General introduction

BACKGROUND

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\(^1\), 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)\(^2\). 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)\(^1\). AD is the most prevalent type of dementia, and is diagnosed in about 60% of the cases\(^3\); it is in the top ten (at number 6) of causes of death in the United States of America\(^4\). VaD is present in about 30% of those diagnosed with ‘dementia’\(^5\). 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\(^6\) 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\(^7,8\). For both types of dementia, prevalence numbers are increasing, among others due to new criteria\(^6,8\).

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 \(\beta\)-amyloid plaques and protein \(\tau\) tangles\(^4\) in the temporal-parietal and frontal areas of the brain, and also in the hippocampus, entorhinal cortex, and amygdala\(^9\). 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 α-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 velocity. 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)\textsuperscript{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.

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