. This group comprised both the participants that were excluded based on the predefined criteria, as well as those excluded by proxy request. Participants that were more dependent were perhaps considered too vulnerable, and therefore excluded by a proxy.
Adherence

During the process of implementing the intervention, there was a growing concern about the actual adherence to the intervention. This was the main reason that an ad hoc terminalis analysis was conducted, rather than the planned end-analysis. Several factors contributed to the concern with regard to intervention adherence.

Reports for intervention success varied greatly between nurses from the same ward, some mentioning all went ‘great’ whereas others indicated major problems. Attendance to the clinical lessons was low, and after a survey, it was found that, among daily nursing staff, the awareness of the project and the importance of oral health in general was also low. There were many changes in nursing staff, dentists, dieticians, and also in management, which did not facilitate embracing and embedding of the intervention.

At a few nursing homes, that had a local dental hygienist, plaque checks were performed, at baseline and at random intervals later on. These plaque checks indicated no improvement over time. The tick-off lists, if filled out, also indicated low frequency of oral care (data not shown). On the other hand, when we were presented with tick off lists showing 100% successful oral care moments, all filled out in the same handwriting and ink, it was felt that this was perhaps not reflecting the actual situation. Deception by those unwilling or unable to comply is common in clinical trials, but also impossible to predict, and hard to prevent or prove ²⁹.

Obstacles for implementation success

The interviews with the daily nursing staff indicated difficulties such as a lack of time, and a lack of money, for example to buy oral care supplies or harder foods. A lack of commitment by the managers was also mentioned, leaving the nursing staff feeling unsupported. These are common, but serious obstacles for innovation ³⁰. This lack of managerial commitment was also felt in participating in the clinical lessons.

It was felt that managers did not facilitate or prioritize attendance, as staff was expected to attend the lessons in their own time, without financial compensation and with no regard for personal commitment such as caring for (young) family members. Only occasionally, adaptations in work schedules were made to facilitate attending clinical lessons. Managers rarely attended the lessons themselves, which was most unfortunate as management support and active leadership is related to intervention success ³¹. Sometimes, instead of the daily nursing staff, replacements attendees were sent, such as high-school students who were on an orienting internship (‘snuffelstage’). Temporary workforce staff was excluded from attending the clinical lessons.
Nurses’ ideas about the importance of oral health and their ability in providing oral care can improve after training, although a clinical effect of education on oral hygiene is not (yet) evident. This conclusion was recently confirmed in a review study. Continuous education and support of staff on providing oral health care is therefore recommended, especially as nurses are typically only marginally trained in providing such care, if at all.

In the present study, nursing staff did not always realize and appreciate the benefit of good oral health and mastication for general health and QoL. For example, it was thought that for elderly persons with dementia, having no teeth and eating or being fed pureed foods would be ‘easy and enjoyable’, which did not help in motivating staff to provide oral health care. Offering one clinical lesson was not enough to change this overall negative attitude towards oral care.

Complexity of change

Besides negative attitudes and (perceived) lack of managerial support, the lack of implementing success might be explained by looking at the complexity of the intervention. According to Sterns, Miller and Allen, complex changes are hard to implement. A change is complex when the outcome of the change is uncertain, and the level of agreement between parties is low. On the opposite, a change is not complex when the outcome is certain and agreement is high. A non-complex change is for example adding plants to the living room to increase a sense of home, or allowing a resident to choose his/her own bedtime, to increase autonomy. These changes do not involve an elaborate interaction or are the potential source of conflict, the outcome is quite certain, and can thus be implemented easily in nursing homes. A complex change, however, is typically only implemented by very committed teams and organizations. Providing oral health care is a complex change, as there is uncertainty of the effect – will oral health increase, will QoL increase, or perhaps cognition? Having the effort being evaluated scientifically might have increased this uncertainty. There is much disagreement between the parties; the resident and nursing staff are likely to have some (initial) conflict as they attempt to provide oral care, and despite clinical lessons and supervision of an dental hygienist, there were questions regarding (or even resistance towards) certain actions; for example, about storing dentures overnight, or about brushing teeth when the gums are bleeding. Having to adapt their approach to each resident individually increases the complexity for the nursing staff even more.

From a literature review on psychosocial intervention, it became clear that knowing the resident personally is an important factor for intervention success. Interestingly, these authors noted that nursing staff seem to be preoccupied with the risk of physical harms (e.g., falling) or causing agitation, and are more focused on prevention of oppositional behavior such as outbursts, than they are on promoting autonomy and improving QoL. This is in line with the current observations;
nursing staff were quite concerned with the physical wellbeing of participants, and with maintaining a level of serenity in the ward, and could therefore be reluctant to start providing oral health care, since it caused (initial) resistance behaviors.

**CLINICAL RELEVANCE**

The clinical relevance of these findings is profound. It was shown in this thesis, in both literature and the clinical sample, that there is an association between masticatory performance and cognition. This would suggest that maintenance or rehabilitation of oral function is important, especially for those persons most affected by cognitive loss and unable to communicate possible pain, such as elderly persons suffering from dementia.

At the same time, it was found that successfully implementing an oral health care intervention is quite challenging. Comparable results for oral care interventions have recently been reported. The implementation of the Dutch 'Oral health care Guideline for Older people in Long-term care Institutions' (OGOLI) has been studied in another longitudinal design in the Netherlands and Belgium. Unfortunately, after six months, the only positive finding was that residents who were completely dependent had less denture plaque. However, all plaque levels were still higher than expected. The results after five years were not much different, as the plaque levels were still high in both intervention group and control group.

Intensive supervision of the implementation seems only marginally beneficial. Similarly, in a residential setting, training the daily nursing staff led to improvements of oral hygiene at one month follow up, mostly in denture hygiene, and with almost half of the residents still having poor oral health. The need for dental treatment also remained high despite training in yet another study, even though the staff's ability to assess oral health and the residents' oral hygiene improved.

Nevertheless, there are also inspiring reports: it was found that an intervention focused on providing oral health care (i.e., brushing after each meal and weekly cleaning by a dentist or dental hygienist) for nursing homes residents was able to differentiate the intervention group from the control group after six months and one/two months, based on MMSE scores. It would be very interesting to further investigate the factors that determine the implementation success of an intervention.

The introduction of a designated Oral Health Coordinator (OHC) who received outside training and ongoing support from a trainer, had a positive effect on the oral health of institutionalized elderly after one year. The level of authority and enthusiasm of the OHC was key in intervention success; more important than education. A positive effect on oral hygiene was reported after 3 months and even after 6 years, of having designated supervising staff members, alongside picture-based instruction cards, providing materials and practical oral care instructions to nursing staff in a residential setting. Assigning a designated oral care nurse each
day and equipping this person with a custom-made trolley was found to reduce plaque scores, gingivitis, and periodontal disease. Presence of a designated oral care professional also increases positive attitude towards oral care in nursing home staff.

Committing specific members of staff to performing the oral health care was found to be effective in improving the oral health of residents suffering from dementia. In this pilot study, dedicated mouth care aides were allowed spending 4 hours per day, for 5 days per week, to providing oral care to all the residents. They received daily training for two weeks, including providing oral care alongside the dentist, followed by expert support for a few hours per week. Training included theory and practical information on oral care and also instruction by a psychologist on dealing with behavioral issues they might encounter. There was a significant improvement in oral hygiene and thoroughness of care, e.g., flossing and tooth picking had become part of the routine.

The addition of counseling on how to deal with resistant behaviors is promising, indeed. Studies confirm that resistant and uncooperative behavior from dependent residents (both cognitively healthy and suffering from dementia) play a major role in oral health. An intervention executed by researchers combining tactics for reducing resistant behaviors and oral health care best practices proved very successful. In fact, loss of cognition does not have to influence oral health, as long as someone is independent for oral health care; however, as one becomes dependent, impaired cognition puts a person at great risk for impaired oral hygiene, most likely due to un-cooperation. Recommendations for reducing care-resistant behaviors in oral care are available, but they are not part of the Dutch guideline nor part of nurses training.

CONCLUSIONS AND RECOMMENDATIONS

From all of the above, some suggestions for future research and policy makers can be made. First, it would still be interesting to investigate the effect of increased masticatory activity on cognition and QoL in elderly persons with dementia. A successful implementation of an oral health care intervention would be key to this.

Secondly, therefore, it would be worthwhile to further investigate how to implement oral care interventions for elderly persons with dementia. Factors for success will most likely include continuous education, including individual coaching and providing the ability to work alongside a dental professional (‘training on the job’), and designating a daily oral care provider, to increase accountability. Training should include both theory and practical instructions; both in providing oral care and in responding to resistant and uncooperative behaviors. In order to practically organize this, our final recommendation would be to commit dedicated professionals to this task, rather than designating a member of the daily nursing staff to provide oral care.
and rotating this responsibility on a daily or weekly basis. This dedicated, designated oral care nurse, the so-called Denticure, will be trained in both providing oral health care for elderly persons and in handling uncooperative behavior. The Denticure provides all daily oral care, is the liaison between nursing staff and dental professionals, and since (s)he does not have other nursing tasks, there is no conflict of priorities, or lack of time or skill. Assigning the task of oral care to one or two specific persons rather than the group also creates transparency, direct accountability, and responsibility. The Denticure can establish good rapport with the residents, and will develop a tailored approach for each individual client.

Simply trying to add the task of oral care to the workload and responsibility of the – already overburdened – daily nursing staff under the premise of ‘it only takes two minutes’ is denying both the value and effort of offering oral health care. As it is of great importance to general health, and, since the nursing homes residents of the future are expected to offer challenging dental situations, we would strongly recommend the appointment of a Denticure in every nursing home. With an estimated possible workload of 4–6 clients per hour, one fulltime Denticure could provide excellent oral health care, once daily, for 40 residents. Specialized training for this job must commence as soon as possible, and adequate funding must be made available.
REFERENCES

15. Zuluaga D.J., Montoya J.A., Contreras C.I., Herrera R.R. – Association be-
 tween oral health, cognitive impairment and oral health-related quality of life. *Gerodontology.* 29(2); e667–e673, 2012.


32. Wardh I., Jonsson M., Wikstrom M. – Attitudes to and knowledge about oral health care among nursing home personnel – an area in need of improvement. Gerodontology. 29(2); e787–e792, 2012.


Willumsen T., Karlsen L., Naess R., Bjorntvedt S. – Are the barriers to good oral hygiene in nursing homes within the nurses or the patients? Gerodontology. 29(2); e748–e755, 2012.


Mastication and oral health in elderly persons with dementia. The relationship with cognition and quality of life.

Oral health care is an important part of the daily care for elderly persons. However, it is often not adequate in the senior population, neither for community dwelling individuals nor for nursing home residents. When oral health deteriorates, the risk for (amongst others) pneumonia, cardiovascular problems such as endocarditis and stroke, diabetes, and even Alzheimer's disease (AD) increases. Loss of masticatory function has also been associated with loss of cognitive performance. As the cognitive skills from persons suffering from dementia, such as AD, are vulnerable, providing them with adequate oral health care to maintain general health and perhaps even cognition, is of the utmost importance.

In this thesis, the relationship between mastication, cognition, and quality of life (QoL) in elderly persons suffering from dementia is investigated, both in the literature and in a clinical setting. The topic is introduced in chapter 1, including a description of the most common subtypes of dementia.

In chapter 2, a review of the available literature on the relationship between mastication and cognition is presented. From experimental animal studies, a causal relationship between inhibition of masticatory activity and cognitive performance emerged. The results from these studies indicated that the stress system (i.e., the hypothalamic pituitary adrenal axis) is likely to play an important role in the modulation of cognition by mastication. For example, neuronal growth is limited by stress, a negative effect which can be countered by chewing. In human studies, with healthy adults, it was found that cognitive performance improved during, or immediately after, chewing a piece of gum. This effect is temporary, and subsides quickly after the participant stops chewing. Although not all studies unanimously confirm this acute effect with regards to the specific cognitive domain, there seems to be agreement on the existence of a general acute positive effect; with individual differences in design explaining the sometimes ambiguous results. Apart from this
transient effect, a more permanent outcome is also reported; the effect of improved cognition which is achieved by improving masticatory function through the application of dental prostheses. Elderly persons with improved masticatory function show better performance on a variety of neuropsychological tasks, and persons who have received prosthodontic treatment show brain perfusion associated with positive cognitive outcomes. Possible explaining physiological mechanisms, besides reduced stress, are the positive effect of an enriched environment due to sensory input of the mouth, the positive effect of increased blood flow due to increased masticatory activity, or a mediating effect of nutrition.

It might also be possible that the presence of pain has a role to play. However, pain is typically hard to diagnose, if it is not self-reported. Due to the diminishing communicative skills in older persons with dementia, their pain is, in general, underrecognized and undertreated. There are a few observation scales available for the assessment of pain in elderly persons with dementia, which are discussed in chapter 3. However, none of these scales were found to pay specific attention towards orofacial pain (i.e., pain relating to the mouth and face). Typical pain indicators are: a contorted expression or rapid blinking, heavy breathing, verbalizing (shouting, crying), and defensive or withdrawn behaviors. Recommended to be included in observation scales, as they are typically indicating orofacial pain, are behaviors such as putting the hands to the affected orofacial area, exhibiting changed eating patterns, making careful (i.e., small and/or slow) oral movements, and resisting oral care.

Besides a review of the literature, a clinical study was performed as well. An intervention to increase masticatory activity, through changes in diet and the implementation of the Dutch Oral health care Guideline for Older people in Long-term care Institutions (OGOLI; Richtlijn Mondzorg voor zorgafhankelijke cliënten in verpleeghuizen; Nederlandse Vereniging van Verpleeghuisartsen, 2007), was studied in several nursing homes in the Netherlands, using a longitudinal design. The main outcome variables were cognition and quality of life (QoL). The protocol for this randomized clinical trial (RCT) is presented in chapter 4. Over a hundred elderly persons suffering from dementia, attending daycare or receiving residential care, participated in the RCT. They were studied over a period of 6 months, and at several predefined moments, repeated measurements were taken (viz., at baseline, 6 weeks later, 12 weeks later, and 24 weeks later).

A test that assesses the ability to mix two-color (pink and blue) chewing gum samples through mastication was developed, for objectively measuring masticatory performance. It was found to have adequate sensitivity for change, and reliability, as described in chapter 5. Validity needs to be further established.

The associations between masticatory performance, measured with this mixing ability test, and cognition, assessed with a test battery of neuropsychological tests have been studied in the data from the baseline assessment. Positive associations
between masticatory performance and the cognitive functions global cognition and verbal fluency were found, and these results are discussed in chapter 6.

The results from the intervention were comparable to recent reports with regard to implementing the guideline. It was found that offering clinical lessons and support to the nursing staff was not enough to effectively change the oral health care routine. There were serious concerns with regards to implementation success, and these are described in chapter 7. Based on these results, it was decided to end the trial, and to focus on devising alternative approaches.

The final recommendation from this thesis, as described in chapter 8, is that daily oral health care for elderly persons suffering from dementia should be organized in the person of a designated, dedicated, oral care nurse. This is preferably someone who has received specialized training in both providing oral care and managing uncooperative and resistant behavior. We suggest that this is arranged as a specific profession, or job description, the ‘Denticure’.
SAMENVATTING

Kauwen en mondgezondheid bij ouderen met een dementie. De relatie met cognitie en kwaliteit van leven.

Mondzorg is een belangrijk onderdeel van de dagelijkse zorg voor ouderen. Mondzorg is vaak onvoldoende, zowel bij nog zelfstandig wonende ouderen als bij bewoners van verzorgings- en verpleeghuizen. Als de mondgezondheid verslechtert, neemt het risico op (onder andere) longontsteking, cardiovasculaire problemen zoals endocarditis (d.w.z. een ontsteking van de binnenkant van het hart en/of de hartkleppen) en beroertes, diabetes en zelfs de ziekte van Alzheimer ('Alzheimer's disease', AD) toe. Het verlies van kauwvermogen is geassocieerd met het verlies van cognitieve vermogens. Aangezien de cognitieve vermogens bij ouderen met dementie, zoals AD, kwetsbaar zijn, is het van groot belang om hen van adequate mondzorg te voorzien, om zo de algemene gezondheid en mogelijk de cognitie te behouden.

In dit proefschrift is de relatie tussen kauwen, cognitie en kwaliteit van leven (quality of life, QoL) bij ouderen met dementie onderzocht, zowel in de literatuur als in de klinische praktijk. Het onderwerp wordt geïntroduceerd in hoofdstuk 1, waar ook een beschrijving van de meest voorkomende subtypen van dementie wordt gegeven.

In hoofdstuk 2 wordt een overzicht van de beschikbare literatuur over de relatie tussen kauwen en cognitie gegeven. Uit dierexperimenteel onderzoek blijkt dat er een oorzakelijk verband bestaat tussen verminderte kauwactiviteit en cognitieve prestaties. Deze studies laten zien dat het stresssysteem (d.w.z. de hypothalamus-hypofyse-bijnier-as) waarschijnlijk een belangrijke rol speelt in deze relatie. Zo wordt bijvoorbeeld de neuronale groei beperkt door stress, een negatief effect dat kan worden tegengegaan door te kauwen. In studies met gezonde volwassenen bleek dat cognitieve prestaties verbeterden tijdens, of direct na, het kauwen op kauwgom. Dit tijdelijke effect verdwijnt nadat de deelnemer stopt met kauwen. Hoewel niet alle studies dezelfde effecten rapporteren en er bijvoorbeeld verschillen
zijn met betrekking tot de specifieke cognitieve domeinen, is er consensus over het bestaan van een algemeen positief acuut effect van kauwen op cognitie. De individuele verschillen in studieontwerp worden als een verklaring gegeven om de soms ogenschijnlijk tegenstrijdige resultaten te verklaren. Naast dit kortdurende effect van kauwen wordt er ook een langdurig effect gemeld, namelijk dat van een verbeterde cognitie door een verbeterde kauwfunctie als het gevolg van tandheelkundig herstel. Ouderen met een beter kauwvermogen presteren beter op een groot aantal neuropsychologische taken, en na een tandheelkundige herstelbehandeling met een prothese vertoonden deelnemers verhoogde doorbloeding van de hersenen, die geassocieerd is met betere cognitieve uitkomsten. Naast verminderde stress zijn andere mogelijke fysiologische mechanismen die deze resultaten kunnen verklaren: het positieve effect van een verrijkte omgeving als gevolg van sensorische input vanuit de mond, het positieve effect van toegenomen doorbloeding als gevolg van de kauwactiviteit, of een mediërend effect van voeding.

Het is ook mogelijk dat pijn een rol speelt. De aanwezigheid van pijn is echter moeilijk te diagnosticeren als deze niet spontaan aangegeven wordt (zelf-rapportage). Doordat ouderen met dementie vaak verminderd communicatief zijn, wordt hun pijn in het algemeen onderschat of onderbehandeld. Er zijn een paar observatieschalen voor pijndiagnostiek bij ouderen met dementie beschikbaar voor de klinische praktijk; deze worden besproken in hoofdstuk 3. Geen van deze schalen besteedt echter specifiek aandacht aan orofaciale pijn (d.w.z. pijn aan de mond en het gezicht). Typische algemene pijnkenmerken zijn: een verwrongen gezichtsuitdrukking of snel knipperen, een zware ademhaling, verbale uitingen (roepen, huilen) en afweer- of terugtrekkingsgedrag. Het verdient aanbeveling om typisch gedrag dat op orofaciale pijn kan duiden, zoals een veranderd eetpatroon, het maken van voorzichtige (d.w.z. kleine en/of langzame) mond bewegingen, het aanraken van het aangedane orofaciale gebied met de handen en/of het zich verzetten tegen mondzorg, in de observatieschalen op te nemen.


Er werd speciaal voor dit onderzoek een test ontwikkeld die het vermogen test
om tweekleurige kauwgom (roze en blauw) te vermengen door te kauwen, om zo objectief het kauwvermogen te kunnen meten. De test was voldoende gevoelig voor verandering en ook betrouwbaar, zoals wordt beschreven in hoofdstuk 5. De validiteit dient nog verder te worden onderzocht.

De associaties tussen kauwvermogen, gemeten met de mengvermogentest, en cognitie, gemeten met een testbatterij van neuropsychologische taken, werden be- studeerd aan de hand van de gegevens van de basismeting. Er werden positieve relaties gevonden tussen kauwvermogen en de cognitieve functies “globale cognitie” en “verbale fluency”. Dit wordt besproken in hoofdstuk 6.

De resultaten van de interventiestudie waren vergelijkbaar met recente andere publicaties over het implementeren van de richtlijn. Het bleek dat het aanbieden van klinische lessen en begeleiding aan de dagelijkse verzorgenden in ouderenzorg-instellingen niet genoeg was om de mondzorg wezenlijk te veranderen. Er waren ernstige zorgen met betrekking tot het implementatiesucces; dit wordt beschreven in hoofdstuk 7. Op basis van deze bevindingen werd besloten om de RCT te be- einigen en om te focussen op het vinden van alternatieve benaderingen.

De uiteindelijke aanbeveling van dit proefschrift, zoals beschreven in hoofdstuk 8, is om de dagelijkse mondverzorging van ouderen met dementie te organiseren in één persoon; een daartoe aangewezen, toegewijde mondverzorgende. Dit is bij voorkeur iemand die gespecialiseerde training heeft gehad, zowel op het gebied van mondzorg als ook in het omgaan met weigerachtig, tegenwerkend en afwerend gedrag. Wij stellen voor dat dit een apart beroep of een nieuwe functieomschrijving wordt, de ‘Denticure’.
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Roxane Weijenberg was born on January 8th, 1979, in Schinnen, the Netherlands. After completing her high school training (gymnasium β) at the Scholengemeenschap Sint Michiel in Geleen, she moved to Bilthoven, to study Biology at Utrecht University. She continued moving on a regular basis, until she settled down in the East of Utrecht. As biologist, she specialized in both neuro-ethology and environmental education. She spent a year teaching students of all ages (K–12, college and beyond) at the Wolfridge Environmental Learning Centre, in Minnesota, USA. During this stay, a great sense of wonder was instilled. After her graduation, she started her career at the faculty of Psychology and Education of the VU University, in the position of research policy officer. As such, she was involved in founding the William James Graduate School. Her enthusiasm and love for research did not go unnoticed, and she was offered a PhD position at the department of Clinical Neuropsychology, which she gladly accepted. This resulted in the current thesis that will be defended on December 18th, 2013. It is her strong wish and desire to be able to continue doing research that is both clinically relevant and satisfies her academic curiosity.
OUTCOMES

PUBLICATIONS INCLUDED IN THIS THESIS


OTHER PUBLICATIONS


OTHER RESULTS