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MASTICATION IN JAW MUSCLE PAIN

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The cover image illustrates a woman biting on an occlusal splint reflecting the overrepresentation of women among patients with TMD and exemplifying one of the main masticatory actions, biting. Photo credit: Samaa Al Sayegh.

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MASTICATION IN JAW MUSCLE PAIN

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my Father in heaven…

The more we learn, the less we know!

POPULAR SCIENCE SUMMARY

Patients with long-term pain of the jaw muscles are the most common patients at specialist oral-facial pain and jaw function clinics. Jaw-related facial pain affects about 10 to 20% of the adult population, being the second most common muscular pain after back pain. The frequency of occurrence is 1.5 to 2 times higher in women, however. Alongside chewing difficulties and headaches, oral-facial pain leads to individual suffering, reduced quality of life, higher rates of sick leave, high health and dental care costs, and various economic and social burdens on society. The annual costs in terms of human suffering and sick leave in Europe and US are estimated in billions. It is therefore important to investigate how human biting and chewing behaviours are affected by pain and dysfunction, as these functions are critically important for humans in order to ensure adequate nutritional intake.

The goal of this project was to increase knowledge and understanding of the chewing and biting functions and how these are affected by long-term muscular jaw pain. This increased understanding may eventually lead to improvements in existing treatments and procedures as well as the development of new tools and techniques to relieve patients' pain and/or improve their jaw function, thereby improving their quality of life. Such knowledge may also lead to improved oral rehabilitation methods that will benefit society by reducing the need for health and dental care interventions and resources and minimising the need for sick leave for affected patients.

Long-term jaw muscle pain seems to affect the chewing performance. Healthy pain-free individuals seem to have an ability to adapt their performance during chewing, while patients with pain exhibit a need to compensate.

ABSTRACT

Background: Integrated Pain Adaptation Models suggest a possible pain-motor interaction. Mechanisms affecting the jaw muscle spindles seem to affect the ability to bite and chew, suggesting that jaw muscle pain may be a potential modifier of mastication in humans.
Objectives: The general objective of this doctoral thesis was to investigate the mastication performance in patients with painful temporomandibular disorders (TMD) and, more specifically, clinical chronic pain within the masticatory muscles. ***Study I*** investigated the effects of chronic and acute jaw muscle pain on oral motor control during precision biting. ***Study II*** focused on the optimisation of excessive gum chewing as an experimental model to induce jaw muscle pain and fatigue similar to that seen in painful TMD. ***Study III*** focused on chewing performance in TMD patients with myalgia.
Methods and Results: ***Study I*** involved a comparison of patients with chronic masseter muscle pain and healthy participants. Experimental acute pain was induced by bilateral, simultaneous sterile hypertonic saline infusions into the healthy masseter muscles. A standardised hold and split biting task was used to assess precision biting. No significant differences were found in the hold forces, split forces or durations of split within or between the pain and pain-free conditions. ***Study II*** was a randomised, double-blinded study that included healthy participants of both sexes. A standardised chewing protocol of either 40- or 60-min of chewing was used, with a wash-out period. Subjective fatigue, pain characteristics, and functional measures were all assessed. Significant high subjective fatigue scores were induced in both the 40- and 60-min chewing trials. Significant but mild pain was induced only in the 60-min trial, and only in men. The induced pain area was significantly larger in the 60-min trial. The induced fatigue lasted up to 20 minutes after the end of the chewing while the increase in pain intensity and pain area did not until the first 10-min follow-up. ***Study III*** involved a series of chewing tasks involving viscoelastic soft and hard candies as well as a two-coloured gum. Optical imaging and analysis were conducted, and both bite force and the characteristics of pain and fatigue were assessed. Patients with painful TMD chewed the soft candies into particles that were fewer in number and which had a larger minimum Feret's diameter after standardised chewing as compared to healthy pain-free control individuals. Surprisingly, the two-coloured gum was less mixed in the control cases. However, there were significant differences between the patients and the healthy controls in terms of self-assessed masticatory ability, mainly driven by pain-related issues. There was also obvious agreement between the patients' self-assessed masticatory ability and the efficiency of their masticatory function.
Conclusion: The three studies that form this doctoral thesis suggest that jaw muscle pain does not affect precision biting in humans; however, TMD patients with chronic myalgia exhibit impaired masticatory performance, with less efficiency of food communition, than those in the pain-free healthy control group. However, the excessive chewing model needs further adjustments in order to mimic TMD-pain, especially in women.

LIST OF SCIENTIFIC PAPERS

I. **Al Sayegh S**, Borgwardt A, Svensson KG, Kumar A, Grigoriadis A, Christidis N.

Effects of Chronic and Experimental Acute Masseter Pain on Precision Biting Behavior in Humans.

Front Physiol. 2019 Oct 29; 10:1369. doi: 10.3389/fphys.2019.01369. eCollection 2019. PMID: 31736787

II. **Al Sayegh S**, Vasilatou I, Kumar A, Al Barwari C, Fredriksson L, Grigoriadis A, Christidis N.

Experimental Pain and Fatigue Induced by Excessive Chewing.

BMC Oral Health. 2020 Jun 29;20(1):179. doi: 10.1186/s12903-020-01161-z. PMID: 32600327

III. **Al Sayegh S**, Christidis N, Kumar A, Svensson P, Grigoriadis A.

Masticatory Performance in Patients with Jaw Muscle Pain.

Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
Borg's RPE	Borg's Rating of Preceived Exertion
CNS	Central Nervous System
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
DOMS	Delayed Onset Muscle Soreness
EBD	Evidence-based Dentistry
EBM	Evidence-based Medicine
EMG	Electromyographic
€	Euro
GAD	Generalized Anxiety Disorder
GCPS	Graded Chronic Pain Scale
GDPR	General Data Protection Regulation
IASP	International Association for the Study of Pain
IBS	Irritable Bowel Syndrome
ICD-11	International Classification of Diseases
ICOP	International Classification of Orofacial Pain
IQR	Interquartile Range
ISI	Insomnia Severity Index
JFLS	Jaw Function Limitation Scale
MOC	Mouth Opening Capacity
MVBF	Maximal Voluntary Bite Force
N	Number, Newton
NRS	Numeric Rating Scale
OBC	Oral Behaviour Checklist
OHIP	Oral Health Impact Profile
PCS	Pain Catastrophizing Scale
PHQ	Patient Health Questionnaires
PMR	Periodontal Mechanoreceptor
PPT	Pressure Pain Threshold
PSS	Precieved Stress Scale

QMF	Questionnaire of Masticatory Function
SD	Standard Deviation
SSS	Somatic Severity Scale
TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint
TSK-TMD	Tampa scale for Kinesiophobia
US$	US Dollar
WPI	Widespread Pain Index

1 INTRODUCTION AND SIGNIFICANCE

The idea underlying this scientific thesis arose at a clinic where patients with orofacial pain and temporomandibular disorders/dysfunction (TMD) come to seek help. These patients frequently suffer from chronic pain in the jaw muscles (myalgia/myofascial pain) and/or temporomandibular joint (TMJ) (arthralgia). The most common painful TMD diagnosis is myalgia/myofascial pain (Schiffman et al., 1990), though patients also often complain about restricted mouth opening capacity and chewing difficulties (Felício et al., 2002). These difficulties are described in terms of dysfunction limiting daily life activities (Tüzün, 2007; Von Korff et al., 1990). Such coexisting dysfunction is something that chronic orofacial pain shares with many other types of chronic pain (Maixner et al., 2011). Sadly, clinicians, in both medicine and dentistry fields, often feel incompetent handling these patients, and the lack of knowledge regarding orofacial pain is a significant barrier to appropriate pain management (Dahlgren et al., 2006; Steenks, 2007).

The complexity of orofacial chronic pain, including in cases of myofascial temporomandibular disorder, lies not only in the fact that it has a multifactorial biological and psychosocial aetiology (Fernández-de-las-Penas & Svensson, 2016; Greene & Research, 2010), but also in the fact that "The complexity increases due to the random pattern of how those different factors interact and the unpredictability of the generated individual outcome." (Svensson & Kumar, 2016). This interplay between pain and dysfunction remains an enigma that must be addressed, as whether pain leads to dysfunction or dysfunction causes pain is a question currently without a concrete answer. In order to treat pain, specifically chronic pain, and to rehabilitate the related function, the mystery of which is the causal factor must be unravelled. Given the current shortcomings in knowledge and management of orofacial pain, there is thus a huge need for progress in this field. Searching for biomarkers (Curatolo & Arendt-Nielsen, 2015) and investigations into effects of/on pain and dysfunction (Arendt-Nielsen & Graven-Nielsen, 2008) are ongoing, yet researchers must still resolve the conflicting findings and overlapping explanatory factors that have emerged, and which continue to emerge.

Chronic pain conditions frequently affect the orofacial region, with studies indicating a prevalence of between 5 and 33% worldwide (Isong et al., 2008; Macfarlane et al., 2004; Macfarlane et al., 2002; Macfarlane et al., 2001; Schiffman et al., 2014). "Temporomandibular disorders" is the collective term for all chronic pain conditions in the orofacial region that affect the masticatory muscles or the temporomandibular joint and any associated structures (Okeson & de Kanter, 1996). TMD has a prevalence of approximately 10 to 20% and an incidence of 2 to 4% (Bush et al., 1993; Isong et al., 2008; LeResche, 1997; Nilsson et al., 2007; Schiffman et al., 2014), being 1.5 to 2 times more prevalent in women than men. Around 5.2% of women have pain localised to the face and jaw at least once per week (Bush et al., 1993; Isong et al., 2008; LeResche, 1997; Schiffman et al., 2014; Svensson & Graven-Nielsen, 2001). One in six patients visits a general dentist because of orofacial pain (Horst et al., 2015), and patients with TMD who seek care are

usually women (Bush et al., 1993; Dworkin et al., 1990; Lipton et al., 1993). The prevalence of TMD becomes higher during adolescence and early adulthood, peaking at midlife (Isong et al., 2008; LeResche, 1997). Patients with TMD rate their average pain intensity at 4.3 using a 0 to 10 numeric rating scale; this is comparable to the average intensity of back pain (Von Korff et al., 1988). Further, TMD can cause impaired jaw mobility and masticatory function (Sato et al., 1996). Studies have shown that difficulties with vertical mouth opening and chewing are significantly more prevalent in TMD patients, who also display a unilateral chewing pattern, longer chewing times, and higher numbers of chewing strokes than controls (Felício et al., 2002; Felício et al., 2007). Chewing time and type thus correlate positively with TMD severity (Felício et al., 2007).

The hope for this thesis is that increased knowledge generated by research in the field of orofacial pain and dysfunction will, in the long run together with future results, lead to development of new diagnostic techniques and advanced therapies, enhancing the application of evidence-based dentistry in the rehabilitation of oral function. This will increase patients' quality of life by decreasing suffering, as well as causing the costs related to sick leave and healthcare to decrease (Steenks, 2007).

2 BACKGROUND

2.1 CLINICAL RESEARCH

Research begins with curiosity piqued by observation, continues with reasoning and experimentation, and ends with application and evaluation. These research elements are thus natural parts of the career of any clinician practicing evidence-based medicine, including dentistry, as clinical research should be an ongoing habit of those practicing healthcare (Nanivadekar, 2017; Wilton & Slim, 2012). Clinical research is the anchor that provides scientific evidence to support clinical experience in terms of appropriately diagnosing and treating patients. The main significance of clinical research lies in its role as a link in the chain of scientific work, which involves identifying and addressing knowledge gaps clinicians encounter while dealing with patients. It also facilitates clinicians staying up to speed with recent results from basic and translational investigations, allowing them to apply these in daily clinical decision-making (Chew, 2019). In order to improve patients' health outcomes, high quality cost effective evidence-based medicine and dentistry should be practiced at all times. Evidence-based medicine (EBM) can further be shaped by individual clinical expertise, the use of the best available research evidence, and patient values and circumstances (Sackett et al., 1996; Szajewska, 2018). EBM also aims to reduce bias in clinical trials; however, this should be done with caution in order for practitioners not to fall into the trap of ideological behaviour, and to instead embrace a humanitarian approach that respects the ongoing need for innovation (Kelly et al., 2015).

However, there are some other obstacles that complicate the conduction and prosecution of clinical trials. Funding restraints affect medical research in general and oral/dental research in particular, with much financial support restricted to the latest "hotness of the research field" (Szajewska, 2018); unfortunately, dentistry is rarely considered "hot" or seen as crucial when compared to other medical fields such as epidemiology and cancer research. On the other hand, researchers into chronic painful temporomandibular disorders may thus be spared some of the restraints placed on other oral/dental research fields, as these issues are believed to have similar mechanisms to chronic pain more generally. Hierarchies in and between various institutions and clinics acting as research sites; personal or institutional conflicts; or personal beliefs related to research topics can also be hindrances that may interfere with the conduction and completion of specific clinical research (Szajewska, 2018).

Many volunteers participating in clinical trials consider clinical research involving humans to be important within the struggle to develop and practice good medicine and dentistry; nevertheless, they also perceive their participation as time-consuming and inconvenient, noting that it interferes with their daily lives and routines (Anderson et al., 2018). Clinical research involving humans is dependent to a great extent on such volunteers' willingness to participate, which in turn is determined by various factors such as age, educational background, experiences, beliefs, and attitudes towards research and clinical trials (Trauth

et al., 2000). Unexpected circumstances, such as the Covid-19 pandemic, may also affect the willingness of participants as well as externally imposing the cancelling or rescheduling of ongoing human trials (Padala et al., 2020).

2.2 PAIN

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (International Classification of Orofacial Pain, 1st edition (ICOP), 2020). Pain can, however, be further classified according to temporal or aetiological categorisations: acute and chronic or nociceptive, neuropathic, nociplastic, idiopathic (pain of unknown origin) and mixed (Orr et al., 2017; Trouvin & Perrot, 2019).

Almost everyone will, at some point in life, experience some type of pain in their body and many will experience pain in the face. Fortunately, most such pain is transient, particularly where it is associated with a lesion or disease that will heal or can be cured over time. However, some types of pain are chronic and despite recent advances in the understanding, diagnosis and treatment of pain, chronic pain remains a significant public health problem (Sessle, 2012). Acute nociceptive pain refers to a physiological sensation which results from the activation of nociceptive pathways by the protective detection of noxious peripheral stimuli of sufficient tissue damaging intensity (Sherrington, 1906; Woolf & Ma, 2007). This protective mechanism helps prevent further injury by generating a perception of an unpleasant sensation which results in complex behavioural strategies to avoid further contact with such stimuli. A phenomenon that further enhances this protective function is the peripheral sensitisation of the nociceptive system that occurs after repeated or intense noxious stimuli which is triggered by the release of endogenous inflammatory substances. The threshold for system activation thus decreases, and responses to subsequent inputs are amplified (Ji et al., 2003; Woolf & Salter, 2000; Woolf & Walters, 1991). When an ongoing tissue injury ceases, this increased sensitivity gradually returns to the normal baseline levels.

However, persisting ectopic activity in the primary noxious neurons may eventually lead to central sensitisation (commonly known in animal research) or central hyperexcitability (clinically known in human research), defined as "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub threshold afferent input" by the International Association for the Study of Pain (IASP, 2019). Central sensitisation is reflected in hyperexcitability of second-order neurons in the subnucleus caudalis, which manifests as prolonged neuronal discharges, amplified responses to noxious stimuli, responses to non-noxious stimuli, and expansion of the receptive fields (Sessle, 2000). While acute pain plays the warning role with regard to potential tissue damage, central sensitisation triggers changes that generate pain hypersensitivity in order to limit the use of an injured body part until full healing is achieved. Central sensitisation is thus responsible for many temporal, and spatial changes as well as for reducing the pain sensibility threshold

and increasing the magnitude and duration of responses to noxious inputs in acute and chronic clinical pain conditions.

Central sensitisation is a result of the increased function of neurons and hyperactivity in nociceptive pathways caused by alterations in membrane excitability and increased synaptic efficacy, as well as reduced pain inhibitory transmission mediated by converging and diverging molecular factors that is affected by the structural plasticity of the somatosensory nervous system and various phenotypic modifications (Woolf & King, 1989). Phenotypic changes in the properties of myelinated neurons in the central nervous system (CNS) due to prolonged periods of central sensitisation as a result of persisting inflammation or nerve injury produce chronic pain hypersensitivity that is neither protective nor properly reflective of the presence, intensity, or duration of any noxious peripheral stimuli. Such central sensitisation becomes pathological and autonomous, offering a dynamic reflection of central neuronal plasticity and dysfunction in the somatosensory system which results in a shift from high-threshold nociception to low-threshold pain hypersensitivity. Pain may thenceforth arise spontaneously or be triggered by normal inputs that usually evoke nonpainful sensations (allodynia), as well as being evoked by progressive increases in responses to repeated unpainful stimuli. The latter process, commonly known as temporal windup in animal research but clinically referred to as temporal summation in human research, offers an exaggerated and prolonged response to painful stimuli (hyperalgesia) that spreads far beyond the site of injury (secondary hyperalgesia) (Latremoliere & Woolf, 2009; Woolf, 2011).

Pain hypersensitivity is a product of the chemical, structural, and functional plasticity of the central nociceptive system and may occur during both normal and pathological states; the difference between these is that pain hypersensitivity becomes pathological by persisting. There are two forms of central sensitisation, which represent two temporal phases: the early phosphorylation-dependent phase, which arises from rapid modifications that lie principally in the glutamate receptor and calcium channels, and the later transcription-dependent phase which drives the synthesis of new scaffolding proteins that are responsible for longer-lasting forms of pathological central sensitisation (Latremoliere & Woolf, 2009; Woolf & Salter, 2000; Woolf & Thompson, 1991). The first phase represents synaptic plasticity triggered in the CNS by intense, repeated and continuous noxious input, which does not necessarily require a peripheral injury (Woolf, 1983). Second-order neurons may develop spontaneous activity and begin to respond to subthreshold inputs, expanding their spatial cover by expanding their receptive fields, which leads in turn in to functional plasticity and changes in synaptic efficacy. Nociceptive-specific neurons may also convert to wide-dynamic neurons that respond to painful as well as unpainful stimuli, causing temporal windup (Ji et al., 2003; Woolf, 2007; Woolf & King, 1990; Woolf & Salter, 2000). Plasticity due to central sensitisation implies excitability in various different parts of the CNS (spinal nucleus pars caudalis, thalamus, amygdale, anterior cingulate cortex, parabrachial nucleus, periaqueductal grey PAG, superior colliculus, and prefrontal cortex) (Burstein et al., 1998; Dostrovsky & Guilbaud, 1990; Maihöfner et al., 2010; Mohr et al.,

2008; Moylan Governo et al., 2006; Neugebauer & Li, 2003; Neugebauer et al., 2003; Peyron et al., 2000; Shih et al., 2008; Wei & Zhuo, 2001), though activity-dependent central sensitisation is reversible when further triggering inputs are absent (Maeda et al., 2005; Zhang, Wu, Fang, et al., 2006; Zhang et al., 2005; Zhang, Wu, Lei, et al., 2006). With regard to longer-lasting pathological central sensitisation, however, transcription-dependent changes, generally a consequence of peripheral inflammation or nerve injury, are required. Some mechanisms involved in pathological central sensitisation are also responsible for activity-dependent central sensitisation, while others are unique to either inflammation or nerve injury (Neumann et al., 1996; Samad et al., 2001; Vardeh et al., 2009). Microglial cells also play an important role in contributing to the development of central sensitisation based on them changing their shape, function, and chemical expression (Honore et al., 2000; Raghavendra et al., 2004; C. I. Svensson et al., 2003; P. Svensson et al., 2003).

In primary musculoskeletal pain conditions such as fibromyalgia and complex regional pain syndrome, patients generally complain about persisting pain. Such conditions, where pain is neither nociceptive nor neuropathic, have created the need for a new descriptor: nociplastic pain. Nociplastic pain is thus defined as altered nociception where there is no evidence of tissue or somatosensory damage (Kosek et al., 2016). Chronic secondary musculoskeletal pain seems to share an underlying and under investigated mechanism with such primary conditions, and there is some evidence suggesting that central sensitisation is the mechanism to blame (Trouvin & Perrot, 2019). Chronic TMD pain may thus be described with this terminology and explained by such mechanisms.

Pain induces changes in both superficial and deep sensitivity in patients with craniofacial muscle pain, and studies have reported both hypo-algesic and localized and generalized hyper-algesic responses, though predominantly the latter (Maixner et al., 1995; Maixner et al., 1998) as well as secondary hyperalgesia in referred pain areas (Graven-Nielsen & Arendt-Nielsen, 2002). Deep tissue hyperalgesia within the local pain area in patients with craniofacial muscle pain has also been observed, which is probably a result of a peripheral sensitisation (Mense, 1977, 1981, 1993; Mense & Meyer, 1988). In contrast to experimental muscle pain studies in healthy subjects, in which deep hypoalgesia outside the local pain area was generally observed, generalised deep tissue hyperalgesia has been reported in patient studies, suggesting a sensitisation of second-order neurons in the brain stem, a decrease in efficacy in pain inhibiting systems, and an imbalance between descending facilitatory and inhibitory pain control systems (Berberich et al., 1988; Coderre et al., 1993; Hu et al., 1992; Maixner et al., 1998; Millan, 1999; Wei et al., 1999). Temporal summation of muscle pain is also more pronounced than skin pain, which is, together with the wind-up phenomenon seen in central neurons (second-order neurons in the subnucleus caudalis), thought to be related to the longer-lasting central sensitisation seen in many patients with chronic muscle pain (Svensson & Graven-Nielsen, 2001; Wall & Woolf, 1984; Wright et al., 2002). Many patients with craniofacial pain also have unrecognised pains in other parts

of their bodies, which may thus explain why studies highlight generalised changes in somatosensory sensitivity in such cases (Türp et al., 1997).

Several different theories to explain the interactions between pain and motor dysfunction have been proposed. However, the vicious cycle theory (Travell et al., 1942) and the pain adaptation model (Lund et al., 1991) both propose generalised changes in muscle activity and have thus been rejected as not applicable in all pain-dysfunction scenarios (Svensson & Graven-Nielsen, 2001; Svensson et al., 1998). The vicious cycle theory suggested that increased activity in agonist muscles led to spasm and further pain and dysfunction, while the pain adaptation model suggested a decrease in the activity of agonist muscles as an adaptation to pain in order to prevent tissue damage. The new theory of pain adaptation (Hodges & Tucker, 2011) and the integrated pain adaptation model (Murray & Peck, 2007; Stohler, 1999; Svensson & Graven-Nielsen, 2001) instead proposed the re-organisation of muscle activity to maintain motor function despite noxious stimulation. This re-organisation is suggested to be accomplished by the recruitment and de-recruitment of single motor units in painful and non-painful synergistic muscles, generated by firing changes in the thresholds, rates, or sequences (Ferreira et al., 2020; Hodges et al., 2008; Malik et al., 2018; Minami et al., 2013). Further, this reorganisation is suggested to be modulated by the individual psychosocial aspects associated with a given painful experience.

Nociceptive stimulation may thus modulate motor units in the jaw muscles by changing the spatial and temporal distribution of the electromyographic activity (EMG) in order to optimise muscle performance (Santana-Mora et al., 2009). This suggested mechanism would be helpful during acute pain to protect the muscles; however, it would be harmful as a long-term strategy, as spatial reorganisation may lead to overuse of specific areas of the muscle and contribute to persistent muscle pain. During prolonged low-level contractions, the smaller motor units are continuously active, which can lead to muscle fibre degeneration, increases in Ca^{2+} and cytokine release, and energy reduction, all of which have been associated with the onset of muscle pain (Castroflorio et al., 2012). Patients with jaw muscle pain do not show a reduced maximum bite force compared with healthy controls and some even displayed less masseter muscle fatigue during sustained contraction tasks. However, such patients do make a slower recovery than the healthy controls after the end of such tasks (Hagberg et al., 1986; Lyons & Baxendale, 1995). This may be explained by the possibility that only a small part of the muscle is affected by pain, indicating selective activation of motoneurons by the CNS to recruit either the whole or parts of a muscle depending on the task at hand (Blanksma & van Eijden, 1995). During maximum voluntary effort, the patients may thus be able to overcome the protective limitation of pain to produce a near-normal maximal force.

In both experimental and clinical studies, all participants are different individuals and an individual's response to pain may be considered to be a unique interaction of the facets of a given sensory-motor system. It has thus been suggested that, as an individual's experience

of pain varies, an individual's motor response must do so as well (Bair et al., 2013; Ohrbach et al., 2013). Pain may therefore have different effects on jaw sensory-motor function in different individuals due to individual variability in both perceptions of pain and behavioural responses, including pain catastrophising, fear-avoidance of movement, and endurance responses (Akhter et al., 2014; Coghill, 2010; Hasenbring, 2000; Hasenbring & Verbunt, 2010; Loeser & Melzack, 1999; Quartana et al., 2009). It has also been suggested that an individual's reaction to pain may depend on the specifics of the required task (Sae-Lee, Whittle, Forte, et al., 2008; Sae-Lee, Whittle, Peck, et al., 2008).

Pain is a subjectively unpleasant experience, and the influence of pain not only leads to an unpleasant sensory experience, it is often also accompanied by an unpleasant emotional experience (International Classification of Orofacial Pain, 1st edition (ICOP), 2020), with feelings of failure, misery, guilt, alienation, and even depression being possible (Thomas, 2000). These may affect patient quality of life considerably (Dahlström & Carlsson, 2010), increasing individual disability and suffering. Physical capabilities, social relations, and learning abilities are also negatively affected, along with sleep (Palermo & Kiska, 2005). This clarifies why patients with pain in the orofacial region also frequently display psychological suffering, impaired social relations, chronic fatigue syndrome, and recurrent sick leave (Maixner et al., 2011) or absences from school caused by sleep disturbances (Yatani et al., 2002).

Chronic musculoskeletal pain disorders are now a major clinical problem, affecting nearly one-third of the world's population (Breivik et al., 2006) and being the most common cause of reduced work capacity and sick leave. These conditions are associated with huge costs with approximately US$150 billion per year spent on medical expenses within the United States alone (Yelin & Callahan, 1995). The total yearly cost during 2012 of such disorders was estimated to be as high as US$600 billion (Gaskin & Richard, 2012). In Europe, approximately 20% of adults suffer from chronic musculoskeletal pain, and the yearly cost was estimated to be €34 billion (Breivik et al., 2006).

2.2.1 EXPERIMENTAL PAIN

In order to investigate the relationship between pain and jaw function, several experimental studies have induced pain, mainly chemically, in healthy subjects (Svensson & Graven-Nielsen, 2001). In one experimental study, experimental pain in the masseter muscle induced decreased EMG during mastication (Svensson et al., 1997), though in another study, experimental pain in the masseter muscle had only a minor impact on the performance of mastication, probably due to a lack of exacerbation of pain during that function (Shimada et al., 2015). Previous studies using experimental jaw muscle pain models also suggest that experimental acute pain has no detectable effect on the hold and split forces or split duration during biting (Kumar, Castrillon, Svensson, et al., 2015; Kumar, Castrillon, & Svensson, 2015; Svensson et al., 1997). The use of pain models that mimic natural pain conditions is essential to increasing knowledge about clinical pain, and experimental pain models provide information about muscle pain in healthy homogenous

subjects in a standardised and controlled manner, allowing quantitative assessment without the risk of confounding factors (Graven-Nielsen, 2006). However, the results remain contradictory, depending on the study populations examined, methodological differences in the experimental models used, and the type and duration of the assessments carried out.

2.3 MASTICATION

Mastication is the first step of digestion, creating a reduction in food particle size that facilitates further break down by the salivary enzymes before food is swallowed (van der Bilt et al., 2006). Mastication is a complex action that involves the facial primary somatosensory and motor cortex, the cortical masticatory area, a central pattern generator located in the brainstem, the jaw muscle spindles, the temporomandibular joint receptors, the periodontal mechanoreceptors (PMRs), the pulpal mechanoreceptors, and several other orofacial structures (Dellow & Lund, 1971; Grigoriadis et al., 2014; Lund, 1991; Lund & Kolta, 2006; Nozaki et al., 1986; Trulsson, 2006; Trulsson & Johansson, 1996a, 2002; Türker, 2002; van der Bilt et al., 2006). Thus, if any one of these components is affected, mastication may become impaired. Several reports have indicated that PMRs, which are activated when force is applied on a tooth, play an important role in the motor control of jaw muscles during chewing (Grigoriadis et al., 2011; Lund & Kolta, 2006; Svensson & Trulsson, 2011). PMRs collect information about contact between the teeth and food for further processing by the CNS in order to execute appropriate motor control of the jaw closing muscles (Svensson & Trulsson, 2009, 2011). The PMRs and all the other orofacial structures participating in the chewing process are, however, innervated by a single nerve, the trigeminal nerve, though the fibres terminating in subnucleus interpolaris are larger and faster than those fibres from facial areas that terminate in the subnucleus caudalis (Capra & Dessem, 1992), which may confirm the importance of PMRs, which terminate in subnucleus interpolaris, with regard to fine motor control during chewing. However, many patients with TMD, even those with healthy periodontia, complain about chewing difficulties, such as finding it hard to chew hard, rubbery foods or difficulties in opening their mouths wide enough. This implies that the chewing pattern, the time of chewing, and the number of chewing strokes are all regulated by other structures alongside PMRs. One such structure which appears to be important in this regard is the muscle spindles.

2.4 MUSCLE SPINDLES AND MOTOR UNITS

A major proportion, 85%, of the jaw muscle activity needed for crushing food is peripherally induced (Ottenhoff et al., 1992). Muscle contraction is regulated by muscle spindles, which are the sensory receptors within the belly of a muscle that primarily exist to detect changes in the length of that muscle. In the case of the jaw, they convey information to the trigeminal nuclei about jaw muscle length, proprioception and velocity of contraction to the CNS via sensory neurons. Muscle spindles are innervated by afferent sensory and efferent motor neurons, of which there are three types: alpha, gamma, and beta motor neurons, which innervate different muscle spindle fibres. Extrafusal fibres are innervated by alpha motor neuron and then generate tension by contracting, thereby initiating muscle

contraction. Intrafusal fibres, on the other hand, are innervated by gamma motor neurons. Unlike alpha motor neurons, gamma motor neurons do not directly adjust the lengthening or shortening of muscles; their main role is in keeping muscle spindles taut, thereby allowing the continued firing of alpha neurons, which in turn leads to muscle contraction. These neurons also play a role in adjusting the sensitivity of muscle spindles, together with beta motor neurons, which innervate both extrafusal and intrafusal muscle cells (Burke et al., 1979; Hunt, 1951).

A motor unit is made up of a single motor neuron and the skeletal muscle fibres innervated by that motor neuron (Buchthal & Schmalbruch, 1980). The multiple motor units in a single muscle thus form a motor neuron pool. There are several different types of motor units, which affect the magnitude of exerted force, the velocity of contraction and the resistance to fatigue; these are Fast fatigable (FF, Type IIb), Fast fatigue resistant (FR, Type IIa), Fast intermediate (FI, Type IIi), and Slow (S, Type I) (Altshuler et al., 2010; Burke et al., 1973; Collatos et al., 1977). The smaller motor units, which have slow twitch fibres that generate low-force and are fatigue-resistant, are activated prior to the recruitment of the fast twitch, high-force, less fatigue-resistant muscle fibres. While the exact sequence of this recruitment depends on the required force, corresponding to the size of load apposed on the muscle, larger motor units are typically composed of faster muscle fibres that generate higher forces (Robinson, 2009).

The muscle spindles assist the brain in determining mandibular position and movement (Hulliger, 1984). Muscle spindles are also believed to be involved in adaptation of chewing forces to food hardness. Based on previous animal experiments (Lavigne et al., 1987; Liu et al., 1993; Morimoto et al., 1989) and human studies (Foster et al., 2006; Woda et al., 2006), the firing frequency of muscle spindles in the jaw closing muscles is dependent on the hardness of the object being chewed. Muscle activity in the jaw closing muscles is enhanced with increased food hardness based on sensory feedback from the periodontal receptors and the spindle afferents. Further, the prediction of food properties, based on information obtained during previous chewing cycles (feed forward) and the changing mechanical and rheological properties of food during mastication, plays a role in regulating jaw muscle activation during the jaw closing phase (Abbink et al., 1999; Grigoriadis et al., 2014). The importance of muscle spindles has been further confirmed by a study showing that experimental blockage of muscle spindles and their afferent input via the trigeminal nerve reduced activity in the jaw muscles (Hidaka et al., 1999). Thus, mechanisms affecting the muscle spindles are likely to affect the ability to bite and chew.

3 AIM

3.1 GENERAL AIM

Studies investigating objective mastication performance in patients with painful TMD and, more specifically, clinical chronic pain from the masticatory muscles or the temporomandibular joints are needed, alongside subjective examination of their mastication abilities; these are required, as both objective and subjective aspects are of importance in evaluating the masticatory function (Pedroni-Pereira et al., 2018; van der Bilt, 2011). The ways in which chronic pain may affect the masticatory function still require further investigation due to a paucity of focused studies, however, despite several studies assessing jaw movements and masticatory performance objectively in other patient groups such as older adults, denture wearers, and patients with dental implants having been undertaken (Eberhard et al., 2015; Grigoriadis et al., 2011; Grigoriadis et al., 2016; Kapur & Soman, 2006; Kohyama et al., 2003; Mioche et al., 2004; Rissin et al., 1978; Weijenberg et al., 2013; Witter et al., 2013). Furthermore, no studies have investigated the effects of clinical chronic pain on precision biting, despite pain seeming to have a significant impact on maximal bite forces (Goiato et al., 2017; Xu et al., 2017). It is thus important to investigate masticatory behaviours in patients with clinical chronic myalgia, to determine if and how pain affects the chewing performance. Such investigation could also confirm any possible interactions between pain and jaw dysfunction.

3.2 SPECIFIC OBJECTIVES

1. To investigate the effects of chronic and acute jaw muscle pain on oral motor control during precision biting and to compare this with precision biting in pain-free healthy controls. (***Study I***)

2. To optimise excessive gum chewing as an experimental model to induce jaw muscle pain and fatigue similar to those observed in painful TMDs based on durations that allow immediate investigation of jaw-motor function. In addition, to determine whether there are any sex differences in pain expression detected in this experimental model. (***Study II***)

3. To investigate how chewing performance in TMD patients with myalgia is exhibited as compared to that seen in healthy pain-free controls. (***Study III***)

4 HYPOTHESIS

4.1 GENERAL HYPOTHESIS

The general hypothesis of the thesis is that jaw muscle pain may be a potential modifier of mastication and of jaw motor control (Arendt-Nielsen & Graven-Nielsen, 2008; Clark et al., 1984). Mechanisms affecting the muscle spindles seem to affect the ability to bite and chew (Foster et al., 2006; Hidaka et al., 1999; Hulliger, 1984; Lavigne et al., 1987; Liu et al., 1993; Morimoto et al., 1989; Woda et al., 2006), and applying Integrated Pain Adaptation Models suggests a possible pain-motor interaction (Hodges & Tucker, 2011; Murray & Peck, 2007; Peck et al., 2008).

4.2 SPECIFIC HYPOTHESES

1. Chronic jaw muscle pain affects precision biting behaviour, which will be reflected in higher holding forces and longer duration of the split phase during the biting task (Capra et al., 2007; Goiato et al., 2017; Nicholas, 2007; Svensson & Trulsson, 2011; Xu et al., 2017). On the other hand, experimental acute jaw muscle pain is not hypothesised to alter fine motor control and thus should not affect the hold force and split duration in healthy participants (Kumar, Castrillon, & Svensson, 2015). (***Study I***)

2. Excessive hard gum chewing induces jaw muscle pain and fatigue mimicking clinical pain and fatigue in TMD patients (Christensen et al., 1996; Farella et al., 2001; Koutris et al., 2009; Louca Jounger et al., 2017; Slade et al., 2013). Further, this induced pain and fatigue will last longer in women than in men (LeResche, 1997) and longer chewing durations are needed in order to induce fatigue and pain in men. (***Study II***)

3. Chronic jaw muscle pain impairs the capacity for grinding food, reflected by the generation of larger food particles and a larger variance of hue values in the mixing test (Clark et al., 1984; Felício et al., 2002; Felício et al., 2007; Goiato et al., 2017; Sato et al., 1996; Shimada et al., 2015; Svensson et al., 1997; Xu et al., 2017). (***Study III***)

5 METHODOLOGY

This thesis includes three studies. Two of these were clinical studies that included both patients and control participants, ***Study I*** (Al Sayegh et al., 2019) and ***Study III*** (Al Sayegh et al., 2021 – Manuscript) while the other, experimental study, ***Study II*** (Al Sayegh et al., 2020), included only healthy participants.

5.1 PARTICIPANTS

Patients were recruited by means of an advertisement distributed among TMD patients referred to the specialist clinic for orofacial pain and jaw function at the University Dental Clinic at the Karolinska Institute, Huddinge, Sweden and among TMD patients referred to the specialist clinic for stomatognathic physiology at the Folktandvården of the Eastman Institute, Stockholm, Sweden. The studies thus initially included 42 patients in total, 32 women and 10 men, of whom 38 patients in total, 30 women and eight men, completed the studies. Four individuals (two women and two men) dropped-out during ***Study I***. The demographic distribution of the patients is presented in Table 1.

The healthy pain-free participants were recruited by means of an advertisement distributed among patients attending for other issues and staff and students at the University Dental Clinic at Karolinska Institute, Huddinge, Sweden. The healthy pain-free participants included in the studies numbered 73 individuals in total, 48 women and 25 men. The healthy participants selected were age and sex matched to the patients in ***Study I*** and ***Study III*** insofar as possible. Four women dropped-out during ***Study I*** and four women did not participate in the second session in ***Study II***, however. The demographic distribution of the healthy participants is also presented in Table 1.

Different individuals were included in the different studies; all participants receive detailed oral and written information about the objectives and procedures of the specific study in which they were involved, as well as completing an informed written consent form prior to participation. The protocols followed good clinical practice and were developed and implemented in accordance with the guidelines of the Declaration of Helsinki. All the obtained data were then handled according to the applicable Swedish law, Datalagen 1998:204, and European law, the General Data Protection Regulation (GDPR).

5.1.1 INCLUSION AND EXCLUSION OF PARTICIPANTS

For *patients,* the general inclusion criteria were as follows:

1. Aged over 18 years
2. Women and men
3. A diagnosis of local myalgia or myofascial pain or myofascial pain with referred pain in the masseter muscle, with or without temporal myalgia, according to the diagnostic criteria for temporomandibular disorders (DC/TMD) (Schiffman et al., 2014)
4. Pain duration of at least 3 months

5. Current pain with a minimum score of 3 (***Study I***) or 4 (***Study III***) based on the Numeric pain Rating Scale (NRS 0-10) (Downie et al., 1978)

Additional criteria for inclusion were added by study:

6. Intact natural central incisors with a normal relationship to antagonistic teeth (***Study I***) and natural teeth within positions 13 to 16 and 23 to 26 with normal relationships to antagonistic teeth (***Study III***)
7. Individuals capable of protruding the lower jaw in order to perform the hold and split task (***Study I***)
8. At least two premolar/molar occlusal contacts per side in the intercuspal position (***Study III***)

For *patients,* the general exclusion criteria were as follows:

1. A diagnosis of arthralgia, degenerative joint disease, or painful jaw clicking or poping/locking according to DC/TMD (Schiffman et al., 2014)
2. Clinically visible dental pathology or mobility, toothache, malocclusions, or tooth wear of grade 3 (exposure of pulp or secondary dentine according to the simplified scoring criteria for tooth wear index I) (López-Frías et al., 2012)
3. Edentulous areas or dentures
4. General chronic pain conditions or systemic inflammatory diseases such as fibromyalgia, rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis.
5. Neuropathic pain or neurological disease such as myasthenia gravis, or craniomandibular dystonia.
6. Whiplash associated disorder
7. Use of any medication that might influence pain response such as analgesics during the 24 hours preceding the experiment, use of cannabinoids, or any medication that might influence neurological function
8. Allergy to any of substances such as food or gum used in the experiment
9. Pregnancy or lactation
10. Any cognitive or physical disability that would impede participation.

Additional criteria for exclusion from particular studies included:

11. Earlier trauma or root-canal treatments or fixed prosthodontics (implants, bridges, or crowns) in the anterior teeth (***Study I***)
12. Orthodontic retainers (***Study I***)
13. Multiple root-canal treatments, single fixed implant prostheses, or tooth-supported or implant-supported bridges within positions 13 to 16 and 23to 26 (***Study III***)

For *healthy participants* the general inclusion criteria were as follows:

1. Aged over 18 years
2. Women and men
3. Good general health.

The additional criteria for inclusion for specific studies were:

4. Intact natural central incisors with a normal relationship to antagonistic teeth (***Study I***) and natural teeth within positions 13 to 16 and 23 to 26 with normal relationships to antagonistic teeth (***Study III***)
5. Individuals capable of protruding the lower jaw to perform the hold and split task (***Study I***)
6. At least two premolar/molar occlusal contacts per side in the intercuspal position (***Study III***)

For *healthy participants,* the general exclusion criteria were as follows:

1. Any diagnosis of myalgia or myofascial pain arthralgia, degenerative joint disease, or painful jaw clicking or poping/locking according to DC/TMD (Schiffman et al., 2014)
2. Additional palpatory tenderness of the masseter or temporalis muscles, or over the TMJ
3. Clinically visible dental pathology or mobility, toothache, malocclusions, or tooth wear of grade 3 (exposure of pulp or secondary dentine according to the simplified scoring criteria for tooth wear index I) (López-Frías et al., 2012)
4. Edentulous areas or dentures
5. General chronic pain conditions or systemic inflammatory diseases such as fibromyalgia, rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis.
6. Neuropathic pain or neurological disease such as myasthenia gravis or craniomandibular dystonia.
7. Whiplash associated disorder
8. Use of any medication that might influence pain responses such as analgesics taken during the 24 hours preceding the experiment, use of cannabinoids, or any medication that might influence neurological function
9. Allergy to any of the substances such as food or gum used in the experiment
10. Pregnancy or lactation
11. Any cognitive or physical disability that would impede participation

Additional criteria for exclusion from specific studies included:

12. Earlier trauma, root-canal treatments or prosthodontics (implants, bridges, crowns) in the anterior teeth (***Study I***)
13. Orthodontic retainer (***Study I***)
14. Self-reported bruxism or chewing gum for more than 30 minutes on a daily basis (***Study II***)
15. Multiple root-canal treatments, single fixed implant prostheses, or tooth-supported or implant-supported bridges within positions 13 to 16 and 23 to 26 (***Study III***)

Table 1. Distribution of the number and age of patients and healthy volunteers.

	Study					
	I		II		III	
	n	Age	n	Age	n	Age
Patients						
All Included	22	34 (12.00)	-	-	20	27 (9.00)
Women Included	16	35 (13.00)	-	-	16	27 (9.00)
Men Included	6	30 (7.00)	-	-	4	29 (7.00)
Women Drop-outs	2	56 (6.00)	-	-	-	-
Men Drop-outs	2	34 (10.00)	-	-	-	-
All Completed	18	31 (9.00)	-	-	20	27 (9.00)
Women Completed	14	32 (10.00)	-	-	16	27 (9.00)
Men Completed	4	29 (5.00)	-	-	4	29 (7.00)
Healthy Participants						
All Included	22	33 (11.00)	31	26 (5.00)	20	27 (9.00)
Women Included	16	34 (13.00)	16	25 (4.00)	16	27 (10.00)
Men Included	6	30 (6.00)	15	27 (5.00)	4	29 (6.00)
Women Drop-outs	4	22 (4.00)	4	22 (4.00)	-	-
Men Drop-outs	-	-	-	-	-	-
All Completed	18	32 (11.00)	27	27 (5.00)	20	27 (9.00)
Women Completed	12	33 (13.00)	12	26 (4.00)	16	27 (10.00)
Men Completed	6	30 (6.00)	15	27 (5.00)	4	29 (6.00)

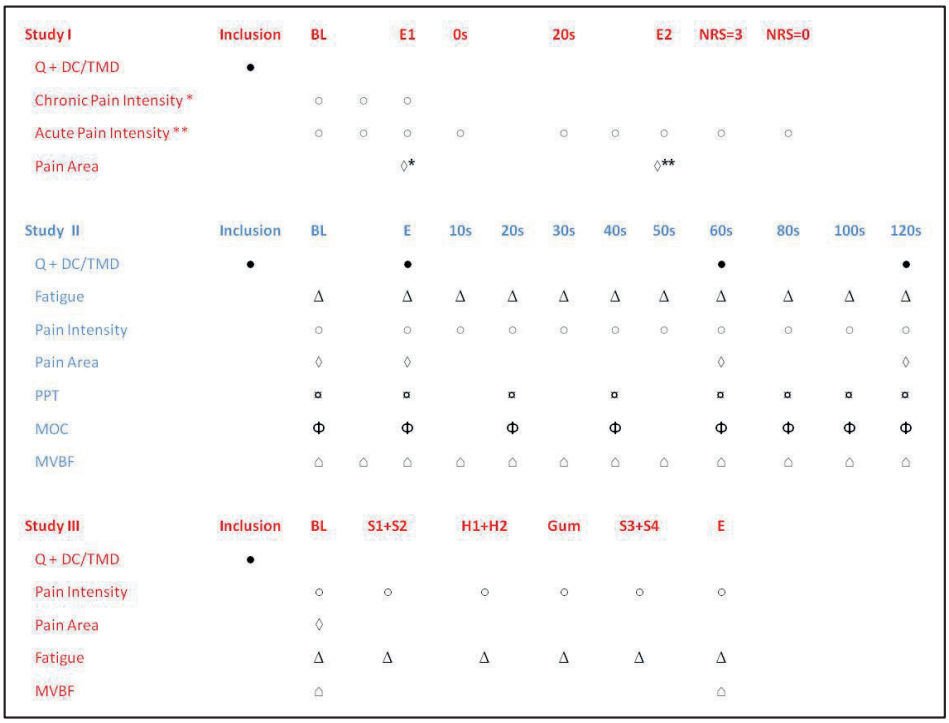
n= number of participants. Age values are expressed in mean (SD) of years.

5.2 CLINICAL EXAMINATION

All examinations in all three studies were performed by trained examiners to a calibrated standard using a standardised mechanical algometer/palpometer with pressures of 0.5 and 1.0 kg (Palpeter®, Sunstar Suisse SA, Aarhus University, Denmark). All participants were clinically examined by a dentist, extra- and intra-orally prior to inclusion. The experimental protocols for all studies (***Study I-III***) are shown in Figure 1. Diagnoses and eligibility were established according to the Diagnostic Criteria of Temporomandibular Disorders (DC/TMD) (Schiffman et al., 2014), an improved version of the previous Research Diagnostic Criteria of TMD (RDC/TMD) (Dworkin & LeResche, 1992; Dworkin et al., 2002). DC/TMD criteria and TMD-diagnoses associated with pain, including myofascial pain, were adopted based on the International Classification of Orofacial Pain (ICOP), aligned with the International Classification of Diseases (ICD-11) and the International Classification of Headache Disorders (ICHD-3) ("International Classification of Orofacial Pain, 1st edition (ICOP)," 2020). The DC/TMD includes:

- **Axis I** – A screening tool for detecting pain-related TMD physical signs and symptoms with a sensitivity of >= 0.86 and a specificity of >= 0.98.
- **Axis II** – A screening and a self-assessment instrument for assessing psychological, behavioural, and disability factors, as well as co-morbid pain conditions.
- An additional **Axis III** – This is proposed and yet to be established; it is currently undergoing development through active research. However, Axis III hopes to offer a tool for assessing biomarkers and risk factors for orofacial pain (Svensson & Kumar, 2016).

Figure 1. Experimental Protocols for ***Studies I-III***.



Assessment points for included variables in each study (***Study I-III***) are shown. Q = questionnaires; DC/TMD = clinical examination; PPT = pressure pain threshold; MOC = mouth opening capacity; MVBF = maximal voluntary bite force; BL = baseline; E = end of experiment; NRS = numeric rating scale; s = seconds; S = soft candy; and H = hard candy.

5.3 QUESTIONNAIRES

The questionnaires that participants were asked to complete varied across the three studies (***Study I-III***). Overall, however, validated and reliable questionnaires were used as instruments in each case to assess multiple subjective variables regarding pain, oral health, jaw function, chewing ability, fear of movement, and various psychosocial aspects. Several such instruments are included in Axis II of DC/TMD (Schiffman et al., 2014), and the questionnaires adopted from this selection were:

- the graded chronic pain scale (GCPS-7), used to assess severity of chronic pain and related disability (Von Korff et al., 1992)
- the oral health impact profile (OHIP-14), used to assess how the respondent's oral health is subjectively perceived by them (Larsson et al., 2004)
- the oral behaviour checklist (OBC-21), used to assess oral parafunctional behaviours (Markiewicz et al., 2006)
- the jaw function limitation scale (JFLS-20), used to assess how jaw function and ability is subjectively affected (Oghli et al., 2019; Ohrbach et al., 2008)
- the questionnaire of masticatory function (QMF-28), used to assess masticatory function and ability subjectively (Muller et al., 2008)
- the modified Tampa scale for Kinesiophobia for temporomandibular disorders (TSK-TMD-18), used to assess the fear of jaw movement (Visscher et al., 2010)
- the widespread pain index (WPI) and the somatic severity scale (SSS), used to assess generalised pain and symptoms of fibromyalgia (Häuser et al., 2012)
- the Diagnostic Criteria for Irritable Bowel Syndrome (Rome-IV), used to assess stomach related pain and symptoms of irritable bowel syndrome (IBS) (Palsson et al., 2016)
- the pain catastrophizing scale (PCS-13), used to assess pain-related catastrophical thoughts (Kemani et al., 2019)
- the patient health questionnaire 9 (PHQ-9), used to assess symptoms of depression (Kroenke et al., 2001)
- the patient health questionnaire 15 (PHQ-15), used to assess somatic symptom severity (Kroenke et al., 2002)
- the generalized anxiety disorder scale (GAD-7), used to assess symptoms of anxiety (Spitzer et al., 2006)
- the perceived stress scale (PSS-10), used to assess subjectively perceived stress (Nordin & Nordin, 2013)
- the insomnia severity index (ISI-7), used to assess severity of sleep disturbance (Bastien et al., 2001)

PHQ-9, PHQ-15, GAD-7, and PSS-10 were applied in all three studies (***Study I-III***). PHQ-9 is a validated questionnaire measuring depression, being a version of the PRIME-MD diagnostic for mental disorders (Spitzer et al., 1999). It has nine items, each scored from 0 to 3; these are summed to create an overall score that is assessed by severity grade: normal (0 to 4 points), mild (5 to 9 points), moderate (10 to 14 points), moderately severe (15 to 19 points), and severe (20 to 27 points). The nine items are based on the criteria for mental disorders used in the DSM-IV diagnostic criteria for depressive disorders.

PHQ-15 measures nonspecific physical symptoms or somatization in patients, which can be caused by anxiety, depression and stress. It consists of 15 items, which are each graded 0 to 2. When summed, these allow the overall PHQ-15 to be graded from normal to severe with regard to nonspecific physical symptoms: normal (0 to 4 points), mild (5 to 9 points), moderate (10 to 14 points) and severe (15 to 30 points).

The GAD-7 questionnaire consists of seven items, and it is used to measure anxiety and identify possible cases of generalised anxiety disorder. The items in the questionnaire are graded 0 to 3 and the total score is ranked according to severity into normal (0 to 4 points), mild (5 to 9 points), moderate (10 to 14 points), and severe (15 to 27 points). High GAD-7 scores are connected to depression and functional impairment in patients.

PSS-10 is a validated measurement for stress that consists of 10 questions, each graded 0 to 4; the overall score is then divided by severity into no stress (0 to 12 points), a moderate degree of stress (13 to 20 points), and a severe degree of stress (21 to 40 points). This measures the individual's perception of external demands within the everyday life and whether life has been unpredictable and overloading in the last month.

5.4 INDUCTION OF PAIN AND FATIGUE

The hypertonic saline model has been one of the most commonly used experimental human muscle pain methods since the 1930s, mainly due to the safety of the model (Kellgren, 1938; Lewis, 1938). It can be administrated as either injections or infusions (Svensson & Graven-Nielsen, 2001), though infusions allow continuous and more standardised and controlled induction of pain, as well as better manipulation of pain intensity (Zhang et al., 1993). The pain thus induced mimics the somatosensory and motor effects involved in acute clinical muscle pain, and it is described as a deep diffuse pain, though referred pain is common (Graven-Nielsen & Arendt-Nielsen, 2002; Korotkov et al., 2002; Svensson & Graven-Nielsen, 2001). Hypertonic saline also induces muscular hyperalgesia in the masticatory muscles (Graven-Nielsen & Arendt-Nielsen, 2002, 2003).

When hypertonic saline is injected or infused, a pool of extracellular fluid is created, and the resulting intramuscular pressure is similar to that induced during exercise (Crenshaw et al., 1995; Graven-Nielsen, 2006; Jensen et al., 1995). The masticatory muscle nociceptors located in the walls of the arterioles and connective tissue are excited by this algesic stimuli and encode nociceptive information to be passed to the CNS, which results in an experience of acute pain. The thin myelinated group III (Aδ-fibers), as well as the non myelinated

group IV (C-fibers), polymodal afferent fibres are activated to carry the nociceptive signals on into trigeminal subnucleus caudalis in the brain stem; these proceed via the spinothalamic tract to the thalamus and thus further into the cerebral cortex (Graven-Nielsen, 2006). The exact types of receptors involved in saline-induced acute muscle pain are as yet unknown; however, the stretch-inactivated channel transient receptor potential vanilloid receptor 1, TRPV1 is considered to be a possible candidate (Schumacher et al., 2000), as this receptor is believed to respond to saline-induced cell shrinkage. Another theory is that the elevation of extracellular sodium and potassium concentrations may result in a depolarisation of excitable membranes and a release of neuropeptides such as glutamate and substance P from activated nociceptors; however, no evidence of this has yet been produced (Graven-Nielsen, 2006; Tegeder et al., 2002).

The additional extracellular fluid disappears a few hours after injection or infusion ceases due to muscle activity. This suggests that the intramuscular pressure observed is not correlated to the pain intensity, as the fluid pool can still be detected in the muscle even after the pain vanishes (Graven-Nielsen et al., 1997). In ***Study I***, the experimental acute pain was induced in healthy masseter muscles bilaterally and simultaneously by means of 0.4 mL of sterile hypertonic saline (58.5 mg/ml, 5.85%) administered over 20 s by infusion pump (Harvard Infusion Pump 22, Harvard Apparatus, Great Britain; infusion rate 1200 ml/min) (Figure 2).

Figure 2. Equipment and apparatus used in ***Study I-III***.

Figure shows a Harvard infusion pump, an Umeå bite force transducer for fine precision forces, a Somedic electronic pressure algometer, an Aalborg bite force transducer for MVBF, a mechanical palpometer Palpeter, and a Fino Balance Mini weighing scale.

Alongside this common exogenous model, several endogenous experimental pain models have been used to mimic clinical pain (Reddy et al., 2012; Staahl & Drewes, 2004). TMD pain and fatigue or exertion in the masticatory muscles (Louca Jounger et al., 2017; Slade et al., 2013) are more similar to exercise-induced pain than the pain evoked by exogenous models, with the latter being more intense and short-lasting (Staahl & Drewes, 2004; Stohler, 1999; Svensson & Graven-Nielsen, 2001). An attempt to optimise excessive gum

chewing using Greek ΕΛΜΑ® Mastiha gum (Figure 3) (Farella et al., 2001; Kiliaridis et al., 1995; Koutris et al., 2009) as a pain and fatigue inducing model to mimic clinical pain and the subjective sense of fatigue (exertion) in patients with painful TMD was thus warranted. However, while these pain models resemble clinical TMD pain, it is not certain that this induced pain can be usefully compared with chronic TMD conditions; this issue arises because, during a chronic pain condition, changes in the nervous system occur that lead to central sensitisation, which in turn may affect motor control (Woolf & Salter, 2000). Further, experimental pain models may provoke non-nociceptive nerve fibres simultaneously with nociceptive ones, and there are large inter-individual responses when using such models (Staahl & Drewes, 2004).

5.5 EXPERIMENTAL CHEWING

Experimental standardisation of the chewing can be made in many different ways (van der Bilt, 2011): number of chewing cycles, chewing duration, chewing rate, chewing pattern, swallowing threshold, or level of EMG activity. In ***Study II***, standardisation was done by the chewing duration (40 or 60 minutes, divided into five minute bouts). The chewing pattern was only semi-standardised, as while chewing was done only on the dominant habitual masticatory side, that side was self-reported, and the rate was not standardised, as chewing followed the participants' natural pattern. In ***Study III,*** the standardisation of chewing was based on the number of chewing cycles (20 cycles) and chewing pattern (habitual/preferred side), while the natural chewing pattern was semi-standardised based on swallowing onset. The difference in how standardisation was achieved was driven by the objectives of each study. The aim in ***Study II*** was to use chewing as an inducing model for pain and fatigue, while in ***Study III*** the aim was to compare performance between TMD pain patients and controls.

5.6 ASSESSMENT OF PAIN AND FATIGUE

All assessments in all three studies were performed by trained examiners in a calibrated manner, as shown in Figure 1. Pain intensities and peak pain intensity were assessed in all three studies (***Study I-III***) using the Numeric pain Rating Scale (NRS-11) (Downie et al., 1978). This scale ranges from 0 to 10, where 0 indicates "no pain" and 10 indicates the "worst imaginable pain". The scale is thus easy to use and comprehend, being generally comparable to everyday clinical settings.

Participants were asked to mark their current maximum pain spread in the orofacial area on a pain drawing, including the location of any referred pain (Wright, 2000). These pain drawings were then scanned and analysed in Adobe Photoshop (version 19.1.3, Adobe Systems Incorporated, San Jose, CA, USA), and the program was used to count the pixels within the marked total area; the total pain area was thus reported in arbitrary units, a method comparable to many previous studies (Christidis et al., 2008; Christidis et al., 2015; Louca et al., 2013).

The pressure pain thresholds (PPT) reflecting mechanical pain sensitivity used in ***Study II*** were assessed by applying the rubber covered tip of an electronic pressure algometer (Somedic Sales Hörby AB, Sweden) (Figure 2) perpendicularly to each participant's skin surface over the most prominent area of the masseter muscles' belly and the anterior part of the temporal muscles bilaterally. PPT was also assessed over the tip of the index finger for use as a reference point and to record any possible systemic sensibility. Participants were instructed to press a button immediately when the sensation of pressure became painful. The pressure was increased at a rate of 30 kPa/s (Cioffi et al., 2017; Koutris et al., 2009; Ohrbach & Gale, 1989), with the assessment repeated twice over each muscle site and the mean value of all trials reported. The electronic pressure algometer was calibrated before each trial and all PPTs were assessed by the same examiner.

Subjective fatigue or exertion of the jaw muscles was assessed in S***tudies II*** and ***III*** using Borg's Rating of Perceived Exertion 6-20 (Borg's RPE 6-20) (Borg, 1974; Louca Jounger et al., 2017). Borg's RPE is a numeric scale ranging from 6 to 20, where 6 represents extremely low effort or no exertion at all and 20 represents maximum effort and maximal exertion. The participants were instructed to choose the number from this scale that best described their perceived level of exertion in the jaw.

5.7 ASSESSMENT OF MASTICATORY PERFORMANCE

In order to fully investigate biting and chewing performance, various methods are required to assess the different components of the mastication process. Combining these methods allows detection of any effects of experimental or clinical pain on jaw function. All assessments in all the three studies were performed by trained examiners in a calibrated manner, as shown in Figure 1.

A hold and split task using the central incisors with peanuts (Estrella salta jordnötter; Estrella AB, Angered, Sweden), on a bite force transducer used to examine the fine forces (Umeå University, Physiology Section, IMB, Umeå, Sweden) (Figures 2 and 3) was used in ***Study I*** to assess fine human bite forces (precision biting). This task was first described by Trulsson and Johansson in 1996 (Trulsson & Johansson, 1996b), though it has been used in several other studies (Kumar, Castrillon, Svensson, et al., 2015; Svensson & Trulsson, 2009, 2011). Previous findings indicate high EMG activity in the jaw closing muscles during tasks involving incisal biting with a protruded jaw position of the mandible (Farella et al., 2008; Lu et al., 2013). The method was thus deemed particularly suitable for the project's investigation of how muscular pain in the jaw closing muscles affects the masticatory process, including precision biting. The force profiles were recorded for later analysis with customised software (WinSC/WinZoom v1.52.0.1; Umeå University, Umeå, Sweden) at 12-bit resolution at 800 Hz (Figure 4).

The maximum voluntary bite forces assessed in ***Studies II*** and ***III*** were gathered by using a bite force transducer (1,000 N, 41.0 × 12.0 × 5.0 mm, length × width × height, Aalborg University, Aalborg, Denmark) (Figure 2). The bite force transducer was inserted between

either the first or second molars on the right or left side, whichever the participant identified as their dominant habitual masticatory side. The participants were then asked to bite on the transducer with maximal volutary force.

Mouth opening capacity, assessed in ***Studies II*** and ***III,*** was measured using a ruler according to Axis I in DC/TMD (Schiffman et al., 2014), inclusive of the vertical overbite.

When assessing masticatory performance and efficiency objectively, comminution and mixing ability are the variables of interest that most closely reflect the masticatory function (Elgestad Stjernfeldt et al., 2019; van der Bilt et al., 2010). Sieving using a silicone based test "food" such as Optosil has thus been used as gold standard method for assessing food comminution (Edlund & Lamm, 1980; Elgestad Stjernfeldt et al., 2019; Sánchez-Ayala et al., 2016; Sánchez-Ayala et al., 2014; van der Bilt, 2011). As sieving requires a lot of time and special equipment, however, alternatives were sought. Several studies have shown that optical scanning and imaging offers comparable results to sieving while being more time effective (Eberhard et al., 2012; Mahmood et al., 1992; Mowlana et al., 1995; van der Bilt, Abbink, et al., 1993; van der Bilt, van der Glas, et al., 1993). Further, as artificial test "food" is not suitable for swallowing, edible laboratory fabricated test food has been used in several studies (Foster et al., 2006; Grigoriadis et al., 2011; Lassauzay et al., 2000; Nokubi et al., 2013; Peyron et al., 2002), while other studies have used commercially available foods such as almonds, carrots, or gelatine candies (Al-Ali et al., 1999; Kapur & Soman, 2006; Shimada et al., 2015). Other methods that have been used include measuring the release of sugar (Heath, 1982), the release of dye from carrots (Käyser & van der Hoeven, 1977), or changes in dye concentrations (Gunne, 1983).

In ***Study III***, the more modern and efficient method of optical scanning was used, with the selected test food being a commercially available viscoelastic candy. Red jelly heart-shaped Stora Gelé Hjärtan candies, re-shaped into cubes, (Konfektyrfabriken Aroma AB) and red circular-shaped sugar coated sour gummy gelatin Haribo Syrlingar candies (Haribo Lakrits AB) were used (Figure 3). The candies were weighed before and after chewing using a weighing scale with a precision of +/- 0.01g (Fino Balance Mini, Fino GmbH, Bad Bocklet, Germany) (Figure 2). The fragmented candies were later scanned using the same scanner and standardised settings (Ricoh eduPrint Scanner). The images were pre-processed in Adobe Photoshop (version 19.1.3, Adobe Systems Incorporated, San Jose, CA, USA) before analysis in Fiji ImageJ (Image Processing and Analysis in Java; National Institutes of Health, USA), again using standardised settings (Figure 4).

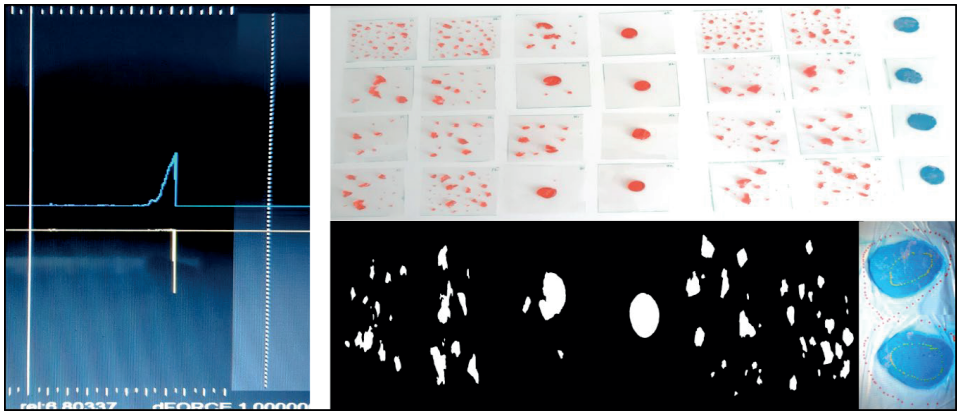
Figure 3. Test food and gums used in ***Study I-III***.

Shown in figure: Estrella peanuts, ΕΛΜΑ® Mastiha gum, Hue-Check gum, Haribo Syrlingar candy, and Stora Gelé Hjärtan candy (re-shaped into cubes).

To examine mixing ability in ***Study III***, two-coloured Hue-Check Gum® was used (Figure 3), which has been previously identified as a valid and reliable method (Liedberg & Owall, 1991, 1995; Prinz, 1999; Tarkowska et al., 2017; van der Bilt et al., 2010). This method also requires optical scanning and image processing. After flattening, the chewed gums were scanned using the same scanner with standardised settings (Ricoh eduPrint Scanner). A validated free View Gum© program was used for image processing of the two-coloured Hue-check gum (Halazonetis et al., 2013; Schimmel et al., 2007; Schimmel et al., 2015) in ***Study III*** (Figure 4). Coloured paraffin wax (H. Sato et al., 2003) and colour changing gums (Kamiyama et al., 2010) have, however, been used in other studies to test mixing ability.

In order to perform the chewing of food, dynamic movements of the jaw plus sufficient force generated by jaw muscle activity are required (Blanksma & van Eijden, 1995). Chewing being a jaw motor behaviour is describable in terms of movements (jaw kinetics) and electromyographic muscle activity (EMG), and it is these variables that need to be investigated when studying masticatory function in TMD patients with chronic jaw muscle pain. Zhang et al. (2017) showed that repeated jaw movements triggered temporal summation effects associated with significant inhibition of motor function in painful temporomandibular joints, and similar studies are thus needed focusing on the jaw muscles. Electromyographic and electrognathographic activity were not, however, assessed in any of the studies included in this thesis.

Figure 4. Analyses of the force profile in ***Study I*** and of the scanned images in ***Study III***.



Left: a sample of the force profile of one hold and split trial in the WinZoom program (***Study I***); Right: samples illustrating the fragmented soft and hard candy after chewing presented together with the Hue-Check gum after chewing as images drawn from the Fiji Image J and the View Gum programs (***Study III***).

5.8 STATISTICAL ANALYSES

Normality of distributions and skewness of data were checked in all three studies (***Study I-III***) using the Shapiro-Wilks test. Detection of outliers in ***Study I*** was then performed using the Adjusted Boxplot Method for skewed distributions (Brys et al., 2005; Brys et al., 2004; Hubert & Vandervieren, 2008), which was also used to confirm the results from the Shapiro-Wilks test.

With regard to the assessment of continuous and normal distributed variables, within the study groups, with regard to changes in all variables, parametric analysis of variance (ANOVA) was used for repeated measures, with Bonferroni applied as a post-hoc test for the associated multiple comparisons, while the between study group comparisons utilised a dependent t-test for matched pairs and an independent t-test for unmatched pairs.

For the categorical and non-normal distributed variables, within the study groups, changes in all variables were examined using nonparametric Friedman's analysis of variance (ANOVA) for repeated measures or the Kruskal-Wallis analysis of variance, with Tukey used as a post-hoc test for associated multiple comparisons, while between study group comparisons were subject to the Wilcoxon Signed Rank test for matched pairs and the Mann–Whitney Rank Sum test for unmatched pairs.

In terms of correlation testing, either the Pearson's or the Spearman tests were used, depending on the nature of the variables and normality of the data involved. Spearman was applied to detect any correlations between force and pain variables in ***Study I,*** as well as to determine correlations between the objective variables of masticatory performance and various subjective variables, including pain, fatigue, and self-assessed masticatory ability, in ***Study III***.

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Data from all studies (***Study I-III***) included in this thesis were analysed using univariate methods in SigmaStat software (version14.0; Systat Software Inc., San Jose, CA, United States). For all tests, the level of significance was set at $P < 0.05$, except where Bonferroni corrections were applied and the P-values were adjusted accordingly. Descriptive data were presented in either mean and standard deviation (SD) or median and interquartile range (IQR) format, depending on the nature of the variables and normality of the data.

6 ETHICAL CONSIDERATIONS

Ethical approval was initially gained from the Regional Ethical Review Board in Stockholm (DNR: 2014/1394-3), and the full doctoral project followed the principles for medical research outlined in the declaration of Helsinki. All individuals who participated were above 18 years of age and participated voluntarily after being given verbal and written information, with written informed consent obtained in each case. The participants were made aware that they could cancel their participation at any time without any penalty and with no need to explain the reason for their withdrawal.

Infusion of hypertonic saline is a scientifically acceptable conventional method used in medicine and dentistry to induce short-term rapid transient acute pain without further side effects (Svensson & Graven-Nielsen, 2001). The acute pain group was, however, exposed to pain and discomfort arising both from the needle insertion and the pain caused by the hypertonic saline solution, and exposing a small volunteer group to discomfort that may greatly benefit a larger group of patients offers an ethical dilemma, putting the "do no harm" principle (for the acute pain group) versus the "do good" principle (for chronic muscular pain patients in general) and the principle of justice against the principle of autonomy (for the participants in the acute pain group). This ethical discussion is also applicable to those participants who perceived pain and fatigue induced by excessive gum chewing.

Another relevant ethical aspect to be discussed is the benefit for the research participants. The patients included were all individuals who already had chronic pain, and who may thus possibly benefit from improved diagnostics and treatment, to which this research may contribute in the future, as such pain is long-lasting. On the other hand, it is unlikely that more than a few currently healthy participants in whom acute experimental pain was induced will benefit from the research they participated in. Can the cinema tickets they received as compensation be considered sufficient recompense, particularly as it is considered unethical to offer more attractive compensations?

Rules and laws are often defined as the tools that make it easier for researchers to act ethically, but the word research itself suggests the search for new knowledge, and novel situations are unlikely to be well regulated in advance where no previous knowledge exists. If no laws or regulations exist regarding a specific research question, it must thus be submitted to examination against the values, ethics and morals of individual researchers. Finding ways for the principle of justice to be fulfilled when different individuals participate in different studies with different researchers in charge, who maybe performing research in different ways and have received approval from different ethical committees and boards with different members, who in their turn may have different values, ethics, and morals, can thus become a matter of concern (Kelly et al., 2015).

For researchers, it is also important to realise and remember that what is observable with the available methods at hand should not be confused with the truth (Kelly et al., 2015). The ethical responsibility that falls on the shoulders of scientists is thus to choose appropriate study designs without extensive flexibility and to apply proper statistical methods in order to avoid biased results and prevent interpretations of results made on false premises. Any interpretation should thus be based on logical, critical reflection and neutral discussion rather than solely depending on p-values, especially in the generalising and decision-making phases (Szajewska, 2018).

7 RESULTS AND DISCUSSION

7.1 PARTICIPANT CHARACTERISTICS

Demographic data reflecting participants' ages and sexes are presented in Table 1. The sample of patients with TMD included in ***Studies I*** and ***III*** is generally representative of the general TMD population, as TMD prevalence becomes higher during adolescence and early adulthood, with a peak in midlife (Isong et al., 2008; LeResche, 1997), as well as being more common in women (Bush et al., 1993; Dworkin et al., 1990; Isong et al., 2008; LeResche, 1997; Lipton et al., 1993; Schiffman et al., 2014; Svensson & Graven-Nielsen, 2001).

Of the 42 chronic TMD pain patients included in the studies in this thesis (***Studies I*** and ***III***), 29% were diagnosed with local myalgia, 17% were diagnosed with myofascial pain, and 55% were diagnosed with myofascial pain with referred pain according to DC/TMD. Other diagnoses included headaches related to TMD, which were exhibited by 79% of all patients, and disc displacement with reduction, which was exhibited by 24%. The median (IQR) of the patients' pain intensity was 4 (2) using the 0 to 10 numeric pain scale, with 8 being the maximum score and 3 the minimum. Patients with TMD usually rate their average pain intensity at 4.3 (Von Korff et al., 1988), further validating the assumption that the population samples in ***Studies I*** and ***III*** are representative of the general TMD population. The median (IQR) pain duration was 60 (84) months, and the median pain area was 204 (559) arbitrary units. According to GCPS-7, 48% of these chronic patients have low pain intensity and low grade disability, 48% have high pain intensity and low grade disability, 5% have a moderately limiting high grade disability and none exhibit severely limiting high grade disability.

Among the participating patients, 29%, 12%, and 10% exhibited signs of mild, moderate and moderately severe depression, respectively, according to PHQ-9; further, 38%, 26%, and 19% of them presented signs of mild, moderate and severe somatic physical symptoms (somatisation), respectively, according to PHQ-15. According to GAD-7, 24%, 5%, and 5% showed signs of mild, moderate and severe anxiety, respectively, while 36% and 14% displayed signs of moderate or severe stress, respectively, according to PSS-10. The sample of patients thus displayed further evidence of being representative of the general TMD population, as all of these psychosocial factors have been found to be associated with the development of TMD, with somatisation being the strongest psychosocial predictor of TMD incidence (Fillingim et al., 2013). In contrast, of the healthy participants included in the three studies, 12%, 7%, 1%, and 1% exhibited signs of mild, moderate, moderately severe and severe depression, respectively, according to PHQ-9, with 29%, 12%, and 3% presenting signs of mild, moderate, or severe somatic physical symptoms (somatisation), respectively, according to PHQ-15. According to GAD-7, 15%, 3%, and 3% showed signs of mild, moderate, and severe anxiety, respectively, while 27% and 14% displayed signs of moderate and severe stress, respectively, according to PSS-10.

The patients perceived various impacts from pain on their masticatory function, reflected in their higher scoring when answering questionnaires regarding their masticatory ability (***Study III***). They indicated negative effects from pain on jaw mobility (JFLS and TSK-TMD) (Oghli et al., 2019; Visscher et al., 2010); chewing (JFLS and QMF) (Muller et al., 2008); and even communication (JFLS). Alongside this perceived impaired quality of masticatory ability, the patients indicated higher discomfort and negative psychological impact associated with pain (OHIP) (Larsson et al., 2014). No such negative perception of masticatory ability was reported by the healthy participants in ***Study III*** or in ***Study II*** (JFLS). These results are in line with previous reports by patients with TMD, who mention encountering functional jaw limitations and difficulties with both vertical mouth opening and chewing (Felício et al., 2002; Felício et al., 2007; Lövgren et al., 2018).

The maximal voluntary mouth opening capacity (MOC) was nevertheless the same in patients with myalgia and in pain-free healthy participants when all patients and healthy individuals from the studies in this thesis were grouped together; the maximum MOC was 55 mm. The MOC without pain on the other hand tended to be more reduced in patients. The healthy volunteers exhibited similar MOC as seen in healthy individuals in previous studies (Dıraçoğlu et al., 2011; Mapelli et al., 2009), while muscle pain seemed to limit the MOC without pain rather than the maximum MOC in patients, a result in line with previous work that showed no significant objective difference in maximum MOC between TMD patients and controls (Felício et al., 2007). In the patient samples of this thesis, maximum MOC and MOC without pain were the same between sexes; this lack of sex difference, particularly in terms of maximum MOC, might be a result of the overrepresentation of women. However, pain-free healthy men exhibited a maximum MOC that was significantly wider as compared to that seen in healthy women, with measurements of 60 mm and 53 mm respectively (P = <0.001). Previous work similarly showed greater vertical opening of the mouth in healthy men when sexes were compared (Mapelli et al., 2009).

7.2 EXPERIMENTAL PAIN MODELS

Two different types of experimental muscle pain inducing models were used in the healthy participants in this project, an exogenous model in ***Study I*** and an endogenous model in ***Study II***.

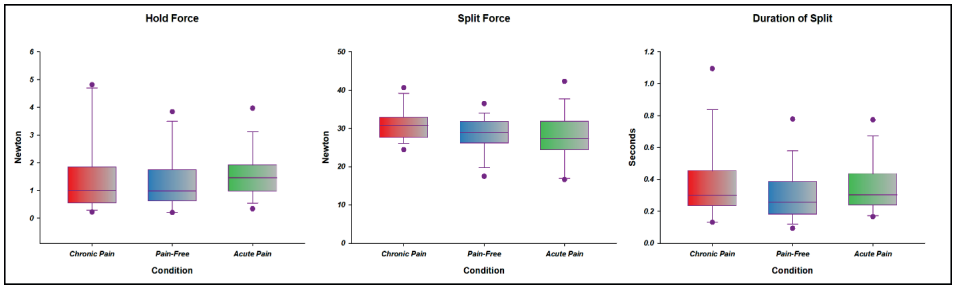
The exogenous model, with hypertonic saline induced for 20 seconds, caused infusion pain with a high intensity, giving a median (IQR) pain score of 7 (1.6) based on the NRS that lasted for a rather short total duration, with a median (IQR) duration of 519 (288.75) seconds. Similar intensity was seen in both sexes, though there was a longer total duration in women and a bigger pain area in men. The longer pain duration in women was expected based on previous studies (Christidis et al., 2008); however, the similarity in pain intensity and the larger pain area in men both contradict previous findings (Christidis et al., 2008). These differences between studies may arise, at least in part, from the fact that in ***Study I*** the amount of hypertonic saline was twice as big as the amount used in Christidis et al. (2008).

In ***Study I***, the acute pain in the masseter muscle induced by the hypertonic saline was not shown to have any effect on precision biting forces. These results were as expected, with similar previous studies involving experimental acute pain also showing no effect in this regard (Kumar, Castrillon, Svensson, et al., 2015; Kumar et al., 2014). The main results of ***Study I*** are illustrated Figure 5.

As the exogenous models induce more intense yet shorter-lasting pain, as well as lacking the exercise-induced fatigue of endogenous models (Staahl & Drewes, 2004; Stohler, 1999; Svensson & Graven-Nielsen, 2001), an endogenous pain inducing model was intended for use in future studies based on the optimisation attempt made in ***Study II***. Excessive chewing of EΛMA® Mastiha gum induced a low intensive but also short-lasting pain as well as a small pain area after a 60 minutes long duration of chewing using five new gums every five minutes. A significant pain intensity exceeding the baseline value occurred only in men after 60 minutes of chewing, though this was still of a relatively low intensity. The main results of ***Study II*** are shown in Figure 6, which illustrates that the model was not sufficient to induce pain, being contraindicated due to the lengthy chewing period needed, the rapidity of recovery, and the contradicting results as compared to previous studies regarding characteristics such as sex differences (Dao & LeResche, 2000; Karibe et al., 2003). Furthermore, the protocol did not have any impact on motor function.

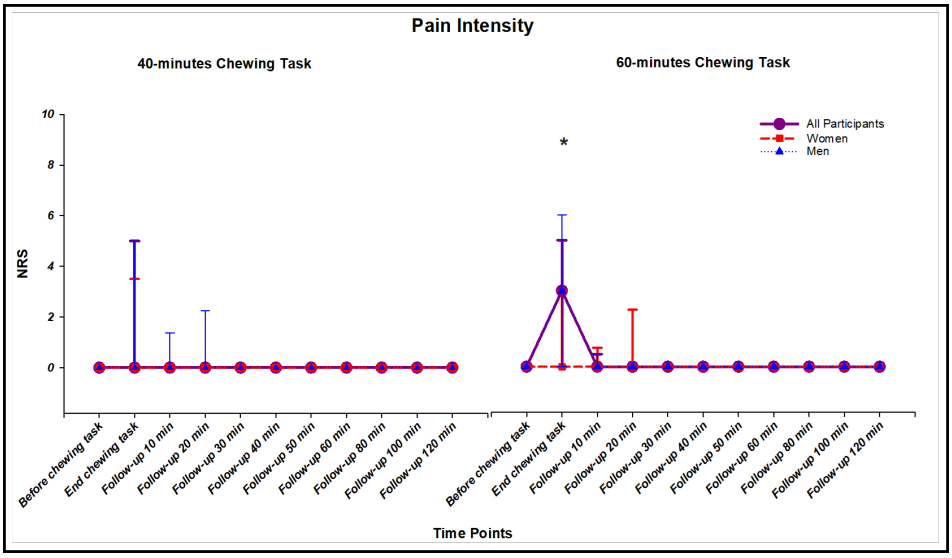
Referred pain was hard to assess in ***Study I*** due to the experimental design, while referred pain occurred in only one participant, who exhibited myofascial pain with referred pain, in ***Study II*** after the 60 minute chewing task. No delayed onset muscle soreness (DOMS) was assessed in ***Study II***, and it has been previously shown that chewing gum excessively does not induce DOMS (Farella et al., 2001; Koutris et al., 2009), indicating that this model is concentric rather than eccentric (Staahl & Drewes, 2004) and thus probably affects the closing jaw muscles to a greater extent than the opening jaw muscles.

Figure 5. Comparisons in hold force, split force and duration of split between conditions in ***Study I***.



Median (IQR) hold force, split force, and duration of split are shown in chronic pain patients and healthy participants when pain-free and during experimentally induced acute pain. No significant differences can be seen in hold forces, split forces, or duration of split between all three conditions (Mann–Whitney Rank Sum; P>0.05 and Wilcoxon Signed Rank test; P>0.05).

Figure 6. Changes in pain intensity with excessive gum chewing in ***Study II***.



Median (IQR) pain intensity scores shown before a chewing task, at the end of the chewing task, and at follow-ups of up to 120 minutes after the task. 15 healthy men and 16 age-matched healthy women participating in sessions of either 40 or 60 minutes of excessive chewing of ΕΛΜΑ® Mastiha chewing gum. The pain intensity increased significantly after the 60 minute chewing task only in men. At the end of the 60 minute chewing task, significantly higher pain intensity scores than baseline were induced in men, but any significant increase did not last for more than 10 minutes after the chewing task. There was no significant increase in pain intensity after the 40 minute chewing task in either sex, or in women at all. *Significant difference compared to baseline for 60 minute chewing task in men (Friedman ANOVA test/Tukey post-hoc; $P<0.05$).

7.3 JAW MUSCLE FATIGUE

Fatigue is one of the most common symptoms in TMD patients with myalgia (Louca Jounger et al., 2017; Slade et al., 2013), which is why it is considered to be of importance in experimental models simulating clinical pain in such patients. Several different methods have been tested in order to induce fatigue and exercise-like ischemic jaw muscle pain, often involving active contractions or passive stretching of the muscles. Such models include resistance exercise (Türker et al., 2010), clenching (Clark et al., 1984; Dawson et al., 2012; Svensson et al., 2001; Xu et al., 2017), and excessive chewing (Farella et al., 2001; Kiliaridis et al., 1995; Koutris et al., 2009), all of which aim to induce minor structural damage in the muscle leading to the release of algogenic substances, which in turn sensitise A-delta and C nociceptive fibres (Cheung et al., 2003; Mense, 2003; Tegeder et al., 2002). Mechanoreceptor afferents from muscles, muscle spindles, and tendons are thus activated and contribute to the pain as well (Barlas et al., 2000; Graven-Nielsen & Arendt-Nielsen, 2003; Weerakkody et al., 2001; Weerakkody et al., 2003).

In ***Study II***, excessive chewing was chosen as an experimental model for inducing pain and fatigue in the jaw muscles. This model proved to be an appropriate method for inducing jaw muscle fatigue that could be perceived and subjectively reported, and the level of the induced subjective fatigue (exertion) seen in this study was in line with previous reports by TMD pain patients (Louca Jounger et al., 2017; Slade et al., 2013). Unfortunately, EMG activity was not monitored, so there was no evidence to confirm this fatigue in the muscle objectively. As participants in ***Study II*** were healthy individuals, their baseline level of fatigue was comparable to the values scored by the controls in ***Study III***. However, the peak fatigue score in ***Study II*** was 16 (5) while the equivalent in ***Study III*** was 7.5 (3) according to Borg's RPE. This difference in scores is likely to result from differences in the experimental protocols, the durations of the chewing, and the properties of the ΕΛΜΑ® Mastiha gum used in ***Study II*** versus those of the candy in ***Study III***.

7.4 FORCE PROFILE IN CHRONIC JAW MUSCLE PAIN

Bite forces vary depending on the task at hand, being generally divided into precision forces, submaximal forces, and maximal forces. Precision bite force requires higher sensitivity and specificity and finer jaw motor control as compared to maximal bite force, which in turn demands greater magnitude of muscle load and higher muscle activity. Depending on the aim and the methodology of an assessment, the assessed force can be static or dynamic.

The profile of precision biting depends on the biting task, being further refined by the phase of the task. Precision bite force for central incisors in patients with TMD myalgia during the morsel holding phase was 1 N when using intact incisors and peanuts (***Study I***). The holding force seen in patients thus did not differ from the force applied by healthy pain-free individuals, which was found to be =<1 N (Al Sayegh et al., 2019; Johnsen et al., 2007; Svensson & Trulsson, 2009, 2011; Trulsson & Gunne, 1998; Trulsson & Johansson, 1996b).

The split forces and event duration depend mainly on the mechanical properties of the food being bitten and the attributes of the teeth used while biting (Johnsen et al., 2007; Svensson & Trulsson, 2009). In the case of peanuts, this was found to be approximately 31 N in patients with myalgia, which did not differ significantly from the split force applied by healthy pain-free participants (Al Sayegh et al., 2019; Svensson & Trulsson, 2009, 2011; Trulsson & Johansson, 1996b), as shown in the main results for ***Study I*** in Figure 5. The split force discussed here is a submaximal type of force that should thus be distinguished from the maximal voluntary bite force (MVBF), which varies between 89 and 250 N for intact incisors in patients with TMD, with a range of 89 to 200 N in women and 196 to 250 N in men (Ahlberg et al., 2003; Goiato et al., 2017; Pereira-Cenci et al., 2007). The maximal force varies between 94 and 290 N for intact incisors in healthy pain-free individuals, with ranges of 94 to 250 N for women and 150 to 290 N for men (Ahlberg et al., 2003; Edmonds & Glowacka, 2020; Ferrario et al., 2004; Pereira-Cenci et al., 2007).

Unilateral maximal voluntary bite force in patients with TMD myalgia using molar teeth was approximately 400 N (***Study III***); this group had an over-representation of women, however. Nevertheless, the results are in line with results from previous studies in patients with TMD (Pereira-Cenci et al., 2007). MVBF in patients with specifically muscular pain has been assessed at approximately 300 to 400 N (Kogawa et al., 2006; Xu et al., 2017), with women with TMD having an MVBF of approximately 200 N, while in men this force was 400 N (Pizolato et al., 2007).

The MVBF in healthy pain-free participants varied between 200 N and 400 N for this thesis (***Studies II*** and ***III***). Healthy women had a maximal force that ranged between 150 and 200 N while for men, this ranged between 240 and 400 N. The results for the healthy individuals in ***Studies II*** and ***III*** were thus all within range of results from previous studies, where the MVBF varied between 200 and 700 N (Ahlberg et al., 2003; Calderon et al., 2006; Ferrario et al., 2004; Kogawa et al., 2006; Testa et al., 2018; van der Bilt et al., 2008; Varga et al., 2011; Xu et al., 2017). Healthy women with normal occlusions usually have lower MVBF than men with the same conditions, 160 to 800 N and 280 to 900 N, respectively (Calderon et al., 2006; Ferrario et al., 2004; Pereira-Cenci et al., 2007; Pizolato et al., 2007; Takaki et al., 2014; Varga et al., 2011; Waltimo & Könönen, 1993). The bite force increases in women until adulthood and then decreases (=> 25 years) (Takaki et al., 2014). With regard to molars, the MVBF varies between 200 and 700 N in healthy people, and this variation is dependent on sex but independent of tooth (06 or 07) or side (right or left) (Calderon et al., 2006; Edmonds & Glowacka, 2020; Ferrario et al., 2004; Varga et al., 2011).

In ***Study III***, no significant difference in MVBF was found between the myalgia and healthy groups, neither at baseline nor after the chewing tasks, though the magnitude of values presented by the myalgia group was a little lower (not statistically significant) than that offered by the control group. Previous studies have reported conflicting results, some in line with these results (Hotta et al., 2008; Pereira-Cenci et al., 2007), and others offering contradictory data (Ahlberg et al., 2003; Kogawa et al., 2006; Pizolato et al., 2007; Testa et al., 2018). Patients thus may not have reduced MVBF, and may even display less muscle fatigue; however, they tend to exhibit slower recovery than healthy individuals (Hagberg et al., 1986; Lyons & Baxendale, 1995), indicating selective activation of motoneurons (whole or parts of the muscle) depending on the task at hand (Blanksma & van Eijden, 1995).

The mixed results and great variations seen in MVBF across studies may arise from the variations in measurement methodology, which are influenced by many factors; these include different populations in various studies in terms of anatomy, age, and sex (Gomes et al., 2014; Koç et al., 2011; Okada et al., 2014; Palinkas et al., 2010), the classification of TMD diagnoses (Goiato et al., 2017; Kogawa et al., 2006; Pereira-Cenci et al., 2007; Xu et al., 2017); the sensitivity and type of force transducers; the position of the mandible during testing; and psychological factors such as the fear of dental damage which may cause a person to exert less pressure (Hagberg, 1987).

The bite forces assessed in the studies included in this thesis are considered to be static. The static bite force in ***Study III*** was also only assessed at baseline and at the end of the experiment, so that no information about the dynamic modulation of the bite force during masticatory sequences was gathered. This gap in information may be filled in later studies by the inclusion of experimental designs involving continuous registration of electromyographic activity, and sensor-based occlusal bite force monitoring (Grigoriadis et al., 2014; Shimada et al., 2015).

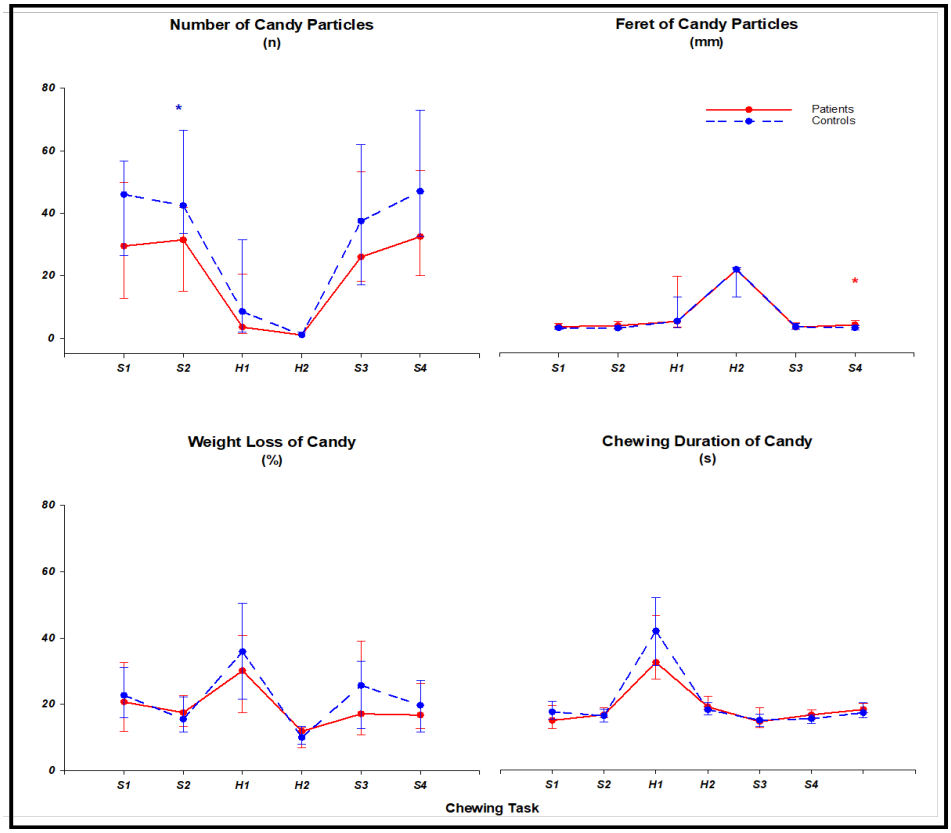
7.5 CHEWING DURING CHRONIC JAW MUSCLE PAIN

TMD patients with chronic myalgia exhibited less efficiency in food comminution as compared to the healthy controls (***Study III***). The fragmented soft candy particles expelled by patients were lower in number and had larger medians of area and minimum Feret's diameter after standardised chewing (20 chewing cycles) as compared to those expelled by controls, as shown in the results of ***Study III*** illustrated in Figure 7. Other studies of TMD patients (Henrikson et al., 1998) and other patient groups with malocclusions and anomalies (English et al., 2002; Feldman et al., 1980; Ngom et al., 2007) have produced results in line with these results.

Examining the results for patients in ***Study III*** shows that the more intense and severe the pain, the longer chewing duration was needed to elicit high fragmentation of candies. This result is in line with previous results showing that chewing duration correlates positively with TMD severity (Felício et al., 2007).

It was also expected that the comminution test and the mixing test would show positive correlation (Sato et al., 2003); however, surprisingly, the findings showed greater variance of hue in controls in ***Study III***. This finding is believed to have arisen due to induced fatigue due to the experimental sequence in which the gum was placed; additionally, the Hue-Check gum may not be a suitable method for comparing individuals with natural dentition and normal occlusions (Speksnijder et al., 2009; van der Bilt et al., 2010).

Figure 7. Comparisons between conditions in ***Study III***.



Data are expressed as medians (IQR; interquartile range) for all variables. P-values refer to comparisons between groups using the Mann-Whitney Rank Sum test. * = significant difference $P < 0.05$. The minimum Feret diameter was assessed in millimetres, with weight proportion loss in percent and chewing duration in seconds.

It is important to distinguish between the area factors assessed in ***Study III*** and the surface area assessed as in some previous studies, such as Manly (1951). The measured area referred to in ***Study III*** is based on particle size, as the candies were fragmented into particles such that, the smaller the size, the smaller the area, indicating more efficient fragmentation. This means that the measure of area used in this study correlates negatively with masticatory performance. However, in Manly (1951), the surface area correlated positively with masticatory performance, indicating that the more efficient performance, the greater the surface area, as Manly did not aim to investigate the fragmentation of the wax used in that study.

8 GENERAL DISCUSSION

8.1 NORMAL VERSUS ADAPTIVE OR IMPAIRED MASTICATION - MASTICATORY EFFICIENCY VERSUS ABILITY

The dynamics of mastication change throughout the masticatory sequence, though these changes become progressively smaller over time (Lucas & Luke, 1984). Such changes occur in muscle activity, bite forces, jaw movements, chewing pattern, chewing rate, and swallowing mechanisms (Grigoriadis et al., 2014; Horio & Kawamura, 1989; Lassauzay et al., 2000; Lucas et al., 1986), and these are mainly affected by the shape, size, texture, hardness, strength, toughness, brittleness, elasticity, plasticity, and viscosity of the food being addressed (Buschang et al., 1997; Chen et al., 2013; Dan & Kohyama, 2007; Grigoriadis et al., 2014; Horio & Kawamura, 1989; Lassauzay et al., 2000; Lucas & Luke, 1986; Peyron et al., 2002; Peyron et al., 2004; Plesh et al., 1986; Ross et al., 2007). As the chewing sequence continues, the performance is adjusted and adapted according to perception of the gradual food breakdown. This adaptation is executed by continuous sensory-motor feedback (Lund, 1991; Lund & Kolta, 2006) that works to optimise the mastication, producing higher efficacy in terms of forming a safe bolus with minimal consumed energy (Woda et al., 2011).

The definition of optimal and efficient chewing performance has been widely discussed. Shorter chewing duration, lower numbers of chewing cycles, faster chewing rates (number of cycles/time unit), lower swallowing thresholds, or smaller sized food particles have all been suggested, with the latter being considered to be the best indicator of efficient performance, as the degree of pulverization is the main determinator of the swallowing threshold (Berretin-Felix et al., 2005; Helkimo et al., 1978; Horio & Kawamura, 1989; van der Bilt, 2011; Witter et al., 2013; Woda et al., 2011). Higher mixing ability has been also suggested as an indicator of better masticatory performance (Kaya et al., 2017; S. Sato et al., 2003; Silva et al., 2018; Speksnijder et al., 2009). The duration of chewing sequence and the number of cycles depends mainly on the initial food size in healthy individuals with normal dentition, however (Lucas et al., 1986). Chewing efficacy is thus poorly correlated with chewing duration until swallowing when food is chewed naturally (Helkimo et al., 1978), and the number of chews taken per minute is not correlated with the particle sizes achieved after a given number of chews.

Swallowing thresholds seem to depend mainly on pulverisation degree (Horio & Kawamura, 1989), with smaller particle size facilitating easier swallowing (Lucas & Luke, 1986; Witter et al., 2013). If the masticatory function is impaired, a person is thus relatively unable to form a safe normal bolus, which is reflected mainly in particle size swallowed, tends to be larger than in a healthy person with normal dentition. Many alternate patient groups to those patients with TMD myalgia examined in ***Study III*** seem to have impaired masticatory function (English et al., 2002; Feldman et al., 1980; Ngom et al., 2007), and when this function is impaired, food choices become limited and food refusal increases (Hennequin et al., 2005; Wayler & Chauncey, 1983). Where the masticatory function is less

severely affected, however, prolonging chewing duration and increasing the number of chewing strokes may offer effective compensatory mechanisms to adapt the masticatory function to form a safe normal bolus to swallow (Mishellany-Dutour et al., 2008; Witter et al., 2013). It is thus necessary to distinguish between adaptive mastication as a compensatory mechanism in masticatory compromised conditions and adaptive mastication as elicited by sensory-motor feedback to fine-tune basic rhythmical mastication generated by the central pattern generator in normal conditions.

In order to differentiate between impaired and adaptive mastication, normative values for particle size are required (Witter et al., 2013). The real challenge in this is that different food types have different normative values, and there are as yet no such normative values for the candy used in ***Study III***. Nevertheless, the criterion for adaptive mastication is for the same degree of pulverisation as seen in normal mastication to be achieved before swallowing (Witter et al., 2013). The TMD patients in ***Study III*** seemed to meet this criterion, succeeding in their attempts to compensate for any possible pain effect on masticatory performance during natural chewing, while their actual impaired masticatory function was uncovered by standardising chewing.

Examining the previous literature (Kumar et al., 2017; Kumar et al., 2019; Svensson & Trulsson, 2011; Trulsson & Gunne, 1998; Trulsson & Johansson, 1996a) together with the results from ***Study I***, the support of intact periodontal mechanoreceptors and the larger and faster neurofibres terminating in the subnucleus interpolaris (Capra & Dessem, 1992) seem to play essential roles, being of greater importance than any jaw muscle pain effects in term of precision biting. Adaptive behaviours may explain patients' ability to overcome pain to perform the required task (Hodges & Tucker, 2011; Murray & Peck, 2007; Stohler, 1999; Svensson & Graven-Nielsen, 2001), and one such suggested adaptation is the re-organisation of motor units in the painful and non-painful synergistic muscles with the aim of maintaining motor function despite pain (Ferreira et al., 2020; Hodges et al., 2008; Malik et al., 2018; Minami et al., 2013; Santana-Mora et al., 2009). As individuals' experiences of pain vary, their motor and endurance responses also vary (Akhter et al., 2014; Bair et al., 2013; Coghill, 2010; Hasenbring, 2000; Hasenbring & Verbunt, 2010; Loeser & Melzack, 1999; Ohrbach et al., 2013; Quartana et al., 2009). The specifics of a given experimental task may also affect performance (Sae-Lee, Whittle, Forte, et al., 2008; Sae-Lee, Whittle, Peck, et al., 2008). Nevertheless, TMD patients, even those with healthy periodontium, complain about mouth opening reduction and chewing difficulties (Sato et al., 1996), implying that the adequate function of PMRs may play a less important role in other masticatory tasks.

Considering the weak correlation between masticatory efficiency as objectively assessed using various methods and the masticatory ability subjectively reported and measured by self-assessment (Pedroni-Pereira et al., 2018; van der Bilt, 2011), further quantitative and qualitative investigations are warranted in order to elucidate mastication in different groups of humans with specific intra-group features. In chronic painful muscular TMD, patients'

perceptions of their masticatory dysfunction seem to be in agreement with their objectively detected impairments, however (***Study III***).

8.2 CONCLUDING REMARKS

The three studies forming this doctoral thesis suggest that:

1. Jaw muscle pain does not seem to affect precision biting in humans. (***Study I***)
2. The excessive chewing model needs further adjustments in order to sucessfully mimic TMD-pain, especially in women. (***Study II***)
3. TMD patients with chronic myalgia exhibit impaired masticatory performance with less communiting efficiency as compared to that seen in a pain-free healthy control group. (***Study III***)

Jaw muscle pain in patients with TMD thus seems to affect their capacity for mastication, their performance endurance, and their ability to attain recovery. Healthy pain-free individuals also seem to have a greater ability to adapt, while such patients exhibit a need to compensate.

8.3 GENERALISABILITY OF THE FINDINGS

The purpose of patient-oriented research is to generate generalisable knowledge that will be useful for future clinical practice (Sacristán, 2015). In order to yield further generalisability, published studies should be repeated in other populations to check that they yield consistent results at the commonly accepted coefficient of variation of less than 5%. This makes it of great importance to develop well designed and documented studies, as well as to ensure adequate interpretation of results (Atkinson & Clark, 2016; Szajewska, 2018).

Oral clinical research, as with all medical research fields, has its own shortcomings and limitations regarding design and interpretation (Atkinson & Clark, 2016). The clinical sites where participants included in the studies of this thesis were recruited by cluster-convenience sampling were limited (Elfil & Negida, 2017), and patients with the condition of interest included in these studies were also referred by general practitioners to the specialist clinics, which might induce referral bias. The selected population might thus not be representative of the full spectrum of the patient group of interest.

Inclusion and exclusion criteria should be well defined and balanced to allow reproduction and generalisation of results, and attempts were made in this case to construct well defined and structured criteria as much as possible, in an attempt to avoid being hazy or overly restrictive (Atkinson & Clark, 2016). The selection of the participants should also be based on validated diagnostic methods, and controls should be matched. The robust internationally used diagnostic criteria of DC/TMD were used (Schiffman et al., 2014) for diagnosing the patients in this thesis and for confirming the eligibility of the controls matched to the patient group by age and sex. The patients included in the research studies in

this thesis thus represent a reasonable sample of the TMD population that reflects the actual prevalence of various age and gender aspects, as well as the specific TMD characteristics of pain, fatigue, and psychosocial aspects (Bush et al., 1993; Elfil & Negida, 2017; Fillingim et al., 2013; Isong et al., 2008; LeResche, 1997; Louca Jounger et al., 2017; Lövgren et al., 2016; Rogers, 2004; Schiffman et al., 2014; Svensson & Graven-Nielsen, 2001; Von Korff et al., 1988).

Methods used in measuring and analysing outcomes should also be validated (Atkinson & Clark, 2016). The outcomes measured in the studies included in the thesis (***Study I-III***) were both subjective and objective, and the methods used were all validated. Subjective measurement of patient-reported outcomes involved the use of validated questionnaires and validated instruments and scales for assessing outcomes that could not otherwise be assessed such as pain and fatigue, while the objective outcomes were measured using methods validated either by previous use in multiple studies or by reliability testing in pilot studies performed prior to ***Studies I, II,*** and ***III***. Power calculations were performed prior to data collection and validated statistical methods were used to analyse the obtained data. When the distributions of the obtained data were plotted and tested, the data appeared to be not normally distributed, with the majority of the variables skewed to the right. Non-parametric analyses were thus performed, and data represented with medians and interquartile ranges (Motulsky, 2015). All outliers were handled systematically (Hubert & Vandervieren, 2008) in order to avoid contamination of the data as whole which might result in misleading conclusions. Where multiple comparisons were applied, the Bonferroni correction was applied as an ad hoc adjustment to avoid statistical Type I errors; however, this has been accused of tending to be rather conservative (Bland & Altman, 1995; Chen et al., 2017; Perneger, 1998), .

8.4 CLINICAL RELEVANCE AND IMPLICATIONS

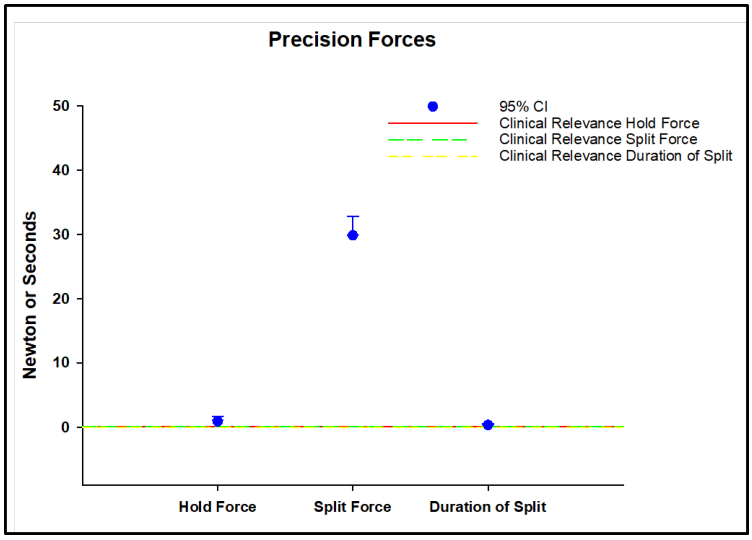
Evidence-based dentistry (EBD) dealing with chronic orofacial pain and temporomandibular dysfunction is often harder to perform and more problematic to establish than research in other medical fields. EBM and EBD tend to have objective scopes, while pain and dysfunction are more prone to subjective comprehension. Nevertheless, subjective outcomes should be considered as these can be more meaningful clinically than statistical measures (Atkinson & Clark, 2016).

Studies I and ***II*** in this thesis offered generally negative results, with no statistically significant outcomes, thus generating insufficient strength of evidence to reject the proposed null hypotheses. However, this must not be taken to mean that the null hypotheses are thus true. These results have been subject to criticism from some peer-reviewers, who commented on them as “disappointing”, “unfortunate” and “detracting from the enthusiasm of the study”. Implying that statistically insignificant results are “disappointing” indicates a prejudice for positive statistical significance, which enhances selective outcome reporting and drives the competition to declare impressive results, also known as “data fishing” or “data dredging” (Smith & Ebrahim, 2002). Furthermore, relying on p-values solely is

Furthermore, relying on p-values solely is unjustified in good research, as neither false-positive nor false-negative results are definitively preventable (Szajewska, 2018). As the studies included in this thesis are rather small in terms of sample size, the risk of making Type II errors (false-negative) and thus failing to find important differences, is more likely than the risk of making Type I errors (false-positive), with p-value depending on the sample size rather than relating to the clinical importance of the findings.

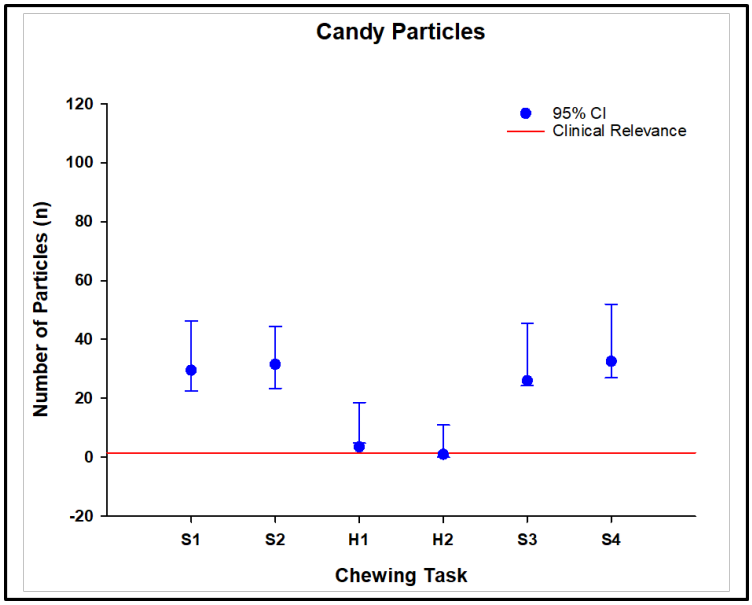
Prior to all of the studies in this thesis (***Study I-III***), power calculations were performed based on previous literature (Farella et al., 2001; Felício et al., 2007; Koutris et al., 2009; Shimada et al., 2015; Svensson & Trulsson, 2011), respecting the internationally recognised rule of accepted clinical effect size of 30% (Aarts et al., 2014). It is thus vital to distinguish statistical significance from clinical relevance. Confidence intervals and estimates of effects, at least for the main outcome variables, indicate the magnitude and precision of the observed differences can be used for that purpose, despite the p-values (Habibzadeh, 2017). As the data were not normally distributed, no standard errors can be calculated; however, approximate 95% confidence intervals for the median can be obtained, and these have the same interpretation. These consist of the range of population values with which the sample is compatible, and in an attempt to simulate and visualise the clinical relevance for the main outcomes from ***Studies I*** and ***III***, Figures 8, 9A and 9B show the approximate 95% confidence intervals and estimates of effects based on the medians and IQRs.

Figure 8. Clinical relevance of the main results of ***Study I***.



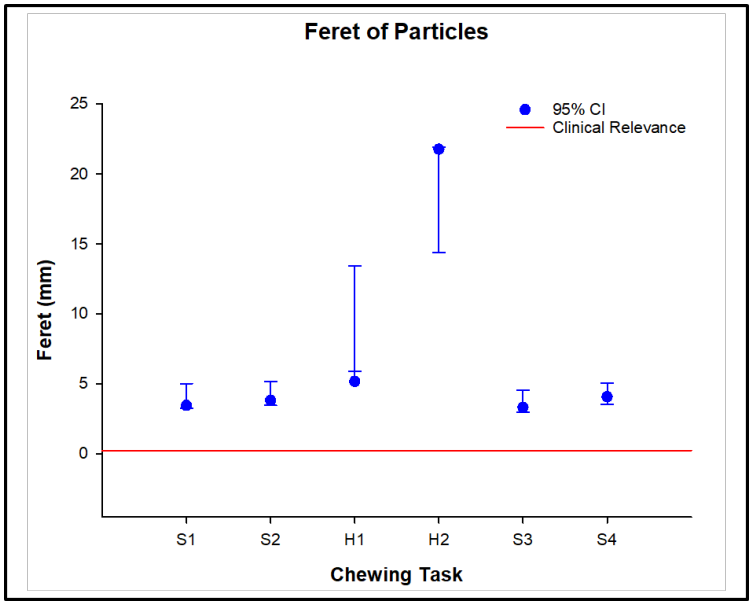
The split force is clinically relevant, while the hold force and the duration of split may be potentially clinically relevant. CI = confidence interval. The hold and split forces are expressed in Newtons, while the duration of split is expressed in seconds.

Figure 9A. Clinical relevance of the main results of ***Study III***.



The grade of fragmentation of the soft candies is clinically relevant, while the grade of fragmentation of the hard candies may be potentially clinically relevant. CI = confidence interval. The fragmented soft and hard candy particles are expressed in terms of number.

Figure 9B. Clinical relevance of the main results of ***Study III***.



The size of the fragmented soft and hard candy particles is clinically relevant. CI = confidence interval. The Feret's diameter of the fragmented candy particles is expressed in millimetres.

8.5 PROSPECTIVE FUTURE RESEARCH

Future masticatory research in cases of myalgia may involve dynamic bite force monitoring, electromyographic and electrognathographic monitoring, as well as motor unit investigations of the thresholds, firing rates and sequence of recruitment of motor neurons in both painful muscles and non-painful synergistic muscles during the chewing of different types of food with various mechanical and rheological properties. Further informative data may also be obtained from motor unit investigation during precision biting. Studies exploring the possible effects of TMJ pain on motor function and the interactions between painful joints and masticatory function/performance should also be pursued. Studies examining and analysing masticatory performance in TMD patients with general pain conditions such as fibromyalgia or systemic inflammatory diseases engaging the TMJ, as well as masticatory performance in TMD patients with malocclusion, are also warranted.

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Jesus, Thank you for always being my way, my truth and my life...# Always&Forever

Al Sayegh family; Samir, Sahera, Saif and Sahar, Thank you for being my rock, my biggest believers, my brightest stars and my special blessings...#Blessed

Karolinska Institutet, Thank you for embracing me. Beneath your sky Samaa grew up...#MinKäftis

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Nikos, Thank you for believing in me. Words are not enough to express my gratitude, appreciation and gratefulness but "I know that you know". My sky has only few special stars and you earned yours...#BlessYou

Malin, Thank you for being there for me when I needed your expertise and wisedom...#Cheers

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