Perception of nociceptive pain. Perspectives on induction, evaluation and gender.

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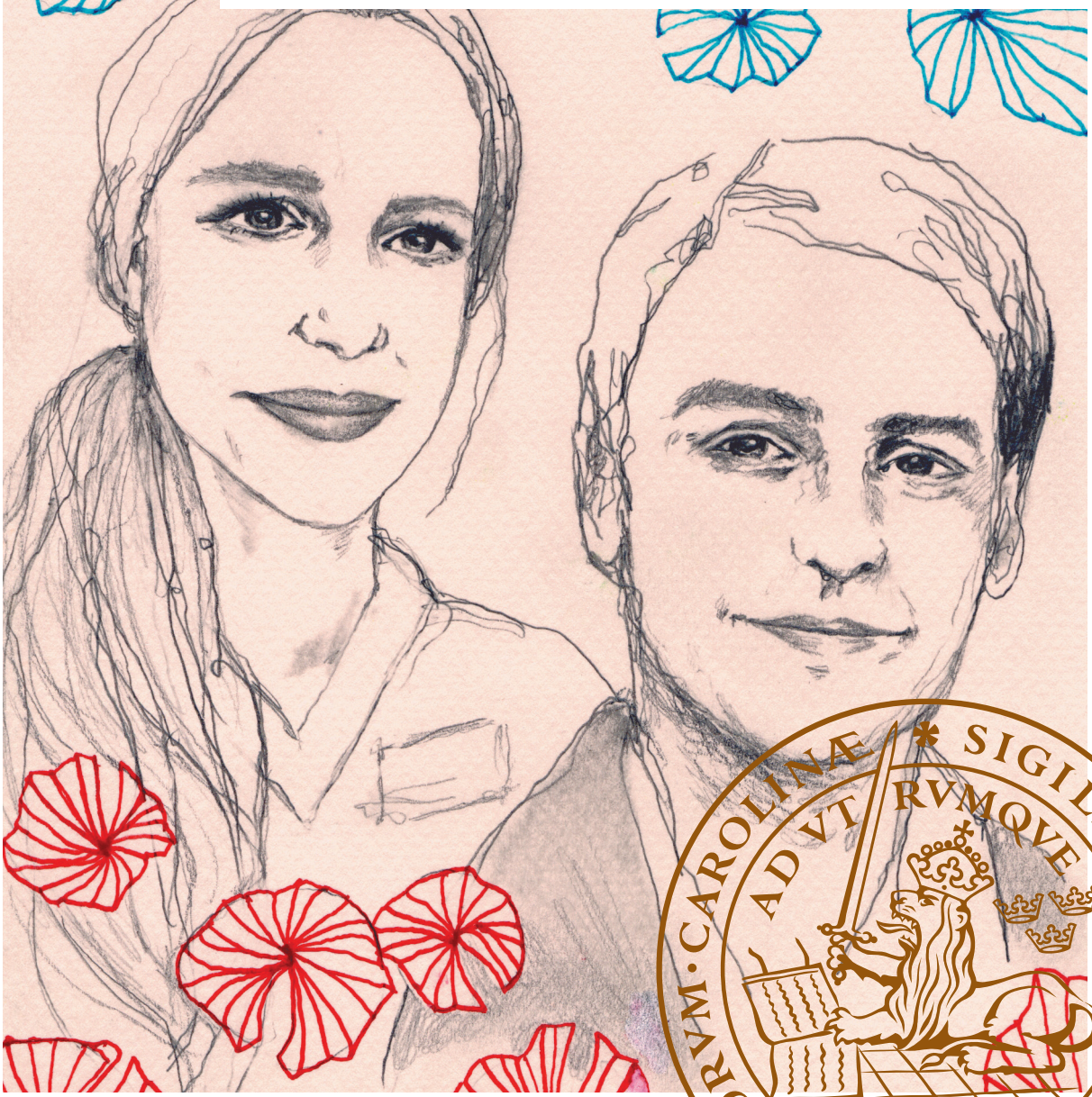

Perception of nociceptive pain

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Perspectives on induction, evaluation and gender

Anna Sellgren Engskov

LUNDS
UNIVERSITET

DOCTORAL DISSERTATION

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Abstract:

Background: Pain is the main reason for seeking medical treatment. Nociceptive pain activates myelinated Aδ-fibres with immediate, distinct, and localized sensation of pain, and nonmyelinated C-fibres, with delayed, aching, and diffuse sensation of pain. Individual pain perception is multidimensional and influenced by interacting physiological and psychosocial factors. Consensus on investigator gender impact on pain perception is lacking. Considering the multifactorial influence on pain, evaluation by adding verbal descriptors of pain quality to pain intensity scales is essential.

Aims: Evaluate abilities of selectively inducing delayed pain (I). Evaluate potential impact of investigator and participant gender on nociceptive acute pain, induced by experimental pain stimuli (I-II) or surgery (III). Evaluate potential associations between verbal descriptors of pain quality (reflecting Aδ- or C-fibre-mediated pain) and pain intensity levels, in postoperative patients early after surgery (IV).

Methods: In 44 healthy volunteers pain threshold was induced by CO_2 laser stimulation and evaluated with visual analogue scale (VAS) (I). In 40 healty volunteers pain threshold was indued by electrical pain stimulation and evaluated with VAS, once by a female and once by a male investigator, according to a randomized crossover study design (II). In a clinical observational study, 245 patients were subjected to various kinds of surgery, and postoperative pain intensity levels were evaluated with VAS according to a paired crossover study design, by a female and a male study investigator (III). In addition, the study patients described their pain with optional verbal quality descriptors early after surgery (IV).

Results: Lower levels of energy density were used (P=0.003) in those 13 subjects reporting single, compared with those 29 reporting double, pain responses (I). Higher levels of electrical pain threshold (P<0.0001) were obtained by the female than by the male investigator (II). Male patients reported lower VAS scores to female than male investigators (P=0.006) after surgery (III). Patients with mild pain more often reported quality descriptors associated with C-fibre- than Aδ-fibre-mediated pain (P=0.007), and lower (P=0.047) pain intensity was associated with quality descriptors of C-fibre-mediated postoperative pain. Subject gender did not influence induction or evalution of pain (I-IV).

Conclusions: Delayed nociceptive pain, presumably reflecting C-fibre transmission, is induceable by ultra-short laser stimulation and selectively assessable in humans (I). Perception of acute nociceptive pain, induced by experimental stimulation or surgery, was not influenced by study participant gender (I-IV), but by investigator gender (I-III), with lower pain sensitivity in male (I, III), and both genders of (II), study participants, when evaluated by a female than by a male. Verbal quality descriptors reflecting C-fibre-mediated pain were associated with lower reported pain intensity in postoperative patients (IV).

Key words: Acute pain, Gender identity, Nociceptive pain, Pain measurement, Postoperative pain, Sex, Visual analog scale

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'The positive thinker sees the invisible,
feels the intangible and achieves the impossible'

Winston Churchill

To my lovely family
– Lars, Alma, Axel & Ida

Table of contents

Summary in Swedish

Smärta är en av de vanligaste anledningarna till att söka vård och ständigt aktuellt inom hälso- och sjukvården. Den vanligaste smärttypen är nociceptiv och utlöses genom stimulering av mottagare i huden (nociceptorer). Smärtsignalerna fortleds sedan genom snabba myeliniserade Aδ-fibrer (omedelbart smärtsvar) och långsamma omyeliniserade C-fibrer (fördröjt smärtsvar). Aδ-fibrerna förmedlar en omedelbar skarp, välavgränsad, stickande varningssmärta och C-fibrerna en fördröjd mer diffus, värkande, tryckande smärta. Detta hänger samman med att olika slags nociceptorer är olika känsliga för värme, och att olika slags nervfibrer fortleder smärtsignaler olika snabbt.

Hur en människa upplever smärta kan ha många förklaringar. Smärtupplevelsen påverkas av både fysiologiska, psykologiska och psykosociala faktorer och av hur dessa samspelar. Något som inte undersökts tillräckligt, och där man ännu inte nått klarhet, är om, och i så fall hur, genus hos en undersökare eller behandlare påverkar hur man som forskningsperson eller patient upplever smärta. Eftersom många faktorer påverkar smärtupplevelsen är det svårt att bedöma och tolka pågående smärta genom att försöka mäta hur ont det gör (kvantitativ smärtskattning) utan att även försöka ta reda på hur smärtan samtidigt upplevs (kvalitativ smärtskattning).

Denna avhandling bygger på fyra vetenskapliga arbeten (I-IV), där vi undersökt hur man kan framkalla och utvärdera smärta som fortleds genom Aδ-fibrer och C-fibrer, om och hur genus hos undersökande och undersökt påverkar hur smärta upplevs, och hur man kan utvärdera smärta hos nyopererade patienter genom samtidig kvantitativ och kvalitativ smärtskattning.

I den första studien (I) har vi på friska frivilliga forskningspersoner undersökt omedelbar och fördröjd smärta. Med hjälp av extremt korta laserpulsar mot fotsulan kunde vi framkalla två kortvariga smärtupplevelser med någon sekunds mellanrum, där den första sannolikt motsvarar snabb fortledning via Aδ-fibrer och den andra långsam via C-fibrer. Samtidigt gjorde vi en intressant iakttagelse av att manliga forskningspersoner behövde starkare laserpulsar när de undersöktes av en kvinna än en man, för att uppnå samma smärtupplevelse dvs samma skattade nivåer av smärta.

Dessa resultat inspirerade oss till en uppföljande studie (II) på friska frivilliga forskningspersoner, undersökta av en kvinna och av en man, där vi ville försöka ta reda på mer om hur smärtupplevelsen påverkas av genus, hos i första hand undersökaren och i andra hand forskningspersonen.

Vi valde att framkalla smärta med en liten dosa som ger svag elektrisk ström när man håller den mellan fingertopparna. Smärtan framkallades vid två tillfällen, en gång med en kvinnlig och en gång med en manlig undersökare. I linje med vår tidigare iakttagelse behövdes det kraftigare elektrisk stimulering för att framkalla samma skattade nivåer av smärta med en kvinnlig än med en manlig undersökare, hos både kvinnor och män. Däremot hade genus hos forskningspersonerna ingen påverkan på upplevd smärta.

Vi ville undersöka om smärtupplevelsen påverkas av genus på samma sätt även på nyopererade patienter, och designade en klinisk studie (III-IV) på 245 postoperativa patienter som genomgått olika typer av kirurgi, och undersöktes på tre olika postoperativa avdelningar på Skånes universitetssjukhus i Malmö.

En kvinnlig och en manlig undersökare frågade ut patienten om smärtan snart efter att patienten kommit från operation, med ca en kvarts mellanrum (III). Vi kunde delvist bekräfta våra tidigare resultat och fann att män, men inte kvinnor, hade mindre ont när de utfrågades av en kvinna än av en man. Trots små skillnader, som antagligen inte är betydelsefulla på gruppnivå, kan våra resultat ha en betydelse för den enkla individen, speciellt med tanke på att skillnaderna i smärtnivå var som störst när det gjorde så pass ont att patienterna började fråga efter smärtlindring.

I den kliniska studien ville vi även titta på om vi kunde få en mer nyanserad bild av patienternas smärtupplevelse och därför bad vi även de postoperativa patienterna beskriva sin smärta med egna ord vid ett tillfälle (IV). Dessa totalt 17 valfria smärtbeskrivningarna kunde vi dela upp i två grupper, som reflekterade snabb (Aδ-fibrer) eller långsam (C-fibrer) fortledning av smärta. Det visade sig att det fanns ett samband mellan smärtbeskrivningar som reflekterar Aδ-fibrer-fortledning och högre skattad smärta, samt C-fiber-fortledning och lägre skattad smärta.

Sammanfattningsvis har vi kunnat visa att det är möjligt att selektivt framkalla fördröjt nocicpetivt smärtsvar med snabb pulsad koldioxidlaser, att kvinnliga undersökare har en positiv inverkan på smärtupplevelsen, samt att smärt-beskrivningar i tillägg till skattade smärtnivåer tillför en ytterligare dimension i bedömningen av patientens smärtupplevelse. Utvärdering av smärta med både kvantitativa och kvalitativa metoder, med en medvetenhet omkring eventuell genuspåverkan, kan förhoppningsvis bidra till att patienter får ett förbättrat omhändertagande och behandling av smärta, med snabbare återhämtning efter kirurgi eller andra akuta smärttillstånd.

List of publications

This thesis is based on the following original scientific papers, referred to in the text by their Roman numerals:

I. Sellgren Engskov A, Troilius Rubin A, Åkeson J.
Single and double pain responses to individually titrated ultra-short laser stimulation in humans.
BMC Anesthesiology. 2019 Mar 4;19(1):29.
doi: 10.1186/s12871-019-0702-1. PMID: 30832563; PMCID: PMC6399816.
https://bmcanesthesiol.biomedcentral.com/articles/10.1186/s12871-019-0702-1

II. Sellgren Engskov A, Lejbman I, Åkeson J.
Randomized cross-over evaluation of investigator gender on pain thresholds in healthy volunteers.
German Medical Science. 2021 Nov 29;19:Doc14.
doi: 10.3205/000301. PMID: 34955699; PMCID: PMC8662746.
https://www.egms.de/static/en/journals/gms/2021-19/000301.shtml

III. Sellgren Engskov A, Ydrefors A, el-Jaleb K, Åkeson J.
Prospective paired crossover evaluation of potential impact of investigator gender on perceived pain intensity early after acute or scheduled surgery.
Biology of Sex Differences. 2023;14: 23.
https://doi.org/10.1186/s13293-023-00508-9

IV. Sellgren Engskov A, el-Jaleb K, Dyhre H, Åkeson J.
Multidimensional evaluation of Aδ- and C-fibre-associated components of postoperative pain.
Submitted for publication.

Abbreviations

Aδ	A-delta
APOP	Acute postoperative pain
ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CO_2	Carbon dioxide
CPT	Cold pressure task
EPT	Electrical pain threshold
FLACC	Face, legs, activity, cry, consolability
GABA	Gamma-aminobutyric acid
IASP	International Association for the Study of Pain
IQR	Interquartile range
MPQ	McGill pain questionnaire
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
P	Levels of probability
PACU	Post-anaesthesia care unit
PPSP	Persisting postsurgical pain
QST	Quantitative sensory testing
SD	Standard deviation
SF-MPQ	Short-form McGill pain questionnaire
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
WDR	Wide dynamic range

Preface

Almost 15 years ago I started as a resident at the Department of Anaesthesia and Intensive care in Malmö, in southern Sweden and shortly after I asked the upcoming professor Jonas Åkeson about a research project. He had an initiated experimental study on pain which was suitable for someone to accomplish and develop. I found it exciting and accepted the challenge, thereby initiating the process of my PhD studies (Fig. 1). The project originally focused on comparing different analgesics after experimentally induced pain. Initially I acted as a study investigator but while analysing the results, I realised that a methodological study concerning 'first' and 'second' pain would be required before dealing with the analgesic drugs. However, my second study ended up being about something completely different, inspired by my incidental findings concerning investigator gender in the first study. I designed an experimental study concerning potential impact of investigator gender on pain perception, where I was one of two investigators. The results on gender impact in the second study entailed me to test my hypothesis in a clinical setting and I designed a study on postoperative patients. Besides studying impact of investigator gender (III) I also wanted to evaluate pain in a descriptive way (IV) in this clinical study. By relating individually reported verbal descriptors of pain to 'first' or 'second' pain, like in the first study, the circle was closed. I never got to the analysis of analgesics though, so I really had turned the research project to mine. I am grateful for the opportunity to act as a study investigator, study designer, and supervisor for medical students involved in my research. I have learnt a lot along this process and have used my curiosity, creativity, and caring abilities to form and develop my PhD-project. Initially I thought the process of a PhD was a straight and pre-determined road trip, but it turned out to be twisting and turning with lots of exciting surprises and challenges along the road. Just like the life itself.

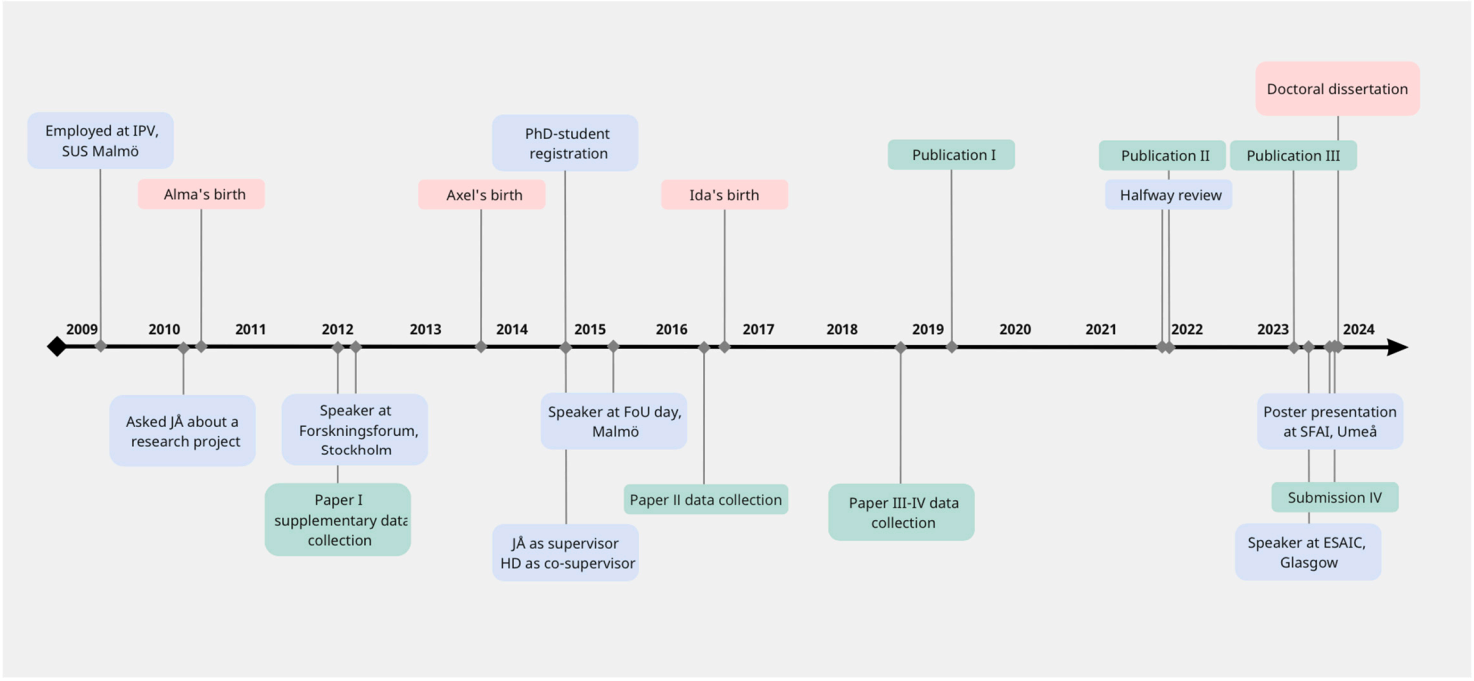

Figure 1.
Time line of my PhD research process and other life changing events. Abbreviations: HD (Henrik Dyhre), IPV (intensiv- och perioperativ vård i.e. Department of Anaesthesia and Intensive Care), SUS (Skåne University Hospital), JÅ (Jonas Åkeson)

Background

History of pain

Pain is complex, multidimensional, and individual, and an important aspect of our survival and well-being as a warning-signal of something harmful to the body (Fig. 2). The word pain originates from the Greek goddess of revenge Poine, or in Latin Poena, meaning penalty or punishment [1]. Pain has afflicted people since ancient times, originally believed to be caused by evil spirits and demons. There is early evidence from 1500 to 1300 BC of treating pain with cocoa plant leaves in pre-inca cultures and with opium in China, India and Egypt, later also used in Greece by Hippocrates in 460 BC [2]. Non-pharmacological pain relief with acupuncture was first recorded in medical texts in China in 300 BC [3]. Use of opioids for painful surgery was first documented in the 12th and 13th centuries, and in 1820-1830 morphine was industrially produced in Germany and the United States [2]. In 1947 William Livingstone established the first research-based pain clinic in the United States and in 1953 John Bonica published the first book on pain treatment options [4]. In the sixties pain was stated to be both physiological and psychological and related to this Ronald Melzack and Patrick D. Wall introduced the gate control theory of pain [5], promoting better understanding of pain perception and improved pain management [6]. Since the nineties pain is considered to be individualized and thereby believed to be best managed with a multimodal personalized approach [6]. and research on non-pharmacological, in addition to pharmacological, pain management is increasing and most relevant today.

The first official definition of pain was presented in 1979 by the International Association for the Study of Pain (IASP): ‘An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.’[7]. This definition of pain was revised in 2020: ‘An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.’[7]. Belonging notes point out that pain is always a subjective experience, influenced by physiological, psychological, and psycho-social factors. Moreover, that pain cannot be inferred only from activity in sensory neurons, and accordingly nociception and pain are different phenomena [7].

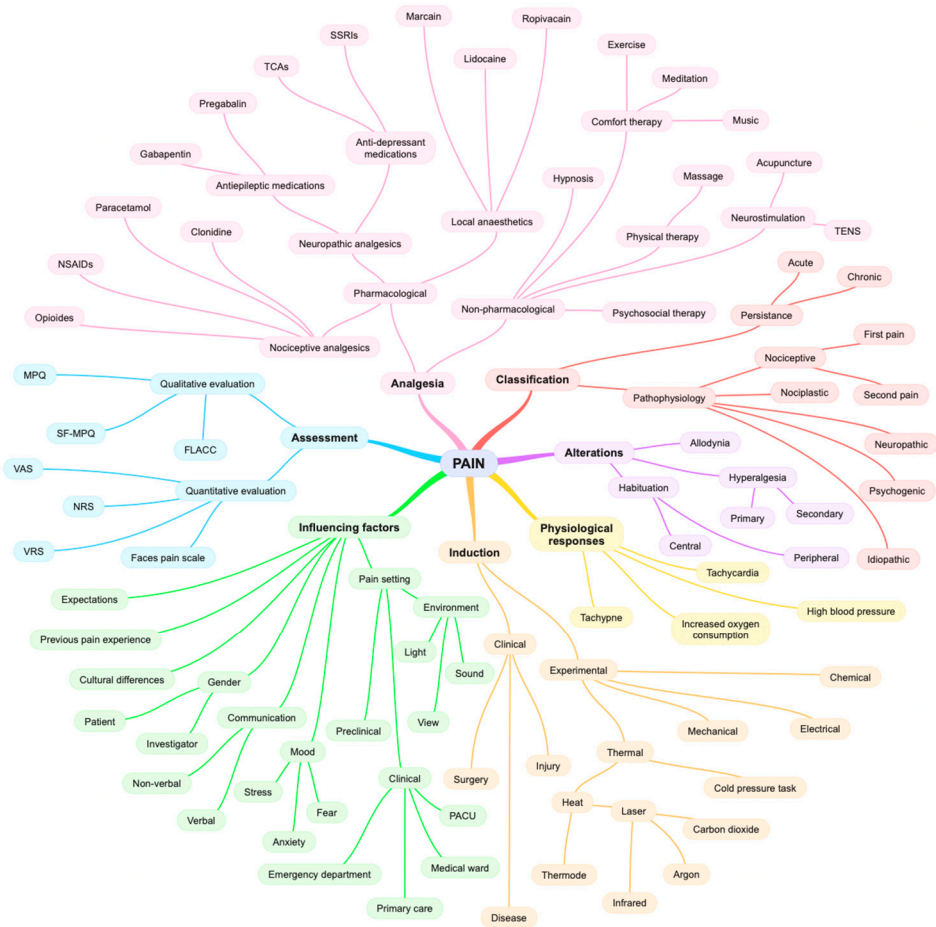

Figure 2.
Mind map showing that pain is multidimensional and individual from induction to perception. Abbreviations: FLACC (Face, legs, activity, cry, consolability), NRS (numeric rating scale), MPQ (McGill Pain Questionnaire), NSAID (Non-steroidal anti-inflammatory drug), PACU (Post-anaesthesia care unit), SF-MPQ (Short-form McGill Pain Questionnaire), SSRI (Selective serotonin reuptake inhibitor), TENS (Transcutaneous electrical nerve stimulation), TCA (Tricyclic antidepressant), VAS (visual analogue scale), VRS (verbal rating scale)

Pain classifications

Pathophysiology

Pain can be divided according to pathophysiology into nociceptive, nociplastic, neuropathic, psychogenic, and idiopathic pain, which is important for basic understanding and appropriate management of pain (Fig. 2 & 3). Nociceptive pain, discussed in this thesis, is caused by tissue damage and the most common kind of pain. Recently identified, nociplastic pain arises from altered nociception with no clear evidence of ongoing tissue damage or inflammation, e.g. fibromyalgia [8]. Neuropathic pain is caused by a primary lesion or dysfunction in the peripheral or central nervous system [9, 10].

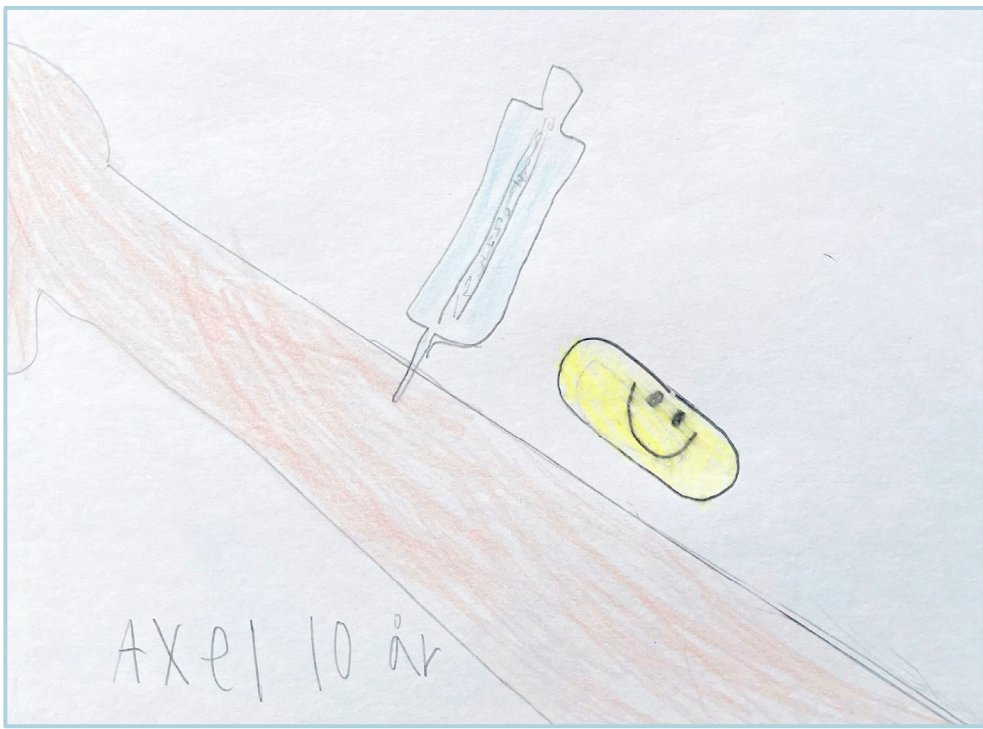

Figure 3.
Acute nociceptive pain induced by injection with a syringe and eased by a following band-aid. Drawing by my 10-year-old son Axel.

Persistence

Pain can be classified according to its duration (Fig. 2), with acute pain lasting less and chronic pain more, than three months [11]. However, the definition of chronic pain (complex long-persisting pain without actual known causes) is questioned since its focus on time, which is not crucial for pain lasting more than three months, overshadows influence of psychological and psycho-social factors on onset, maintenance, and exacerbation of pain, possibly affecting strategies of patient management [12].

Neurophysiology of nociceptive pain

Nociception – derived from the Latin words 'noxe', meaning damage, and 'recipere', meaning catch – is the process of detecting and responding to noxious or potentially harmful stimuli of heat, cold, pressure or chemicals. Tissue damage activates nociceptors, which are free nerve endings in the epidermis, branched from the main axon of a nociceptive neuron, converting the physical or chemical energy into action potentials travelling along primary nociceptive neurons to synapse on second-order neurons within the dorsal horn of the spinal cord [13]. Axons of these neurons then traverse to the opposite side of the spinal cord and ascend within the spinothalamic tract to the thalamus [13, 14] (or to the medulla oblongata, activating the autonomous nervous system). Via tertiary neurones from the thalamus the nociceptive signal ascends to the somatosensory cortex where awareness of pain occurs, to the limbic system where emotional responses like anxiety, fear and stress are trigged, and to the frontal cortex where interpretation of impact analysis of pain takes place – altogether creating a pain sensation [13].

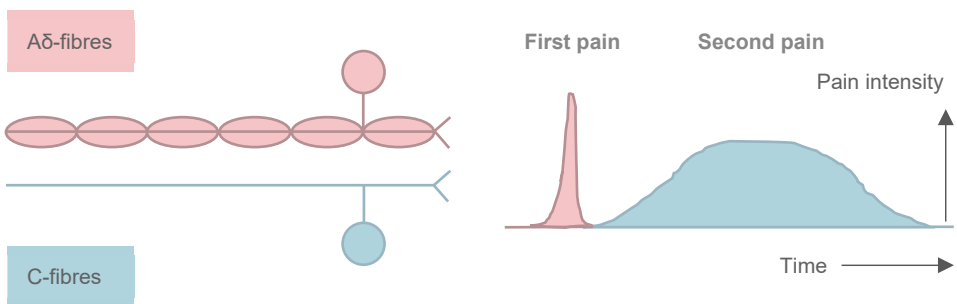

Figure 4.
Principal outlines of myelinated Aδ-fibres and nonmyelinated C-fibres, mediating 'first' and 'second' pain responses, respectively.

A process of pain perception involves various neurotransmitters, including both inflammatory mediators, such as prostaglandins, serotonin, histamine, glutamate and norepinephrine, and non-inflammatory mediators, such as gamma-aminobutyric acid (GABA), opioid peptides and cannabinoids [10].

There are two kinds of primary nociceptive neurons (Fig. 4). Myelinated Aδ-fibres with noduli are characterized by transmitting immediate (5-30 m/s), distinct, pricking, and localized sensations of (warning) pain, connecting to a few interneurons within a small area in the spinal dorsal horn – 'first pain' [15]. Thinner nonmyelinated C-fibres are characterized by transmitting delayed (0.5-2 m/s), dull or pressing, aching, and less well-confined sensations of pain, branching in a more diffuse manner in the dorsal horn – 'second pain' [14, 15]. Thermal activation thresholds of the nociceptors (to fire action potentials) are 44.3–46.5°C for Aδ-fibres and 41.8–42.4°C for C-fibres at foot level [16]. Acute pain is mediated by both Aδ- and C-fibres and chronic pain primary by C-fibres [17]. In contrast to mechanoreceptors, nociceptors do not adapt to repeated stimuli, leading to continuous firing if the painful stimulation persists [18].

Altered perception

Primary hyperalgesia (Fig. 2) is increased sensitivity to pain at the site of tissue damage [19]. Peripheral sensitization is the underlying mechanism of this enhanced and prolonged response to painful stimuli, involving decrease in activation threshold and increase in firing rate of primary afferent nociceptors facilitated by prostaglandins [10]. This process may also cause allodynia, where normally non-painful stimuli suddenly become painful [19].

Secondary hyperalgesia (Fig. 2) is due to central sensitization in the spinal dorsal horn, where interneurons called wide-dynamic-range neurons, usually transmitting non-nociceptive signals from larger body regions, are activated by repeated stimuli causing amplifications of the nociceptive information, leading to excitability of these neurons involving inflammatory mediators (including substance P and glutamate) [10]. This upregulation (wind-up) will cause hyperalgesia within a larger area surrounding the site of injury [19]. By promoting release of prostaglandins, central sensitization can also cause allodynia, i.e. triggering of pain responses by light touching, normally not provoking pain [10].

The opposite of sensitization is habituation [20], which is a passive process to repetitive painful stimuli (Fig. 2), either peripheral by a decrease in sensitivity of peripheral nociceptors with fatigue [21] or central by a reduction in the responsiveness of the CNS [22]. There are also pain descending inhibitory systems involving active modulation of pain signals within the CNS, primarily within the dorsal horn, by release of serotonin, norepinephrine, dopamine, and GABA [10]. This phenomenon of endogenous analgesia is mediated mainly by opioid and

cannabinoid signalling in the periaqueductal grey of the midbrain [23]. Dysregulation of these counter-balanced systems of pain modulation may promote transition of acute pain to chronic pain [19].

Spinal modulation

The gate control theory [5] is a widely accepted neurophysiological model and facilitates understanding of pain processing. It implies a 'gate' in the spinal cord that controls transmission of pain by inhibitory and exhibitory signals from nociceptors and other sensory receptors to the brain. A strong nociceptive input can open the gate allowing more pain signals to pass through, whereas a strong non-nociceptive sensory input e.g. gentle touch, can close the gate. Likewise, psychological, and emotional factors, like anxiety or stress, can promote opening of the gate, while relaxation or distraction can close the gate. The theory also emphasizes that pain perception is individual and influenced by neurophysiological and psychological conditions, and by earlier experiences [5].

Physiological responses

Pain triggers neuro-endocrine stress responses (Fig. 2), activating the hypothalamic-pituitary-adrenocortical and sympatho-adrenal systems, with increased sympathetic tone and higher plasma levels of catecholamines elevating the heart rate, blood pressure, oxygen consumption, and respiratory rate [24] – vital parameters also recently confirmed to reflect early individual medical deterioration at the bedside in various clinical settings.

Experimentally induced pain

To evaluate pain perception in experimentally settings, individual responses to controlled painful thermal (heat or cold), mechanical, electrical, or chemical stimulation (Fig. 2), are quantified. These various methods, designed to evaluate pain sensitivity, are referred to as quantitative sensory testing (QST) [25].

Thermal induction of pain based on laser stimulation enables reproducible, reliable, individually adjustable, non-inflammatory and rapidly transient activation of the nociceptive system without simultaneous activation of mechanosensitive afferents [26], thereby providing selective activation of Aδ- and C-fibres [27, 28]. Argon and carbon dioxide (CO_2) laser techniques have often been used in experimental pain studies, with no or minimum skin damage [26], whereas infrared laser is less used for induction of pain [29]. Direct dermal contact heat with a thermode can be used for rapid heating, activating Aδ- and C-fibres, or slow heating, mainly activating C-

fibres [30]. Thermal induction of pain with cold pressure task (CPT) is a reliable and reproducible technique, where study participants submerge their hands and forearms in ice-cold water, while pain threshold, intensity and tolerance are being determined [31].

Mechanical induction of pain, also considered reliable and easily applicable [32], includes pinprick stimulation with a needle mainly activating Aδ-fibres [15], and pressure stimulation with an algometer, activating both Aδ- and C-fibres [30].

Electrical induction of pain, with short-lasting and reproducible pulses, bypasses nociceptors and activates neurones directly with standardized timing and intensity, producing EPT [33] and mainly activating Aδ-fibre-mediated pain [34]. Stimulation is delivered by transdermal weak electric current in the finger pulps (Painmatcher®) [35], and at the dorsum of the hand [36], or by intraepidermal electrode technique [37].

Chemical induction of pain, primary with low-dose capsaicin (chili pepper), reproducibly produces long-lasting cutaneous hyperalgesia with low risk of skin injury [38].

Surgical pain

Early postoperative pain (Fig. 2) is reported by up to 80 % of surgical patients [39-41], and pain relief after surgery is often insufficient [41-43] despite improvements in prediction and treatment of pain [41]. Acute postoperative pain (APOP) has been estimated to turn into persisting postsurgical pain (PPSP) beyond three months after surgery in 10-50 % [44, 45], and was reported to be the highest risk factor of PPSP beyond six months after surgery in a recent study [46]. Especially severe postoperative pain may contribute to conversion of APOP to PPSP [44, 45]. Efficient early management of APOP is essential to avoid delayed mobilization and rehabilitation, immediate and long-term impact on patients' life and in a wider perspective higher healthcare cost. A prerequisite for this is appropriate assessment of pain. However, evaluating pain early after surgery might be difficult due to potentially reduced cognitive ability after anaesthesia [47], postoperative nausea [48], and potential anxiety [49].

Assessment of pain intesity

The most common way of assessing pain is by rating the level of pain intensity (Fig. 2).

Verbal rating scale

The verbal rating scale (VRS) (Fig. 5), used for a long time, includes few eligible words with corresponding numbers (0–3) for pain description of pain as: 'no' (0), 'mild' (1), 'moderate' (2), and 'severe' (3) [50]. This scale, developed to readily evaluate pain treatment, is short, simple, and easy to use in clinical practice, but lacks enough accuracy for research. Nevertheless, the VRS has been reported to provide reliable scientific information [51].

Numeric rating scale

The numeric rating scale (NRS) (Fig. 5) is an eleven-level scale from 1978 where the patient is asked to assess the perceived pain intensity of ongoing pain from 0 ('no') to 10 ('worst imaginable'). The NRS can be applied visually – positioned vertically or horizontally – or verbally [52], and is easy to administer and use with high compliance and good responsiveness [53]. NRS scores correspond well with VAS scores [54] but have lower accuracy. When applied verbally, auditory memory may influence scores obtained, particularly with repeated NRS assessments at short time intervals.

Visual analogue scale

The visual analogue scale (VAS) (Fig. 5) is a 101-level horizontally or vertically used 100-mm slide ruler, originally introduced in 1921, and still considered to provide accurate, valid, reliable and reproducible information. The patient, blinded to the scored level, is asked to assess the perceived level of intensity of ongoing pain between 'no' and 'worst imaginable' by sliding a marker along the ruler [55]. The investigator records the scored level of pain intensity with one decimal from the backside of the ruler. Incorrect recording is a potential source of error [56, 57], recently reported to be avoidable with digital instead of a paper-based tools for evaluation [55, 58]. Until recently, it was still controversial whether the VAS is linear or non-linear [59]. However, non-linearity of the VAS has now been confirmed, based on considerable differences in clinical relevance of the same numeric changes in score levels along the scale [33, 60, 61]. Accordingly, study data obtained with the VAS should be reported, analysed, and interpreted based on continuous methods for ordinal data.

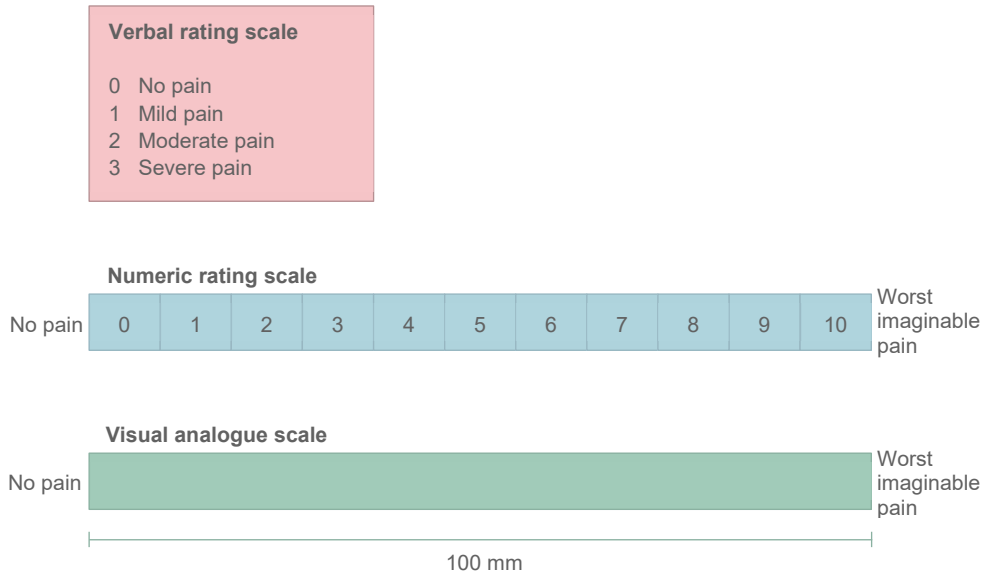

Figure 5.
Unidimensional pain evaluation tools for assesment of pain intensity.

Faces pain rating scale

The Wong-Baker faces pain rating scale was originally created in 1983 with children for children to help them communicate about their pain and thereby facilitate pain assessment. It is simple and quick and suitable for children from three years of age, extensively validated in healthy school children with postoperative pain [62].

Face, legs, activity, cry, consolability scale

The five-category face, legs, activity, cry, consolability (FLACC) scale was developed in 1997 to help parents and professionals to assess pain levels in children from two months to seven years of age with limited or no expressive communication. Each category is scored on a three-level scale (0/1/2), with a total maximum of score 10. Based on the total score, the level of pain or discomfort is classified as ‘relaxed and comfortable’, ‘mild discomfort’, ‘moderate pain’, ‘severe discomfort of pain or both’. The FLACC pain scale has been found to be valid and reliable, but a disadvantage is that children might show these behaviours also without pain [63].

Matching ongoing pain

Direct matching of ongoing pain intensity with an experimentally induced pain has been proposed to provide more objective assessments than with NRS or VAS [64]. The Painmatcher® device (Cefar Medical AB, Lund, Sweden), introduced in the early zeroes, was designed to induce gradually increasing electrical stimulation of sensory nerve fibres in the finger tips until the perceived intensity of pain matches the intensity of ongoing other pain [64]. It has been reported to be as reliable as VAS [64] but less sensitive to changes in pain intensity [65]. Poor correlation has been reported between study data obtained with Painmatcher and VAS in acute [65] and chronic [35] pain. The 'Hardy-Wolff-Goodell dolorimeter' is another pain matching tool, producing thermal painful stimulus by focusing light on a blackened area of skin, developed in the 1940's and used for the first time in 1951 during labour, however without success as parturients were unwilling to cooperate [66].

Assessment of pain quality

In addition to traditional quantitative pain evaluation tools, instruments for qualitative pain assessment (Fig. 2) have made progress over the last 50 years.

McGill pain questionnaire

The McGill pain questionnaire (MPQ) (Table 1) focusing on both physiological and psychological components of pain, was developed in 1975 by Ronald Melzack. It comprises 78 verbal pain descriptors, categorized to reflect sensory-discriminative, emotional-affective or cognitive-evaluative aspects on pain. In addition, there are three major measures: the pain rating index (1), depending on two types of numerical values that can be assigned to each verbal descriptor, the number of words chosen (2) and the current pain intensity (3), based on a five-level intensity scale from 1 to 5 [67].

'How we come by our knowledge of another person's pain is a nice study in communication. It has much in common with the sort of communication attempted by the painter, the poet and the musician – the conveying of moods and feelings'

James Parkhouse 1963

Table 1.
The 78 chosable quality verbal descriptors of pain included in the McGill pain questionnaire.

Group	Pain descriptor
1	Flickering, quivering, pulsing, throbbing, beating, pounding
2	Jumping, flashing, shooting
3	Pricking, boring, drilling, stabbing, lancinating
4	Sharp, cutting, lacerating
5	Pinching, pressing, gnawing, cramping, crushing
6	Tugging, pulling, wrenching
7	Hot, burning, scalding, searing
8	Tingling, itchy, smarting, stinging
9	Dull, sore, hurting, aching, heavy
10	Tender, taut, rasping, splitting
11	Tiring, exhausting
12	Sickening, suffocating
13	Fearful, frightful, terrifying
14	Punishing, grueling, cruel, vicious, killing
15	Wretched, blinding
16	Annoying, troublesome, miserable, intense, unbearable
17	Spreading, radiating, penetrating, piercing
18	Tight, numb, squeezing, drawing, tearing
19	Cool, cold, freezing
20	Nagging, nauseating, agonizing, dreadful, torturing

Short-form McGill pain questionnaire

In 1987 Ronald Melzack developed a short-form of the MPQ (SF-MPQ) with 15 (eleven sensory and four affective) verbal pain descriptors. Perceived intensity of each descriptor is rated on a four-level intensity scale as 0 (‘none’), 1 (‘mild’), 2 (‘moderate’), and 3 (‘severe’), and three total pain scores reflecting sensory, affective and total descriptors are calculated. The SF-MPQ also includes the PPI of the MPQ and the VAS [68].

Factors influencing pain perception

Individual pain perception (Table 2) is multidimensional (Fig. 2) and influenced by interacting physiological, psychological, and social factors [69, 70].

Gender and sex

The term gender, based on social (instead of sex based on biological) characteristics according to the World Health Organization, is used in this thesis. There is increasing evidence for gender differences in pain sensitivity and analgesic response due to sex-related factors and gender roles, according to clinical and experimental studies regarding both acute and chronic pain [71].

Experimental studies reported higher pain sensitivity in females compared with males [18, 72-83][84-87], possibly reflecting sex differences [84] or psychosocial factors like gender-role expectations [88, 89]. Others did not find any gender difference in pain sensitivity to experimental pain [83, 88, 90]. In several clinical studies females perceived more pain than males after surgery [91-95], while others did not find any gender difference in postoperative pain [72, 96] or pain related to venous cannulation [97].

According to a recent review, chronic pain is more common in females [71], possibly because of differences in sex hormones [98]. Feminizing hormones (oestrogen and progesterone) were associated with higher pain sensitivity and with more musculoskeletal pain or headache, while masculinizing hormones (e.g. testosterone) were found to be protective against pain [98]. During labour elevated levels of oxytocin enhance positive mood and reduce anxiety, stress and pain [99].

Regarding investigator gender, there are experimental findings of lower pain sensitivity (higher pain threshold or lower pain intensity) in study participants evaluated by females [80-82, 85, 87, 88, 100-103]. Lower levels of pain intensity have been reported to female investigators in non-surgical orthopaedic patients [104, 105], but not in emergency care patients [106, 107] or early after cardiac surgery [108].

Age

The prevalence of pain in elderly has been reported to be higher than in [109, 110], or not differ from [111, 112], the general population. Pain sensitivity decreases with ageing, as recently established in an extensive review [83], also reporting decreased pain thresholds especially in lower pain range, in response to thermal heat, but not to pressure or electricity.

There is neurophysiological support of diminished ability of detecting harmful signals [113, 114], due to a decrease in grey masse [115] and Aδ-fibres replaced by proliferating non-neuronal glial cells [116]. According to MRI studies, there is reduced activation of heat-induced pain in the insula and somatosensory cortex with increasing age [117, 118]. However, pain assessment might be challenging in elderly patients due to under-reporting, cognitive and sensory impairment [110].

Culture

Culture is a wide conception including ethnic background, religious beliefs, and socioeconomic affiliation. In the context of pain, it refers to social groups with similar predisposing characteristics [119]. Studies on pain and culture have primarily been performed in the United States comparing different ethnicities (using American established terms), finding patients of black American [120-124] and Latino [124-126] descent to have higher pain sensitivity than those of European descent, with more pronounced differences in females after surgery [127]. A study outside the Unites States on experimental pain found that Italian females had higher pain intensity scores compared with Swedes and Saudis [128]. According to a recent review [119] those culture-associated pain differences are probably most due to sociodemographic factors.

When to seek treatment for pain [129] and call for analgesics [130] is influenced by culture. Cultural differences in expression of pain [129], and knowledge of language [131], may affect communication of pain – with potential misinterpretation [132] and impaired interaction [133, 134] between patients and healthcare providers – more than actual pain. Being aware of cultural differences is a precondition for providing equal medical care and improving pain management [119].

Mood

Pain and mood are closely associated [135], with higher pain intensity following negative mood and lower pain intensity following positive mood, in acute [136] and chronic pain conditions [137]. Pain associated with a joyful experience e.g. childbirth, is probably easier to deal with than pain associated with malignancy.

Pain might be the primary symptom in depressed patients. Hence, responses to experimentally induced pain in those patients vary more various concerning pain threshold and pain tolerance. Depression and anxiety have been found to increase individual perception of acute pain intensity, and prolonged duration of acute pain has been found to be associated with mood dysregulation [138]. Imagination of expecting the worst may also exaggerate pain in terms of pain catastrophizing (Table 2).

Stress-induced analgesia, allowing an injured person ignoring the pain because of other stressful situations ongoing at the same time, is well documented in animal

studies [139-142], and suggested to be influenced by norepinephrine [143]. Humans, compared with animals, have higher levels of cognitive processing of pain [144], which make it difficult to study one specific parameter (e.g. stress, which is also difficult to measure) affecting pain perception. Few studies have reported stress-induced analgesia in humans after noxious heat [145-147] or physical stress [148], and of enhanced pain during stress has also been found in patients with chronic pain (42), gastro-oesophageal reflux (98) or fibromyalgia [149], and accordingly stress-reducing psychological interventions have been used to alleviate pain in patients undergoing surgery [49, 150].

Experience

Individual perception of pain is also potentially influenced by earlier painful experiences [151, 152], and anticipation of pain has been reported to alter cortical nociceptive activity, despite no actual noxious stimulation, in study participants expecting a painful stimulus [153].

Individuals with more lifetime pain reacted more, i.e. had lower tolerance to cold pressure-induced pain [152], and females with recent painful occasions had higher pain sensitivity to thermal heat stimuli [87]. Higher pain sensitivity was also found in patients with chronic pancreatitis and previous experience of pain [154].

Associations have been found between pain history and tolerance to experimental pain in patients with chronic pain [155], and also in patients evaluated for prediction of postoperative pain [156]. This has been further explored in clinical studies on pain intensity levels associated with peripheral venous catheterization prior to surgery, where patients reporting cannulation-induced intensity of pain at or above 2.0 VAS units more often also developed moderate or severe surgical pain in the early postoperative period [157, 158].

Environment

Pain experience might be affected by the surroundings, situation, and social context. A bright recovery room with natural light and view of a landscape, might have a positive impact on pain [159], and patients listening to music after elective cardiac valve replacement, were found to have less postoperative pain and anxiety [160]. Intimate study settings with one-to-one environment facilitate nonverbal patient-physician interaction [74], possibly alleviating the patients' pain experience. In patients with chronic pain there is an association between more supportive social interactions, enhancing positive mood, and less pain [161, 162]. Accordingly, study participants have also been found to report lower intensity of ongoing pain after noxious thermal stimulation while viewing pictures of their partner than of a stranger [163].

Table 2.
Terminology of pain related expressions.

Pain vocabulary	
Pain sensitivity	Individual proneness to react to painful stimuli. (Previously difference between pain threshold and pain tolerance.)
Pain perception	Individual response to a noxious stimulation influenced by sensory, emotional, cognitive and behavioral dimensions.
Pain intensity	Magnitude of percieved pain.
Pain threshold	Individual minimum intensity of stimulus percieved as painful.
Pain tolerance	Individual maximum amount of pain percieved as bearable.
Pain catastrophizing	Negative cognitive-affective response to anticipated or actual pain with tendency to magnify the severity of pain, feel helpless in dealing with it and expect the worst possible outcomes.
Pain management	Pharmacological and non-pharmacological measures to prevent, reduce or stop pain sensations.

Aims

Aims of this thesis on various aspects of acute nociceptive pain in humans were to evaluate

- selective induction and assessment of delayed responses to nociceptive pain in humans (I).
- impact of participant gender on perception of nociceptive pain induced by stimulation with ultra-short laser, weak electrical current or surgery (I-IV).
- influence of investigator gender on assessment of nociceptive pain in experimental and clinical settings (II, III).
- relationship between investigator gender and energy levels of electrical stimulation to attain individual pain thresholds (II).
- association of investigator gender with postoperative pain intensity early after surgery (III).
- correlation of optional verbal descriptors of pain quality with Aδ- and C-fibre-associated pain early after surgery (IV).
- associations between reported optional descriptors of Aδ- and C-fibre-mediated pain and reported intensity levels of early postoperative pain (IV).

Methods

This thesis comprises two preclinical and two clinical scientific studies (Table 3). The first two papers (I-II) are based on two prospective preclinical studies in adult volunteers, with randomized paired crossover design in the second one (II). The third and fourth papers (III-IV) are based on a prospective observational study in three post-anaesthesia care units (PACUs) at Skåne University Hospital, Malmö, in southern Sweden.

All studies (I-IV) were approved by the regional Human Research Ethics Review Board in Lund, Sweden. The two clinical ones (III-IV) were also registered in the clinicaltrials.gov research database.

Study participants

Table 3.
Basic data on analysed study participants in papers I-IV. Abbreviations: n (number of patients)

Paper	Study design	Study participants	n (female)
I	Prospective unpaired	Healthy volunteers	42 (12)
II	Prospective randomized paired crossover	Healthy volunteers	40 (22)
III	Prospective observational paired crossover	Postoperative patients	244 (128)
IV	Prospective observational unpaired	Postoperative patients	227 (119)

Paper I

Forty-four healthy adult volunteers with no current history of pain were included in this preclinical prospective study (Table 3). Thermally induced individual nociceptive pain thresholds were determined based on ultra-short pulsed CO_2 laser stimulation in the plantar arc in each study volunteer by one of three study investigators (one female and two males). Each participant was subjected to four complete series, comprising three stimuli each, of laser stimulation, with predetermined individually titrated laser energy levels.

Paper II

Forty healthy adult volunteers with no current history of pain were included (Table 3 & Fig. 6). Each participant was subjected to electrical pain stimulation to induce pain threshold (in a series of three) and evaluated pain intensity, twice at 10-to-15-minute intervals, according to a predefined randomized crossover design schedule, by a female and a male investigator. The participants were blinded to the main purpose of the study.

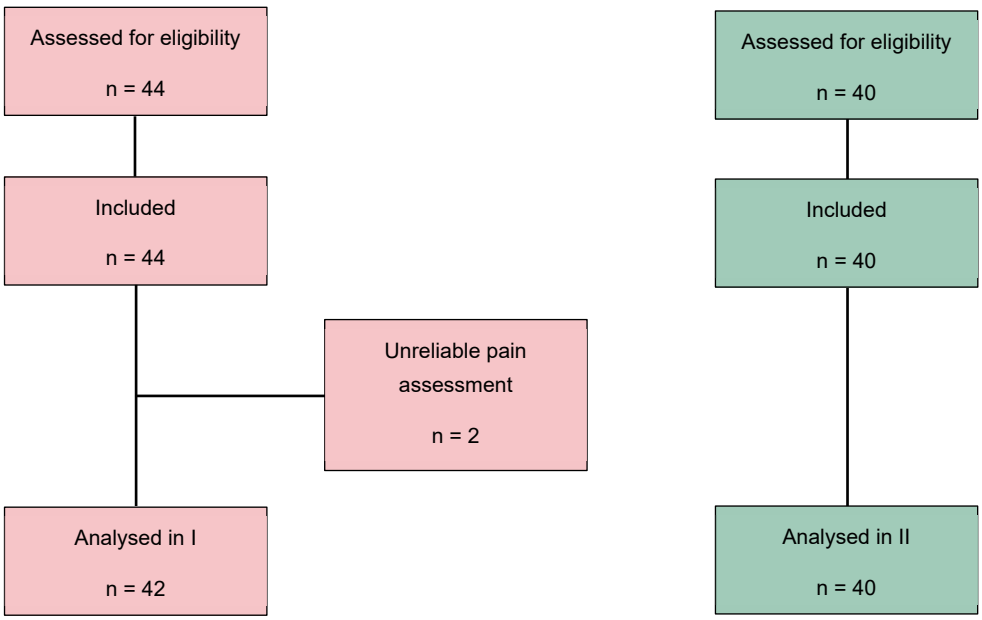

Figure 6.
Flow charts of the inclusion process of study participants in papers I and II.

Papers III-IV

In total, 245 adult patients subjected to scheduled or acute, in- or out-hospital, abdominal, urological, gynaecological, vascular or breast surgery with different surgical techniques, aged 18 years or above, with cognitive and linguistic abilities to participate, and with perceived postoperative pain at the time of initial evaluation, were included in this prospective observational clinical study (Fig. 7 & Table 3).

The study patients, blinded to the main purpose of the study, received study information on evaluation by verbal pain descriptors and pain intensity scores, but

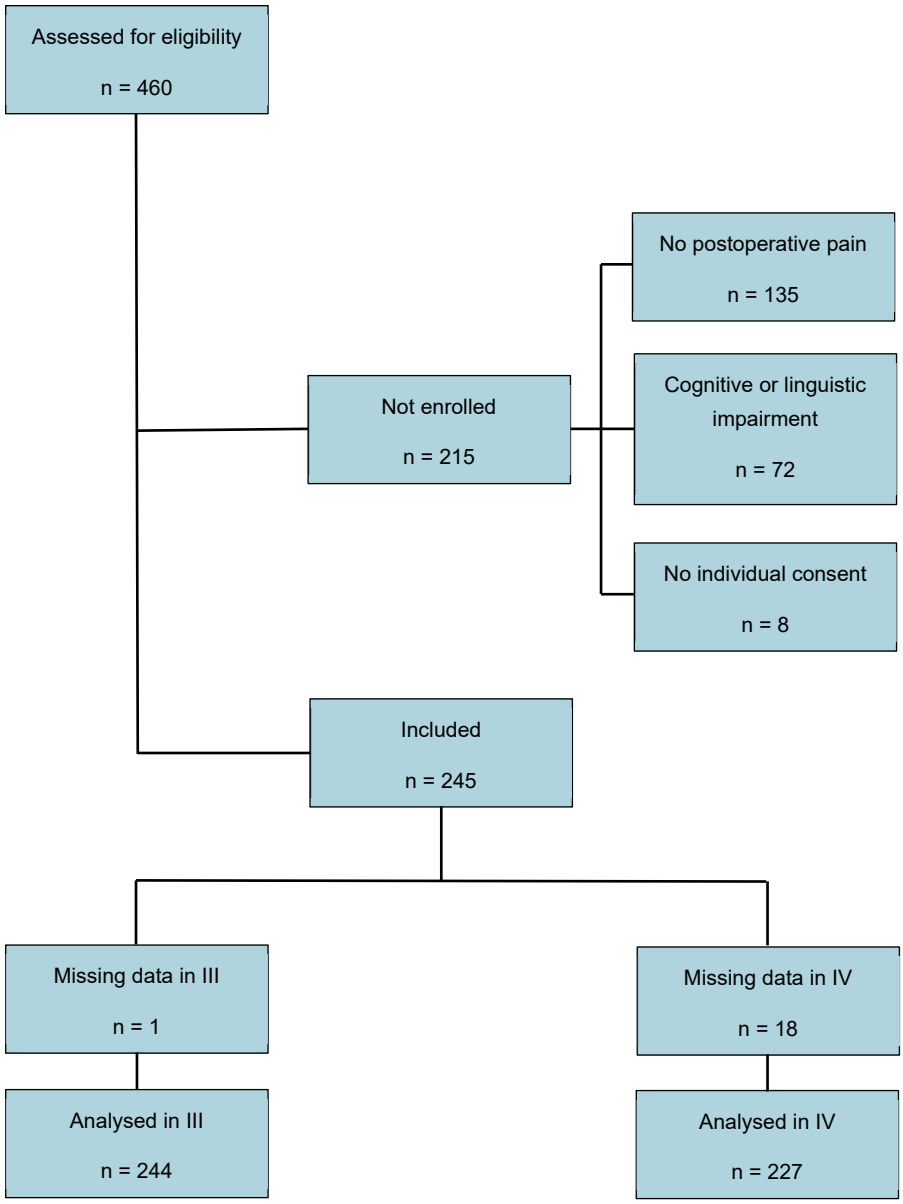

Figure 7.
Flow chart of the inclusion process of study patients in papers III and IV.

not on potential impact of investigator or patient gender. Postoperative pain was evaluated with verbal pain descriptors and VAS early after arrival in the PACU (IV). Pain intensity levels were evaluated twice in each study patient – with approximately 15 minutes in between – according to a paired crossover study design, by two investigators of opposite genders (III).

Induction of pain

Laser stimulation (I)

Nociceptive pain was thermally induced by ultra-short pulsed CO_2 laser stimulation (10 W effect, 3 mm beam diameter), with a Coherent Ultrapulse 2500C w CPG Laser (Coherent Inc., Santa Clara, California, USA), in the plantar arc. A primary outcome parameter was individual level of laser energy density. At the time of evaluation, the study participants were familiar with the technique of CO_2 laser stimulation, since the laser energy to be consistently used in each participant was determined at least 48 hours in advance by incremental five-millisecond increases in pulse duration, starting at 10 ms, until mild intensity levels of immediate and/or delayed pain were consistently induced. Individual levels of laser energy density (mJ/mm^2) were calculated from laser effect, pulse duration, and beam diameter. During the following study session individually titrated levels of laser energy were delivered in series of four in slightly different skin areas at minute-long intervals.

Electrical stimulation (II)

Weak electrical current was used to induce nociceptive pain (Fig. 8), and thereby determine individual electrical pain thresholds (EPT), with a stimulation device called Painmatcher® (Cefar Medical AB, Lund, Sweden), delivering monophasic rectangular electrical pulses of 10 Hz frequency and 15 mA amplitude on closure of a circuit between the thumb and index finger. To gradually increase pain intensity, the pulse duration is increased to a maximum of 396 μs in steps of 4 μs. The maximum energy delivered in pain magnitude scores (0–99) is recorded by the investigator from a display hidden to the subject. The study participants were told to press two buttons simultaneously on the device between their finger pulps, and then to release them as soon as the level of stimulation was considered to be painful, in series of three, and individual mean scores of EPT were calculated.

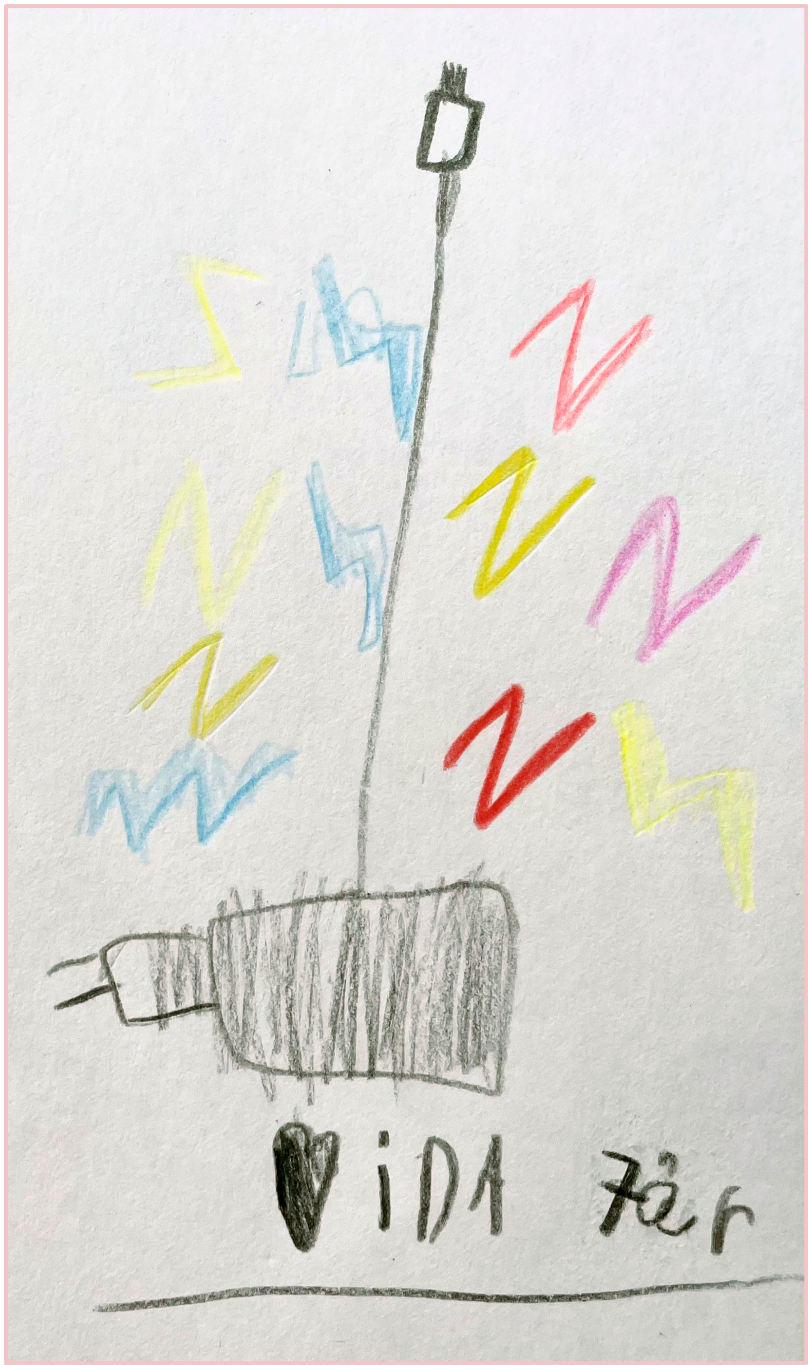

Figure 8.
Stimulation of pain with electricity. Drawing by my 7-year-old daughter Ida.

Surgical stimulation (III-IV)

Clinical acute pain was evaluated early after various kinds of acute or scheduled in- or our-hospital surgery in a mixed cohort of adult postoperative patients. The procedures comprised abdominal, urological, gynaecological, vascular or breast surgery with endoscopic/minimally invasive, laparoscopic, or open techniques.

Evaluation of pain

Assessment of pain intensity (I-IV)

For quantitative evaluation of pain, we have chosen VAS, considered as the golden standard for assessment of pain intensity levels with high accuracy. A primary outcome parameter in all studies included in this thesis was pain intensity assessed with VAS. Mild and moderate-to-severe pain was defined as pain intensity scores below and above 4.0 VAS units.

Assessment of pain quality (IV)

Individual verbal descriptors were chosen for qualitative evaluation of pain. The study patients were asked to describe the character of perceived ongoing pain in their own words in Swedish (subsequently translated into English). The first pain descriptor reported by each patient was recorded and categorized according to its association with myelinated Aδ-fibre-mediated, nonmyelinated C-fibre-mediated or non-specific pain, based on a proposed MPQ pain quality descriptor ranking for discrimination between nociceptors [29].

Statistics (I-IV)

Parametrical data is reported as mean ± standard deviation (SD). Non-parametrical data (of laser energy density, EPT and pain intensity levels) is reported as median with interquartile range (IQR). Proportions are reported with 95 % confidence interval (CI).

The Mann-Whitney U-test was used to compare continuous variables (of laser energy density, EPT and pain intensity levels) between study groups (I-IV).

The Wilcoxon signed rank test was used to compare the nonparametric distribution of paired variables (EPT and pain intensity levels) between female and male investigators, and between first and second study occasions (II, III).

Individual mean values of pain intensity levels were tested for order effect with the Friedman´s test, and linear regression with a mixed model approach (I).

Proportions of categorical variables were compared with Pearson's Chi-square test (investigator gender, and pain intensity scores below/above 4.0 VAS units) (III), and Fisher's exact test (Aδ- and C-fibre-associated categories of verbal pain descriptors, pain intensity scores below/above 4.0 VAS units, and patient gender) (IV).

The Bland-Altman plot was used to compare individual differences of pain intensity scores between the investigators, and individual mean values of pain intensity (III).

Levels of probability (*P*) below 0.05 were considered statistically significant (I-IV). The Bonferroni test was used to adjust for multiple significance when necessary (II).

Results and reflections

Table 4.
Demographic data on study participants in papers I-IV. Abbreviations: ASA (American Society of Anesthesiologists), n (number of patients)

	I	II	III	IV
	n (%)	n (%)	n (%)	n (%)
Gender				
Female	12 (29)	22 (55)	128 (52)	119 (52)
Male	30 (71)	18 (45)	116 (48)	108 (48)
Age				
18-29 years	36 (86)	33 (83)	23 (9)	21 (9)
30-49 years	6 (14)	7 (17)	53 (22)	53 (24)
50-64 years	0 (0)	0 (0)	53 (22)	46 (20)
65+ years	0 (0)	0 (0)	115 (47)	107 (47)
Weight				
≤ 50 kg	0 (0)	0 (0)	3 (1)	3 (1)
51-89 kg	38 (90)	40 (100)	182 (75)	167 (74)
≥ 90 kg	4 (10)	0 (0)	58 (24)	56 (25)
ASA classification				
I	42 (100)	40 (100)	47 (19)	45 (20)
II	0 (0)	0 (0)	127 (52)	116 (51)
III	0 (0)	0 (0)	67 (28)	64 (28)
IV	0 (0)	0 (0)	3 (1)	2 (1)

Induction of pain (I-IV)

Is stimulation with laser or electricity appropriate for induction of pain? (I, II)

All patients (Table 4) reported either single or double pain responses to CO_2 laser stimulation (I). Thus, this technique meets criteria for induction of nociceptive pain in a reliable and reproducible way, as also confirmed by others [164]. The CO_2 laser

enables use of carefully titrated energy density levels to determine individual pain thresholds while avoiding skin damage. In contrast, predetermined energy levels of laser stimulation have been used by others [16, 164-167]. Individual titration by gradually increasing the laser pulse duration [168, 169] at slightly different sites, also reduces potential risks of peripheral sensitisation and habituation [21].

All study participants (Table 4) repeated self-induced series of electrical pain stimulation with the Painmatcher® once, and individual EPT levels did not differ between the first and second series ($P > 0.300$) (II). Hence, this user-friendly, affordable, and portable device [37] induces nociceptive pain in a reproducible and reliable way [33], in agreement with results obtained by electrical stimulation of the thumb and index finger with a similar device [83].

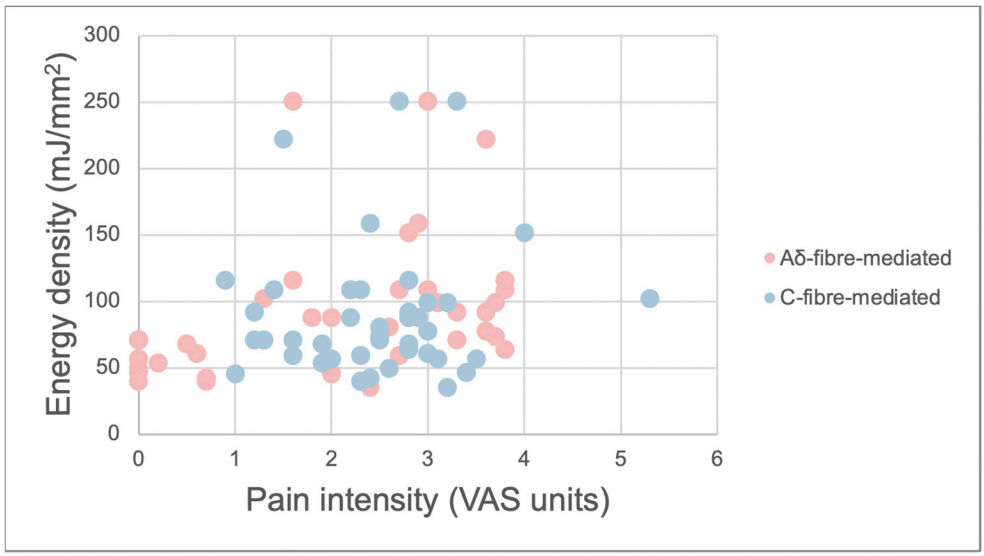

Figure 9.
Individually titrated levels of energy density and correspondingly reported intensity levels of immediate and delayed pain responses to ultra-short stimulation with CO_2 laser in 42 healthy adult volunteers (I). Immediate and delayed responses are interpreted to reflect Aδ- and C-fibre-mediated pain, respectively. Abbrevation: VAS (visual analogue scale)

Can ultra-short laser stimulation selectively induce delayed pain? (I)

In our study cohort (I), the first component of pain appeared immediately and the second at least one second after the laser pulse, with all single pain responses being delayed. Twenty-nine study participants consistently reported double pain responses to each nociceptive stimulus, whereas thirteen reported single pain responses at least once. In study participants with single, compared with double, pain responses, significantly lower median (IQR) levels of energy density were used (62 (54-71) vs.

88 (64-110) mJ/mm^2; $P = 0.003$) (Fig. 9), in agreement with warning signalling by Aδ-fibres [16]. Thus, ultra-short laser pulses allow both pain components to be independently evaluated provided that temperature thresholds of both kinds of nociceptors are exceeded [16, 28, 164, 165, 170, 171]. Maximum separation in time, to improve registration, of first and second pain responses, is achieved by inducing pain in the foot [16, 166, 170] instead of in the hand [28, 171-174], enabling 35 % more delayed transmission of the delayed pain response.

Although nociceptor thresholds are dependent on baseline skin temperature [164], this ultra-short laser technique has been shown to induce similar local heating patterns at skin temperatures between 27 and 32 °C [16, 169]. We did not measure skin temperature, but considering that Aδ-fibre nociceptors demand 2.5–4.1°C higher temperature than C-fibres to fire action potentials, immediate pain responses to high-energy laser stimulation might primarily be interpreted to represent Aδ-fibre-mediated pain [16].

Though we did not use neuronal or cerebrocortical electrophysiological measurements like others [28, 169] to distinguish between immediate and delayed pain responses, our one-second latency between those double pain responses is consistent with neurophysiological findings [174], indicating that first and second pain responses represent Aδ- and C-fibre-mediated nociception. This is in line with previous studies using reaction time to distinguish between first and second pain responses [29, 164, 167], also confirmed by combining reaction time with pain-related evoked potentials [37].

How much pain is induced early after surgery? (III-IV)

In our mixed cohort of postoperative patients (Table 4) subjected to various surgical procedures and evaluated with VAS scoring (III), study data was analysed in 244 (128 females) patients (Table 3). Their reported median (IQR) pain intensity was 2.5 (1.4-3.9) VAS units, and three fourths reported mild postoperative pain. This is in agreement with recent findings in a comparable study cohort after various kind of surgery, evaluated with NRS scoring [175]. According to a German multicentre study from 2013 in 70 000 patients after various surgical procedures [176], the maximum pain intensity on the first postoperative day was 5 (3-7) NRS units, i.e. considerably above results obtained in our study cohort, interpreted to reflect better perioperative pain relief. However, postoperative pain intensity levels were not correlated to degree of surgical incision, in line with our findings of no difference in VAS scores between endoscopic, laparoscopic, or open surgery ($P > 0.300$). Moreover, reported pain scores after some major surgical procedures were lower, presumably due to sufficient epidural analgesia or high-dose opioid, than after some minor procedures where analgesic requirements might have been underestimated [176].

Evaluation of pain (I-IV)

What are the benefits of using VAS? (I-IV)

By using VAS, considered to have higher sensitivity [177-179] than few-point categorical pain scales (VRS and NRS) for evaluation of pain intensity in our studies (I-IV), we were able to detect and statistically confirm quite small differences. The accuracy [180] of VAS enabled us to significantly verify differences far below 1.0 VAS units in our clinical study (III), in contrast to pain evaluation with NRS. Though these findings may not be relevant at group level, they may still be relevant to individual patients, especially those reporting pain intensity where analgesic intervention should be considered. Besides, because VAS is considered to be non-linear [60, 181], standardized minimum clinically significant changes are meaningless, because they will either under- or overestimate [56, 57] true changes. The high precision of VAS [177-179] must also be considered when studies report lower error rates with VRS [182] and NRS [183] than with VAS, probably reflecting errors not being detectable with few-point categorical pain scales.

Although VAS, VRS and NRS are all considered valid, reliable, and appropriate for use in clinical practice, some patients find it more difficult to assess pain intensity with VAS than with other scales [184-186]. Nevertheless, in our studies only two participants (I) were excluded due to difficult pain assessment with VAS. To make VAS easier to use, practice before pain assessment has been proposed [183]. In our studies (I-III) verbal instructions for assessment with VAS were given to the study participants by the investigators before pain evaluation, and in the first study (I) the study participants got even more familiar with VAS during titration of individual pain thresholds. VAS has also been found by others to be useful in individuals able to adequately understand basic principles and respond to simple instructions [178].

According to a review from the mid-zeroes [186], correlations between VAS and VRS cannot be properly established, and although associations between VAS and NRS have been reported, available data indicates that direct conversion between those scales cannot be made [56], plausibly cohering with their non-linear properties. The ordinal properties of VAS data [60, 181] call for use of non-parametrical statistics (I-IV).

The similar levels of pain intensity recorded in this project (I-IV), corresponding to mild pain with median values of pain intensity at around 2.5 VAS units, make comparisons between the studies (I-IV) easier and more relevant (Table 5).

Table 5.
Reported median (IQR) levels of pain intensity in study participants in papers I-IV.
Abbreviations: IQR (interquartile range), VAS (visual analogue scale)

Study	I	II	III	IV
Median (IQR) pain intensity, VAS units	2.4 (1.4-3.0)	2.0 (1.1-3.2)	2.5 (1.4-3.9)	2.6 (1.4-4.0)

Do verbal pain descriptors add valuable information to VAS scores early after surgery? (IV)

In our study, data from 227 (119 female) patients (Table 4) was analysed considering qualitative and quantitative evaluation of pain early after arrival at the PACU, and around half of them reported optional verbal quality descriptors associated with either Aδ-fibre-mediated (26 %) or C-fibre-mediated (28 %) postoperative pain. Reported verbal pain descriptors, 17 in total and 13 MPQ-validated, are shown, in proportion to relative occurrence, in Figure 10.

Qualitative tools for pain evaluation (MPQ and SF-MPQ) have been found to add valuable information on pain character to unidimensional pain intensity scores [187]. Moreover, it might be easier for patients to describe their pain in (eligible or optional) words than according to a unidimensional scale, especially after surgery with potential cognitive dysfunction, nausea, and mood dysregulation. In contrast, patients responded better to clinical change with VAS than MPQ evaluation over the first 24 hours after lumbar scheduled surgery [188].

We found that patients with mild pain more often reported quality descriptors associated with C-fibre- than Aδ-fibre-mediated pain (P = 0.007). Accordingly, lower (P = 0.047) pain intensity levels were associated with verbal descriptors reflecting C-fibre-mediated postoperative pain. These correlations between descriptors and scores of pain might facilitate understanding and rapid interpretation of mild and moderate-to-severe early postoperative pain, as also suggested in an experimental study relating MPQ descriptors to Aδ- or C-fibre-mediated pain [29].

Our reported high incidence of verbal descriptors reflecting non-specific pain (46 %), might reflect problems describing perceived pain in optional words (possibly because of low pain intensity) instead of predefined eligible words [67, 68]. Nevertheless, optional verbal descriptors might have made it easier for some study patients to convey their ongoing postoperative pain, considering that 76 % of patients reported optional Aδ- or C-fibre-associated quality pain descriptors without difficulty.

By not including patients with linguistic impairment, potentially unnuanced or incorrect translations of verbal pain descriptors were avoided. Each original Swedish verbal descriptor was translated into English, based on a validated Swedish version of the SF-MPQ [189], or (if not included there) by repeated translation and

retranslation between the two languages, made independently by two investigators, until the descriptor in English no longer differed from the original descriptor in Swedish.

By providing a more gradated picture of the patient's perception of ongoing postoperative pain, multidimensional evaluation, based on simultaneous use of qualitative and quantitative bedside tools, might optimize pain management, both regarding immediate pain relief and promotion of rapid recovery after surgery.

Figure 10.
Optional verbal quality descriptors of pain, included in the McGill pain questionnaire, reported in the early postoperative period by 124 adult surgical patients, and shown in proportion to their relative occurrence (IV).

Gender aspects on pain perception (I-III)

Does gender influence experimentally induced pain? (I, II)

Evaluation of experimental pain induced by ultra-short laser (I) or weak electrical (II) stimulation did not differ significantly between females and males with respect to levels of laser energy density ($P = 0.060$) – but with a tendency towards higher energy laser density levels in males – or EPT levels ($P > 0.300$), and neither to pain intensity scores of pain threshold ($P > 0.300$) (I, II) as shown in Table 6.

Our lack of subject gender impact on experimental pain is in line with earlier findings in thermally induced pain [88, 90, 190]. On the other hand, many studies

have found higher pain sensitivity in females compared with males after various experimental stimuli [18, 72-82, 84-87, 190]. Those various findings were confirmed in a review from 2012 [191], reporting lower pain thresholds in females subjected to pressure-induced experimental pain.

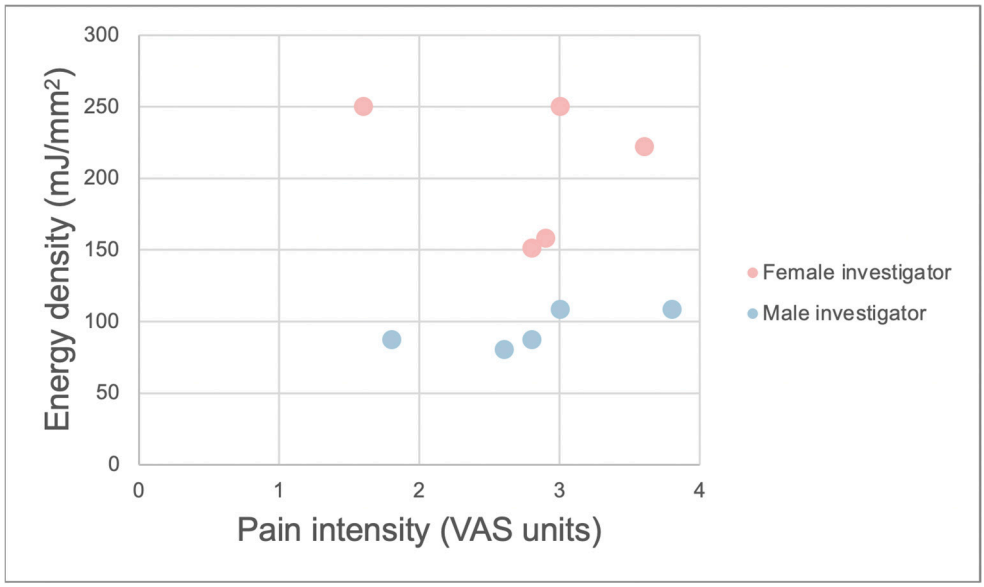

Figure 11.
Levels of individually titrated laser energy density in five males evaluated by a female investigator compared with five males, matched for pain intensity, evaluated by a male investigator (I). Median (IQR) energy density levels were 224 (160-253) mJ/mm^2 with a female, and 74 (60-81) mJ/mm^2 with a male, investigator (P = 0.008).

Interestingly, in study I we found that significantly higher (P = 0.008) titrated levels of laser energy density were used in five males evaluated by a female than in five males, matched for reported pain intensity, evaluated by a male (Fig. 11). This finding was the source of inspiration for our next paper (II), where we, based on randomized paired crossover study design, were able to confirm our results of gender impact, with higher levels of EPT ($P < 0.0001$) obtained by the female than by the male investigator (Table 6). Moreover, individually calculated EPT levels were higher in four fifths of evaluations made by the female investigator, and pain intensity levels did not differ depending on investigator gender (Table 6).

Our findings are in line with earlier studies reporting lower pain sensitivity (higher pain threshold or lower pain intensity) in study participants evaluated by females after various kinds of stimuli [80-82, 85, 87, 88, 100-103]. In contrast to some of those studies [85, 100], we did not exaggerate gender stereotypes (I, II), as also done elsewhere [102], but used study investigators with similar age, BMI, and education,

dressed in gender-neutral hospital-clothing (white physician coats), thereby reducing bias beyond investigator gender. Furthermore, the investigators used predefined study instructions to minimize individual or gender-based verbal influence. Those factors strengthen the use of only one study investigator of each gender, also avoiding interindividual variations, which otherwise might be considered as a disadvantage compared with similar unpaired studies [82, 102] using several investigators. Blinding of our study participants (but not investigators) to the main purpose of the study (potential impact of investigator gender on pain perception) is believed to have diminished potential psychosocial impact of gender role expectations on results obtained (II).

Table 6.
Reported median (IQR) levels of EPT and pain intensity in female and male study participants evaluated by female and male study investigators (II). Abbreviations: EPT (electrical pain threshold), IQR (interquartile range), VAS (visual analogue scale)

	Female investigator		Male investigator	
	EPT (pain magnitude scores)	Pain intensity (VAS units)	EPT (pain magnitude scores)	Pain intensity (VAS units)
Female participant	22 (13-34)	2.0 (1.2-2.9)	7 (6-9)	2.1 (1.2-3.4)
Male participant	22 (9-28)	1.5 (1.2-3.0)	9 (7-11)	1.6 (1.0-3.4)

Does gender influence surgical pain? (III-IV)

Pain intensity levels did not differ between female and male study patients in our clinical study (III-IV), as also reported in two recent studies on postoperative pain [72, 96]. In contrast, whereas other studies have reported higher pain intensity levels in females after various kind of surgery [91-95]. In line with this, a recent review concludes that higher extents of femininity or female social roles are associated with lower thresholds and less tolerance to clinical pain [192]. Reported quality pain descriptors (categorized as Aδ- or C-fibre-associated) did not differ between female and male study patients (IV). In contrast, female patients with shoulder pain have been reported to use C-fibre-associated verbal pain descriptors more often than male patients [193].

Lower VAS scores of pain intensity were reported by more patients to the female than to the male investigator ($P < 0.001$). Accordingly, and in line with our experimental findings (I, II), pain intensity levels obtained by the female investigator were significantly lower ($P = 0.006$) than those obtained by the male investigator regardless of pain intensity level. Previously, lower levels of pain intensity have been obtained by female investigators in non-surgical orthopaedic patients [104, 105], but not in emergency care patients [106, 107] or early after cardiac surgery [108]. The female investigator recorded lower reported pain

intensity in male ($P < 0.001$), but not female, patients (Fig. 12 & 13). Although the levels of pain intensity reported to the female study investigator were just slightly lower than those reported to the male investigator, this small difference was large enough to be statistically confirmed. These findings might still be relevant to individual patient management, particularly considering that the largest difference was recorded at clinically relevant intensity levels of pain, around 3 VAS units, where postoperative patients usually start calling for pain relief.

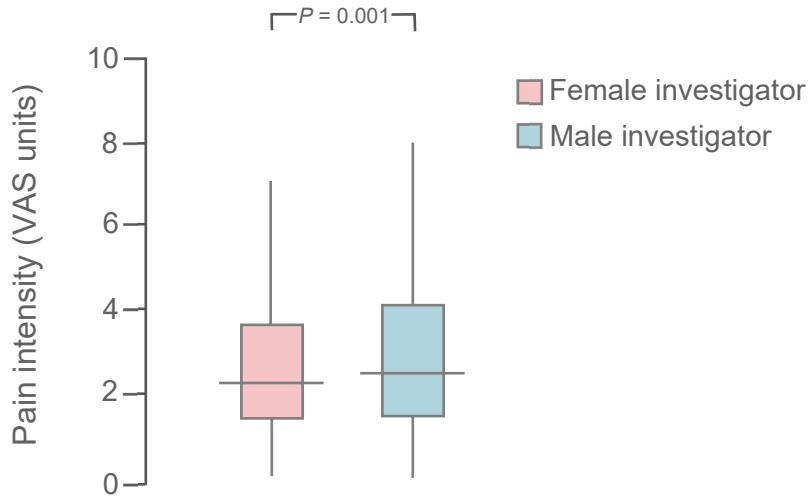

Figure 12.
Pain intensity levels in 116 male patients obtained by a female investigator and by a male investigator according to paired crossover study design (III). Median values are indicated by horizontal lines, interquartile ranges by boxes, and total ranges by vertical lines. Abbreviations: VAS (visual analogue scale)

One can argue that with only one investigator of each gender, the findings might be more due to individual investigators characteristics than to investigator gender. On the other hand, interindividual variations between female and male investigators are avoided, ensuring the same approach of gender evaluation in each study patient, in contrast to a previous similar study [175]. Moreover, higher electrical stimulation found to induce the same intensity of perceived pain in males evaluated by a female than by a male (II), encouraged clinical evaluation by one female and one male investigator (III-IV), equally dressed in white gender-neutral hospital clothes and similar in age, BMI, and education, not to exaggerate gender stereotypes like in earlier studies [85, 100]. Furthermore, the study patients received predefined verbal study instructions not including the main purpose of the study (of potential impact on investigator gender), to potentially avoid gender role expectations [194]. Despite standardized verbal communication instructions read from predefined protocols by the investigators, non-verbal communication, reported to be more used by females

[195] comprising more intense eye-contact and frequent smiling [196], might have been enhanced in our study setting, also considering that stronger empathic abilities of females dealing with pain in others have been reported [197], possibly promoting non-verbal communication.

Figure 13.
The same male patient reporting lower pain intensity levels to a female than to a male investigator. Drawing by my 13-year-old daughter Alma.

Other aspects on pain perception (I-IV)

What else may influence pain perception? (I-IV)

In our preclinical studies (I, II), the more intimate study setting with calm and quiet one-to-one environment might have facilitated non-verbal subject-investigator interaction, found in a study on communication in primary care [74]. In contrast,

our clinical study setting in the PACU (III-IV) might have been stressful and noisy with constant flow of other patients and busy healthcare staff (III-IV), not promoting intimate communication with the individual patient. However, the ability to describe pain in the PACU was not considered to be an issue in our studies (I-IV) designed to evaluate pain, in contrast to postoperative patients after orthopaedic or general surgery who were affected by attitudes from the healthcare staff, with following fear of conflicting with them or being perceived as whining [198].

Our mixed study cohort of patients subjected to various kinds of acute or scheduled surgery might have been affected by negative moods of stress and anxiety after perilous or complicated surgery as well as by positive moods of joy and relief after safe and successful surgery, potentially exaggerating, or easing, their experience of pain in the early postoperative period [136]. We did not take earlier pain experiences into account when evaluating pain perception (III-IV), which might have influenced expectations as well as results obtained [156].

Although our study cohort was diverse in age, sociocultural background, comorbidity, and surgical procedure, we chose not to evaluate pain perception in those specific contexts to avoid multiple significance testing and maintain enough statistical power. Pain intensity levels were not associated with surgical technique ($P > 0.300$).

Do methodological aspects affect outcome of pain perception? (I-IV)

An advantage of paired crossover study design, i.e. that study participants are their own controls, is that fewer study participants are required to reach a large enough cohort (II-III). Findings of higher pain intensity scores reported during the first than during the second series of stimulation is compensated for with our paired crossover design (II).

Individual titration at least two days before start of each study session (I) and minute-long time intervals between laser-induced nociceptive stimulations, are both measures taken to elude overlap of laser heat pulses, thus avoiding carry-over effects. There was no statistical order effect in immediate pain intensity levels ($P > 0.300$), but the intensity of delayed pain was significantly higher ($P < 0.001$) during the first (out of four) series of stimulation. Nevertheless, order effects were decreased, and data accuracy improved, by using median values of individually calculated average data (I), and paired crossover design (II-III). There was no significant difference ($P > 0.300$) in EPT levels between the first and second series of stimulation (II).

Another potential weakness of the first clinical study part (III) is that the investigators were unable to obtain scores of pain intensity simultaneously in the study patients. However, we estimate small individual changes in postoperative pain intensity within the approximate 15-minute interval between assessments, since few

patients were given analgesic drugs immediately before or between the evaluations, and since those interventions did not have an impact on overall results.

To compensate for potential differences in induction of pain with two identical calibrated electrical devices, each one was used by each investigator in half of the study participants. Carry-over effects were avoided by allowing enough time (approximately 15 minutes) between the study sessions (II).

In the clinical study randomization was not possible due to inclusion of the postoperative patients close to discharge from the PACU (III). Nevertheless, approximately half of them were first investigated by the female according to the crossover design.

Conclusions

- Delayed nociceptive pain, presumably reflecting neural transmission by C-fibres is selectively inducible and evaluable in humans, considering that individually titrated ultra-short pulses of CO_2 laser stimulation were found to enable separate intensity scoring of immediate and delayed pain responses (I).
- Gender does not considerably influence how acute pain is being perceived, considering that study participant gender was not found to affect individually reported intensity levels of acute nociceptive pain induced by stimulation with ultra-short laser, weak electrical current or surgery (I-IV).
- Pain perception is influenced by investigator gender, considering that lower pain sensitivity was confirmed in study participants evaluated by female than by male investigators (I-III) without also emphasizing traditional gender roles in the experimental or clinical study settings (II-III).
- Being investigated by a female is associated with higher resistance to experimentally induced pain, considering that higher levels of electrical stimulation were found to be required, regardless of participant gender, to attain individual pain threshold levels with a female than with a male investigator (II).
- Being investigated by a female is associated with higher resistance to postoperative pain in males, considering that lower reported intensity levels of surgical pain in the early postoperative period were obtained by a female than by a male investigator in a mixed cohort of adult study patients (III).
- Most optional verbal descriptors of pain quality reflect Aδ- or C-fibre-mediated postoperative pain, considering that associations were confirmed between Aδ- or C-fibre-associated postoperative pain and more than half of reported optional pain descriptors, early after surgery in a mixed cohort of adult postoperative patients (IV).
- Aδ-fibre-associated verbal quality descriptors of pain reflect higher levels of postoperative pain intensity than do C-fibre-associated descriptors, considering that reported quality descriptors reflecting Aδ-fibre-mediated pain were found to be associated with higher levels of pain intensity than those reflecting C-fibre-mediated pain, and that pain intensity corresponding to mild postoperative pain was more frequently reported together with verbal descriptors reflecting C-fibre- than Aδ-fibre-mediated transmission of pain, early after surgery in a mixed cohort of adult postoperative patients (IV).

Future perspectives

This thesis emphasizes the fact that pain is multidimensional, with physiological and psychosocial components, and that pain perception is individual.

Further experimental and clinical studies are highly desirable on investigator gender and pain perception, also taking other factors influencing pain into consideration. Besides facilitating future studies, hopefully our results will encourage healthcare staff to focus more on factors influencing pain, particularly investigator gender, considering that females comprise a vast majority of healthcare staff.

Further development on how to use verbal quality descriptors of pain is most desirable, and especially studies on potential rapid discrimination of pain intensity levels by verbal pain descriptors. In a clinical context, promoting combined use of qualitative and quantitative tools for pain evaluation is important for a more multimodal approach to improve pain management, clinical recovery and return to daily life in patients undergoing surgery.

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