No pain no gain
Harbers, Marten

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1
GENERAL
INTRODUCTION
1.1 PAIN: BOTH VALUE AND BURDEN

Pain can and should be regarded as one of our most valuable human sensations. Although the unpleasant nature of pain does not make it a desirable experience, its functional importance in daily life is undisputed. If someone senses pain, in most cases, he will act or adjust his behaviour to alleviate the pain and minimize the harm done to the body. Pain is part of our lives and is a sensation almost all people are familiar with; without this crucial experience we would struggle to stay alive. This functional view on pain is simple and true: pain is a warning signal that helps us navigate through a world full of danger and threats; without pain we would be lost.

The danger of not feeling pain is clearly illustrated by a rare genetic abnormality called 'congenital analgesia' that results in the absence of any pain perception. Many people with this condition develop injuries at a young age and have to remain under constant supervision. When they are older there is a very high risk of injuries involving broken bones. Breaking a bone can become extremely dangerous when people continue to walk on a broken leg with only feeling a slight discomfort but no pain at all (Schmid, 2006). This is an extreme but clear example of the importance of having intact pain perception to protect us from serious injuries in daily life.

More common examples of the functionality of pain as a warning signal in life are the burning pain you feel when you touch a hot pot on the stove, the stinging pain when you accidently rub your eyes after cutting a hot chilli, the overwhelming pain of breaking your leg or the never ending gnawing pain of a toothache. These situations are all straightforward examples of signalling damage to the body by a pain sensation indicating that something is wrong. These kinds of short lasting direct pain signals are classified as acute or nociceptive pain (see paragraph 1.5). Although unpleasant, these pain signals serve a clear function.

In contrast, sometimes short lasting pain can turn into a long lasting persisting experience of pain that severely limits the daily life of humans. This long lasting chronic state of pain is no longer a functional warning signal, but becomes a disabling disease state by itself. A few years ago when I started my PhD, I visited the Pain Management Unit of the University Medical Center Groningen and had the opportunity to attend the consults of dr. M. van Wijhe. Here I came in to contact with some people who suffered from all kinds of chronic pain and I learned first-hand how great the impact was on their lives. I would like to give two examples of the patients I encountered.

One of the first patients I met was a young man who maybe 25 years old and who now could not move his right arm without having severe pain. The year before he was involved in a motor accident and he suffered severe damage to the nerves in his arm. He could not perform the sports he enjoyed and he was no longer able to ride his motor bike. His doctors had tried several nerve blocks to alleviate the pain but without success. He had been taking
several types of medication which at best reduced the pain but the side effects gave him great discomfort. He decided to stop the medication apart from the occasional ‘over the counter’ pain killers. Nothing seemed to work for this patient and together with his doctors he kept trying different medications and alternative treatment options. I hope he found something that gave him some relief.

During another visit I met a woman who was in her fifties and was bound to a wheelchair. She had suffered a broken ankle after a fall on a hike in the mountains. The broken ankle healed well but now her whole lower limb had become very painful; even a slight touch or a mild cold temperature would inflict severe pain in her foot and leg. To stay fit she swam three times a week but the feeling of the water of 26 degrees Celsius was very painful. However, every time she endured the pain and tried to enjoy the swim and keep in mind that she needed this exercise to stay in shape.

These patients gave me insight in the impact of chronic pain and made me realize we need to do more research in order to understand the mechanisms behind these chronic pain conditions of the patient to be able to develop the proper treatments.

The International Association for the Study of Pain has estimated that the prevalence of persistent chronic pain to be around 35% (range: 10-55%) (Harstall & Ospina, 2003) (Pain clinical updates, Volume XI No 2, 2003). This means that 1 in 3 people will experience some period in their lives where they suffer from chronic pain. Another overwhelming figure comes from a telephone survey in Europe, out of the almost 50,000 participants 19% had experienced an episode of chronic pain lasting longer than 6 month (Breivik et al., 2006). This underlines the high burden that pain and particularly chronic pain places on our society and underlines the importance of developing useful and effective analgesic therapies.

1.2 ALARM BELLS AND GATES

For a long time people thought that the signalling of pain within the body was a straightforward sensory mechanism: a simple mechanism where a harmful stimulus would induce a pain signal in the nervous system resulting in a purely bottom up driven pain experience mediated by some pain processing centre in the brain. This view can be easily depicted by an old illustration in Descartes ‘Treatise of Man’ (1664) where a fire causes a specific signal to be sent to the brain and resulting in pain (Descartes & Hall, 1972).

From this early theory of pain by Descartes, the biomedical specificity theory of pain emerged within the scientific community which would become the most imparted theory on pain for centuries. The specificity theory simply states that within a static neurological pain system, an injury will activate specific pain receptors and nerve fibres, which transmit nociceptive signals through an upward spinal pathway to the pain centre of the brain. This
theory is also known as the ‘alarm bell’ theory (Melzack, 1973). Within this framework the pain experience was held to be proportional to the peripheral injury or pathology. Even though the complexity of the specificity view increased over the years, up until the 1950’s there was little room for the modulatory influence of psychological, psychophysical and cognitive concepts like emotion, attention, anxiety or past experience in the scientific community studying pain (Hadjistavropoulos & Craig, 2004). Half-way the 20th century scientists began to change their view on pain. Gradually, it was acknowledged that the physiological processing of pain was a much more complex system. I always like to explain some of this complexity and dynamic features of pain by the simple phenomenon that most people start rubbing the skin on the area where they have pain, for instance when you bumped your head or knee on something hard. Based on the idea of the ‘alarm bell’ theory, one would think that rubbing the area of the injury would make things worse. If there is more sensory input at that location, it should increase the painfulness. Instead, it actually gives people some relief of the pain. If pain was just the simple sum of all the sensory input signalled through the nervous system rubbing the painful area of the body would inflict even more pain.

A new theory was developed in the 1960s by Patrick Wall and Ronald Melzack. This theory provided a good explanation why rubbing the painful area actually reduces the pain. It introduced the presence of gating systems at the level of the spinal cord. The nerve impulses from the periphery can be inhibited or facilitated depending on the input, fibre type and the psychophysical state of a person. The nerve fibres signalling light touch actually inhibit the nerve signal from fibres signalling painful input. Therefore, by sending a competing

Figure 1.1 Specificity Theory of Pain depicted in a figure from Rene Descartes (1664). Specific pain input travels bottom up through the nervous system to the ‘pain center’ in the brain.
signal (input from rubbing) through the nervous system the pain experience will decrease even though the severity of the injury has not changed. This mechanism is also known as the gate control theory of pain (Melzack & Wall, 1965). This theory has become the most influential theory of pain processing and has paved the way for a dynamic and modulatory view on pain. The gate control theory of pain was the first broad theory of pain mechanism that acknowledged that the transmission of pain signals from the peripheral nerves through the spinal cord could be modulated (inhibited or facilitated) by additional sensory input. Furthermore, research showing that descending neural pathways could inhibit afferent sensory patterns and produced endogenous analgesia, lead to the suggestion of central control mechanism in the brain (Melzack et al., 1958). This theory changed the view on pain from a static one-dimensional signal to a dynamic multi-dimensional phenomenon. It opened the door for psychological and cognitive factors influencing and modulating the pain sensation itself instead of only being the result of the pain experience.

### 1.3 A MODERN VIEW

Nowadays the scientific field of pain has evolved into a multidisciplinary scientific endeavour where a bio-psycho-social view on pain has become the standard. The current theories on pain are no longer limited to a simple reaction to a harmful stimulus but view pain as a very complex phenomenon. Pain is regarded as a multi-dimensional experience where physical input, environmental factors, psychological factors, gender, genetics, age, illness, coping style, emotions, motivation and many other variables can influence pain perception. Nowadays, pain is investigated in a wide variety of scientific disciplines like biology, genetics, pharmacology, medicine, psychology, neuroscience, physical therapy, rehabilitation and even the social sciences. This is also reflected in the definition of pain proposed by the International Association for the Study of Pain (IASP): “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. This definition illustrates that pain should not be considered only as a physiological mechanism but must also be regarded as a ‘bio-socio-psycho-physiological’ experience.

Within the dynamic view of pain a distinction has been suggested between specialized systems that are involved in the sensory-discriminative, motivational-affective and cognitive-evaluative dimension of pain (Melzack & Casey, 1968). The former involves the location, intensity and modality of the pain. The latter two relate to the emotional experience, the unpleasantness of pain and the motivation for pain specific behaviour resulting from the pain (Melzack & Casey, 1968; Treede et al., 1999; Tracey, 2007). Although it is difficult to strictly separate these concepts, they are often used to provide a framework for the
experience of pain and the description of different neurophysiological systems involved in
the neural processing of pain. These concepts are used, for instance, in the most commonly
used pain questionnaire, the McGill pain questionnaire, but also in the functional allocation
of different brain regions that are related with pain processing (see paragraph 1.4). In
this thesis I will focus on the optimal way to reliably measure the sensory discriminative
aspect of both acute and chronic pain.

1.4 A BRIEF NEURO-ANATOMY OF PAIN

The cascade of neural processing, leading to the perception of pain, starts in the peripheral
nervous system and follows several tracts all the way up to the cerebral cortex of the brain
(see Figure 1.2). It begins with the detection of possible harmful stimuli like extreme
heat, cold or pressure by specialized nociceptors such as the fast myelinated Aδ- and
slow unmyelinated C-fibres. Signals from these nociceptors are conducted through the
peripheral nervous system to the dorsal horn of the spinal cord in Rexed’s laminae I, II and
V (Craig, 2003). From the spinal cord the pain signals are transported to the brain via the
‘anterolateral’ system, which can be subdivided in three major tracts: the spinoreticular
tract (SRT), the spinomesencephalic tract (SMT) and the spinothalamic tract (STT) (Martin,
2003; Calvino & Grilo, 2006). The STT, originating from predominantly wide dynamic range
neurons of lamina V, projects to three thalamic nuclei: the ventral posterior lateral nucleus
(VPL), the ventromedial posterior nucleus (VMPn) and the ventral caudal portion of the
medial dorsal nucleus (MDn) (Price, 2002; Craig, 2003). The SMT and the SRT both originate
in nociceptive-specific lamina I neurons and have projections terminating in different areas
of the brainstem and midbrain (Martin, 2003; Tracey & Mantyh, 2007). Information from
the SMT and the SRT reaches the thalamus via several brainstem and midbrain areas. The
SMT terminates among others in the periaqueductal grey (PAG), raphe nuclei and nucleus
cuneiformis, SRT projections go to neurons of the reticular formation which project to
intralaminar thalamic nuclei (Martin, 2003; Tracey & Mantyh, 2007). From the thalamus and
the midbrain the pathway continues to the cortical areas of the brain. The VPLn and the
VMPn send afferent information to the primary and secondary somatosensory cortices (SI
and SII) and to the posterior insular cortex, respectively (Craig, 2002; Price, 2002; Martin,
2003; Craig & Zhang, 2006). These projections are essential in the sensory-discriminative
component of pain processing (Bushnell et al., 1999; Coghill et al., 1999; Peyron et al., 1999).
The MDn has major outputs to the anterior cingulate cortex (ACC), anterior insula and
the prefrontal cortices (PFC), areas that have been implicated in the affective-motivation
component of pain processing (Craig, 2002; Peyron et al., 2002; Rainville, 2002; Craig, 2003;
Singer et al., 2004).
Figure 1.2 Pain processing pathways in the nervous system. Pain signals travel from the periphery through different fiber types to the dorsal horn in the spinal cord. From the spinal cord several tracts run up to the brain, where a complex network of regions is involved in pain processing.

Functional neuroimaging studies with PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging) have shown that within the brain a complex network of regions is associated with the processing of pain. This is in line with the modern view that pain is a complex dynamic experience with both sensory, cognitive and emotional dimensions. This broad network of cortical brain regions found to be commonly activated by nociceptive stimulation includes the anterior cingulate cortex (ACC), insula, (pre-) frontal cortices, somatosensory cortices (SI and SII) Thalamus and the amygdala (Peyron et al., 2000; Apkarian et al., 2005) (See Figure 1.3).

This pain network is often referred to as the ‘Pain Matrix’ of the brain. One should however be careful in regarding these brain regions or this network of brain regions as pain specific. Recent results and insights have shown that this network is involved in the processing of other non-painful salient stimuli in other sensory modalities. Therefore, some authors point out that the brain regions associated with pain processing might be part of a more
general stimulus saliency network instead of being pain specific (Iannetti & Mouraux, 2010; Iannetti & Mouraux, 2011; Mouraux et al., 2011).

Figure 1.3 The Pain Matrix: brain regions associated with pain processing (From Apkarian et al 2005). Meta-analysis shows a complex network of brain regions involved in pain processing. The most important regions are: Thalamus, primary sensory cortex (S1), secondary sensory cortex (S2), Insula, anterior cingulate cortex (ACC), pre-frontal cortex (PF).

1.5 ACUTE NOCICEPTIVE PAIN
The most common experience of pain is acute pain resulting from a direct injury, harm or damage to the body. The experience of acute pain is almost always directly linked to a specific cause, for instance, the pain when you burn yourself, pain after surgery or after breaking an arm. This type of pain is also known as nociceptive pain and is caused by some form of tissue damage where the injury activates specific nociceptive receptors on specific nerve fibres classified as C-fibres and Aδ-fibres. These nociceptive pathways carry the nervous signal through the central nervous system to the brain (Besson, 1999) (see Figure 1.2).

Within our peripheral nervous system we can classify three major types of somatosensory nerve fibers: Aβ-fibers, Aδ-fibers, and C-fibers. Aβ-fibers are large diameter, highly myelinated fibers, facilitating the conduction of action potentials at high velocity. These fibers have a low activation threshold and normally activate in response to light touch. Aδ-fibers are small diameter, only thinly myelinated fibers, resulting in slower-conduction of action potentials than Aβ-fibers. Aδ-fibers have a higher activation threshold and respond to both thermal and mechanical painful stimuli. C-fibers are non-myelinated fibers with the smallest diameter and are the slowest conducting type of primary afferents. They have the highest activation thresholds for selectively detecting nociceptive painful input. Together, both Aδ- and C-fibers can be termed as nociceptors or ‘pain fibers’, responding to noxious stimuli which may be mechanical, thermal, or chemical, whereas Aβ-fibres are sensory fibres (Besson, 1999). (See Figure 1.2)
1.5.1 TREATMENT OF ACUTE PAIN

Acute or nociceptive pain can be treated with common pain killers like paracetamol (acetaminophen) and NSAIDS (non-steroidal anti-inflammatory drugs) like ibuprofen and aspirin. If the acute pain is of a stronger nature it can be treated with opioids like codeine, tramadol (weak opioids) or morphine, fentanyl, buprenorphine and remifentanil (strong opioids). Opioids are the most common treatment option for moderate and severe nociceptive pain (Staahl et al., 2009a). The strong opioid remifentanil is used in two pharmacological intervention studies described in this thesis. Remifentanil is a potent, ultra short-acting, selective mu-opioid receptor agonist with a typical opioid pharmacodynamic profile that can produce both analgesia and anaesthesia depending on the dose. Remifentanil has a rapid onset of analgesic action (one minute) and a fast offset of action (3 – 10 minutes) irrespective of the duration of the infusion. Therefore, remifentanil is considered a useful tool in evaluating experimental acute pain measurements for clinical trials (Scott & Perry, 2005). In this thesis the application of the short acting potent opioid remifentanil plays an important role in the pharmacological validation of acute pain tests and our newly developed neuropathic pain model (chapter 4 and 6).

1.6 CHRONIC PAIN

As stated above acute pain is viewed as ‘pain of recent onset and probable limited duration which has an identifiable temporal and causal relationship to injury or disease’. In contrast chronic pain ‘commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause or biological value’ (Ready & Edwards, 1992; Harstall & Ospina, 2003). When for some reason pain lasts longer than three months or longer than the anticipated healing time, the IASP regards the pain as chronic. One defining aspect of chronic pain is that the pain sensation is no longer functional; for example when tissue damage has healed, but the pain is still present. In these situations the pain itself becomes the problem instead of the previous injury. There are many forms of chronic pain like (low) back pain, migraine, arthritis, complex regional pain syndrome and neuropathic pain. In this thesis I will investigate neuropathic pain and will present scientific results from studies in patients and from experimental pain models for neuropathic pain in healthy volunteers.

1.6.1 NEUROPATHIC PAIN

In general any form of chronic pain resulting from some kind of nerve damage is called neuropathic pain. The IASP uses the following definition: “neuropathic pain is a chronic pain state that arises as a direct consequence of a lesion or disease affecting the somato-sensory
nervous system” (Treede et al., 2008). An intuitive example of chronic neuropathic pain can be found in patients who are fully recovered from surgery, where all the tissue damage is healed but still experience pain. This type of pain often involves the damage of a nerve during the surgery that has not healed properly.

Two surveys in France and the UK estimated the prevalence of neuropathic pain in the general population to be as high as 7-8% (Torrance et al., 2006; Bouhassira et al., 2008). Neuropathic pain can be a disabling condition that often has a strong impact on quality of life (O’Connor, 2009; Dworkin et al., 2010; Moore et al., 2011). Typical examples of neuropathic pain include: diabetic neuralgia, post herpetic neuralgia, traumatic and post-surgical nerve lesions and central post stroke or spinal cord injury pain. Neuropathic pain remains difficult to manage because a patient’s response to most medication is difficult to predict.

In clinical trials only half of the patients report clinically meaningful pain relief but even then in most cases pain of moderate severity remains (O’Connor, 2009; Attal et al., 2010) and the treatments for neuropathic pain are associated with sub-optimal side-effect profiles (Bridges et al., 2001). Although new treatment and combination of treatments are available and have certainly improved the management of neuropathic pain, the response to most treatments is still considered to be modest. This is indicated by the fact that numbers needed to treat to achieve a 50% pain reduction lie between 3 and 6 patients. A 100% pain reduction is almost never achieved by any form of treatment.

The most common clinical signs of neuropathic pain are abnormal sensory signs such as loss of sensory function (negative symptoms), paresthesias (a sensation of tingling, tickling, prickling, pricking, or burning), spontaneous pain and stimulus-evoked pain associated with peripheral and central sensitization (positive symptoms) (Walk et al., 2009). Loss of sensory function is directly associated with damage or death of primary sensory neurons in the periphery. Spontaneous pain is pain that arises in the absence of any external stimulation. It is typically caused by spontaneous activation anywhere in the nociceptive neural pathway. Often this spontaneous activation is the result of hyper-excitability of primary sensory neurons as a consequence of nerve lesions. This hyper-excitability leads to so called ectopic firing of neurons meaning action potentials generated without the normally necessary neuronal input. The ectopic firing can result in both paresthesia and pain (von Hehn et al., 2012).

As mentioned above, nociception is generally mediated by specific fiber types (Aδ, C-fibers and Aβ fibers). However in pathological conditions like chronic neuropathic pain these fibres can malfunction and start acting as nociceptors resulting in the painful experience of light touch stimuli due to peripheral and central sensitization (Bridges et al., 2001). Peripheral sensitization is a reduction in threshold and an increase in responsiveness of peripheral nociceptors in response to an inflammation or nerve lesion.
Central sensitization is an increase in the excitability of neurons within the central nervous system in such a way that normal sensory inputs produce abnormal responses. Peripheral sensitization can often change the activation of pain pathways at the spinal cord inducing central sensitization which can lead to abnormal functioning of pain pathways in the brain resulting in the overall dysfunction of the somato-sensory system in neuropathic pain patients (Woolf, 2011; von Hehn et al., 2012). The two main hypersensitivity symptoms are allodynia: ‘pain in response to a non-noxious stimulus’ and hyperalgesia: ‘increased pain sensitivity to a nociceptive stimulus’.

These mechanisms underlying neuropathic pain can result in irreversible mal-adaptive changes in the central nervous system in the periphery, at spinal and supra-spinal level. In neuropathic pain the nervous system itself is damaged; for these reasons neuropathic pain should be regarded as autonomous disease of the nervous system (von Hehn et al., 2012).

1.6.2 QUANTITATIVE SENSORY TESTING IN NEUROPATHIC PAIN PATIENTS

For the diagnosis of neuropathic pain it is important to assess the location, intensity, quality, onset and duration of the pain. This disease etiology can provide clues for the underlying patho-physiological mechanisms associated with the experienced pain. Testing the functioning of the somatosensory nervous system is thus essential in this assessment.

For decades now, the use of standardized Quantitative Sensory Testing (QST) batteries is considered highly important for an objective assessment of sensory functions in research settings and is considered an extension of traditional bedside clinical examination. In contrast, in the clinical practice QST is not yet widely applied and accepted (Backonja et al., 2013) even though standardized QST enables clinicians and researchers to make a more precise analysis of the functionality of the somatosensory system in patients with chronic pain. QST is specifically aimed to detect both negative symptoms and positive symptoms such as a loss of function, paresthesia, hyperalgesia and allodynia for thermal and mechanical stimuli (Haanpaa et al., 2009).

One of the major reasons why QST is not widely used among clinicians is the lack of standardization of QST procedures. In a major initiative for standardization, the German Research Network on Neuropathic Pain (DNFS) has established a standardized QST protocol measuring 13 parameters for innocuous and noxious mechanical and thermal stimuli. This extensive QST battery allows for a comprehensive somatosensory characterization of chronic neuropathic pain patients. Reference values from a large database of age and gender matched healthy volunteers are available to evaluate the somatosensory functioning of individual patients (Rolke et al., 2006a; Rolke et al., 2006c; Konopka et al., 2012a; Konopka et al., 2012b). The parameters in the QST battery can be divided into four categories: thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations;
thermal pain thresholds for cold and hot stimuli; mechanical detection thresholds for touch and vibrations; and mechanical pain sensitivity (van Wilgen et al., 2011). These different parameters can also be associated with the functioning of the previously mentioned pain processing fibres (see Table 1.1).

QST can contribute to the identification of differences in somatosensory functioning between patients. This may reveal multiple underlying pathophysiological mechanisms that are responsible for the neuropathic pain symptoms. Identifying specific pathophysiological mechanisms could be a first step in developing mechanism-based therapies for neuropathic pain. In line with this approach, a recently published QST study by Maier and colleagues, showed that sensory abnormalities along the thirteen different QST parameters can be categorized into specific patterns of abnormal sensory function associated with different clinical diagnosis of neuropathic pain (Maier et al., 2010).

**Table 1.1 Simplified overview of nerve fibers sub-modalities tested by QST**

<table>
<thead>
<tr>
<th>QST parameter</th>
<th>CPT</th>
<th>HPT</th>
<th>WDT</th>
<th>WUR</th>
<th>CDT</th>
<th>TSL</th>
<th>PHS</th>
<th>MPT</th>
<th>MPS</th>
<th>MDT</th>
<th>DMA</th>
<th>VDT</th>
<th>PPT</th>
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<tbody>
<tr>
<td>C-fibre</td>
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<td>Aδ-fibre</td>
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<td>Aβ-fibre</td>
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</table>

Potential overlapping modalities for each nerve fibre type are not shown. QST parameters are: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Wind Up Ratio (WUR), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Mechanical Detection Threshold (MDT), Dynamic Mechanical Allodynia (DMA), Vibration Disappearance Threshold (VDT) and Pressure Pain Threshold (PPT). All nerve fibre functionality tests are applied to the skin with exception of PPT (deep tissue C-fibre / Aδ-fiber test).

* Aβ-fiber can become involved in mechanical pain processing in pathological neuropathic pain states as a consequence of maladaptive neural plasticity.

### 1.6.3 Treatment of Neuropathic Pain

The pain management of neuropathic pain patients remains challenging. Many patients don’t respond to treatment and responders typically only experience a pain reduction and almost never a full pain relief. In neuropathic pain patients a decrease of pain of more than 50% is only achieved in less than one-third of the patients studied in clinical trials. Although any pain relief should be considered an improvement it also means that most patients must still cope with the residual pain (McQuay et al., 1996; Sindrup & Jensen, 1999; Argoff et al., 2006; Ziegler, 2008).

For the Neuropathic Pain Special Interest Group (NeuPSIG) within the IASP, Dworkin and colleagues (Dworkin et al., 2007; Dworkin et al., 2010) have developed evidence based guidelines for the pharmacological treatment of neuropathic pain. They have proposed a
stepwise approach based on proven efficacy. First line treatments are anti-convulsants (calcium channel ligands like gabapentin and pregabalin), tricyclic anti-depressants or SS(N)RI (Selective Serotonin (Noradrenaline) Reuptake Inhibitors) and topical lidocaine. Second line treatments are tramadol and opioids. More recently strong topical capsaicin patches are also considered to be an effective treatment option (Maihofner & Heskamp, 2013; Wagner et al., 2013). NSAIDs are not found to be effective in the treatment of neuropathic pain.

Both remifentanil and gabapentin are described in this thesis as interventions for the pharmacological validation of our improved experimental pain model for neuropathic pain. Gabapentin is regarded as reasonably effective first line medication for treatment across different neuropathic pain conditions (Attal et al., 2010; Dworkin et al., 2010; Moore et al., 2011). Gabapentin is thought to bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels and inhibit neurotransmitter release by blocking new synapse formation (Eroglu et al., 2009; Dworkin et al., 2010; Moore et al., 2011). Several studies using human experimental capsaicin models report that gabapentin reduces the area of mechanical hyperalgesia and allodynia but not acute nociceptive pain (Dirks et al., 2002; Gottrup et al., 2004; Mathiesen et al., 2006). However, other capsaicin studies failed to find an effect of gabapentin on hyperalgesia (Gustorff et al., 2004; Wallace & Schulteis, 2008). Remifentanil has been studied in several human experimental capsaicin models and has shown to reduce hyperalgesia and allodynia and continuous pain (Petersen et al., 2001; Hood et al., 2003; Petersen et al., 2003).

Because of the diversity in aetiology and symptoms of neuropathic pain patients a clear treatment response for different subtypes of patients may be masked by using heterogeneous patient groups in clinical trials. Therefore a more individualized treatment approach is deemed necessary for an improvement in the pain management of this group of patients (Dworkin et al., 2007; Attal et al., 2010; Dworkin et al., 2010). Neuropathic pain models in combination with QST have the potential to play an important role in the development towards a more mechanism based personalized medicine approach. Indeed, some studies indicate that patients with allodynia respond better to pregabalin and that patients with a preservation of thermal sensation react positively to topical therapies (Attal et al., 2011).

1.7 EXPERIMENTAL PAIN MODELS

Experimental pain models in healthy volunteers can play a vital role studying the efficacy of novel analgesic drugs (Drewes et al., 2003). Experimental pain models try to mimic or model the pain state of patients in healthy volunteers for a short period of time without causing any long lasting physical harm in the volunteer. An ideal model mimics as many aspects of the clinical pain state or disease as possible to be able to successfully predict the analgesic efficacy of novel drugs.
In a review discussing the applicability of human pain models for opioid efficacy, Staahl and colleagues concluded that “there is still a need for basic investigations of opioids in well-designed human experimental pain models” (Staahl et al., 2009a). Furthermore several reviews recommend more standardized outcome measures and clinical trial designs to achieve a better comparison between pain studies and clinical trials in early drug development (Handwerker & Kobal, 1993; Woolf & Max, 2001; Staahl et al., 2009b).

A very important reason for using an experimental pain models is to provide the investigator with strict control over the stimulus intensity, duration and location and result in a clear outcome measure for drug efficacy (Drewes et al., 2003; Staahl & Drewes, 2004). In contrast small patient trials in an early development phase often suffer from confounding psychological and social illness characteristics (Staahl et al., 2009a).

1.7.1 MODELS FOR NOCICEPTIVE PAIN

Human models for acute pain have always used a wide variety of external stimuli to create a pain experience (Gracely, 2006). The most commonly used stimuli are heat, cold, mechanical stimulation, pressure, chemical stimulation or electrical stimulation (Staahl & Drewes, 2004). Using different types of measurements in a multi model approach can mimic aspects of chronic pain very accurately and gain advanced and differentiated information on the anti-nociceptive properties of the studied compound (Drewes et al., 2003).

An important aspect of pain research is how to measure the painfulness of pain stimulation and which measures provide a reliable outcome measure for analgesic efficacy. Acute pain is commonly measured as a psychophysical measure of the subjective experience of the pain expressed on standardized pain rating scales or as pain thresholds (Gracely, 1999; Staahl & Drewes, 2004). Pain detection thresholds attempt to identify the minimal intensity of a physical stimulus that elicits a painful experience (Gracely, 1999). Pain detection thresholds have been found to be sensitive to a number of different analgesic compounds and are a fast and reliable indicator of analgesic efficacy (Gustorff et al., 2001; Petersen et al., 2001; Gustorff et al., 2003; Rolke et al., 2006b). In addition, a visual analog scale (VAS) or Numeric Rating Scale (NRS) consisting of a vertical bar on a screen anchored with the descriptors ‘no pain’ (numeric value = 0) and ‘worst possible pain’ (numeric value = 100) is often used to rate the subjective intensity of the pain. Both methods are easy and quick outcome measures for pain sensitivity and commonly used in early clinical trials to test the efficacy of novel analgesics (Handwerker & Kobal, 1993; Gracely, 1999). In Chapter 3 of this thesis the results of a large battery of acute pain tests to induce pain consisting of both sensory and pain thresholds as well as tonic pain stimuli will be discussed.
1.7.2 MODELS FOR NEUROPATHIC PAIN

Simulating neuropathic pain is less straightforward than acute pain. Although there are animal models available that inflict nerve lesions and nerve constrictions to induce a state of neuropathic pain, for obvious ethical reasons these cannot be applied to humans. Therefore, human experimental pain models for neuropathic pain try to model specific neurophysiological mechanism to mimic the most common positive clinical symptoms of neuropathic pain like hyperalgesia and allodynia. There are various models that all use different methods and stimuli to achieve a relatively short lasting, reversible neuropathic pain like state. Examples are: the burn injury model which applies 53 °C heat for 30 seconds or 47 °C heat for 7 minutes to the skin (Raja et al., 1984; Pedersen & Kehlet, 1998; Pedersen et al., 1998); intradermal capsaicin (the active ingredient in hot chili peppers) which injects a capsaicin solution into the skin (Simone et al., 1989; Simone et al., 1998; Hughes et al., 2002); topical capsaicin cream, which is applied to the skin (Arendt-Nielsen et al., 1996) (Nielsen 1996); topical capsaicin in combination with heat stimulation (Petersen & Rowbotham, 1999; Dirks et al., 2000; Petersen et al., 2001; Dirks et al., 2002; Dirks et al., 2003; Petersen et al., 2003); the UV burn model mimics a sunburn (Koppert et al., 2004); the freeze lesion model freezes the skin with a copper cylinder of -30 °C for 9 seconds (Schmidtko et al., 2007) (Koppert et al., 2004); the electrical stimulation model applies two electrodes to the skin simulating long term potentiation (Koppert et al., 2001); the Nerve Growth Factor (NGF) model injects NGF into the skin (Rukwied et al., 2010). All these models are known as neuropathic pain models and all induce some kind of sensitization and/or painfulness. All models have their own specific mechanism of action, but measure similar outcome measures like painfulness, hyperalgesia and allodynia (For a review see (Klein et al., 2005; Staahl et al., 2009b; Reddy et al., 2012)).

The last two chapters of this thesis describe the development and pharmacological validation of the Heat Capsaicin Warmth (HCW) model; therefore the present discussion is limited to the capsaicin models. Several capsaicin models (both intradermal and topical) have shown analgesic efficacy and anti-hyperalgesic effects for known analgesics like ketamine, alfentanil, fentanyl, cannabis, morphine, pregabalin, gabapentin and others, although some studies also failed to find any analgesic effects (Wallace et al., 2002; Voller et al., 2003; Waller et al., 2004; Kraft et al., 2008).

In this thesis a model is described that was newly developed to improve and optimize the heat-capsaicin sensitization model that was first described by Petersen & Rowbotham (Petersen & Rowbotham, 1999). Furthermore, we wanted to develop a model that would not only induce a more reliable state of sensitization especially for allodynia but also a continuous state of pain. This continuous state of pain allows for a separation between evoked and continuous tonic pain in neuroimaging studies and provides an additional
outcome measure to test analgesic efficacy of novel compounds. Our newly developed model is the only capsaicin model to date that combines a stable period of continuous pain with secondary hyperalgesia and alldynia. Although intradermal capsaicin models also induce ongoing pain, in these models the duration of the ongoing pain is very short and is quickly reduced to a pain rating below 10 (out of 100) within 30 to 60 minutes (Gustafsson et al., 2009). Only the electrical model described by Koppert et al. (Koppert et al., 2001) induces continuous pain, but seems to be less successful in inducing alldynia which was only developed in 50% of the subjects (Geber et al., 2007).

1.8 DRUG DEVELOPMENT: THE NEED FOR NOVEL ANALGESICS

I have already mentioned the striking estimated 35% of all people who will suffer from a period of chronic pain earlier this thesis. These people will need treatment. But as we now know, almost half of the people suffering from chronic pain do not receive proper pain management (Breivik et al., 2006). In fact, pain is the number one symptom for which people consult their general physician. Pain is very often the first cause for seeking medical attention and estimates indicate that up to 80% of the visits to a primary care giver were initiated due to a complaint where pain is involved (Hadjistavropoulos & Craig, 2004). This makes pain one of the most common symptoms in modern day medicine. It is not surprising that many people would agree that effective pain treatment should be one of the most important goals in drug development and medical sciences.

The process of finding a possible new target for a new drug and receiving a market authorization for patients is a very lengthy process known as the ‘drug development cycle’ and can take up to ten years. This cycle involves a broad range of scientific and safety regulatory studies in different scientific fields that have to be performed successfully before the drug is deemed safe and a market registration is granted for treatment of a group of patients (see Figure 1.4 for an overview of all stages).

![Figure 1.4](image-url) 

FIGURE 1.4 The drug development cycle. Out of every 10,000 molecules discovered as a potential pharmacological target, only one will receive market authorization.
The target finding phase (drug discovery) involves the discovery of promising physiological targets in the human body and possible chemical or biological molecules that will interact (block or activate) with these targets. Once a target is discovered the new compound will have to be extensively tested in vitro to validate the mechanism of action. If the in vitro tests are successful the new molecule will be tested in a wide range of animal studies. Out of a possible 10,000 new compounds only 250 reach this pre-clinical animal study phase. Pre-clinical studies are performed to test the pharmacological profile of the new compound, the pharmacological mechanism of action and the safety and toxicity. The pre-clinical phase experiments will be performed in specific animal models to indicate the clinical efficacy for a disease. For instance, a novel analgesic for neuropathic pain will be tested in a mouse model for diabetes with neuropathy. If the preclinical studies show that the new molecule is safe in animals and if there is enough evidence for efficacy, the compound will be tested in humans for the first time. From the 250 possible new drugs that entered the pre-clinical phase only 5-10 will be tested in humans. In this early phase (phase I) of clinical drug research the new drug is first tested for safety and tolerability in healthy volunteers. Typically a very low dose is given to humans and if there are no undesirable side-effects the dose will be slowly increased to test up to which dose is well tolerated. Apart from gathering safety information in these studies in healthy volunteers, the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the new compound will be investigated. Once the drug has been proven safe the first studies in small patient groups can be performed to show the efficacy of the drug, this is called phase II. If the efficacy is satisfactory and the right dose level is defined, a large scale clinical trial in thousands of patients is performed to test if the new drug is an improvement compared to any existing treatment (phase III). Once all these studies and trials are finished the data will be reviewed by a regulatory agency like the FDA (Food and Drug Administration, for the US) or the EMA (European Medicine Agency, for Europe). They will decide whether the new drug can be registered as a treatment for patients. Of course this is a very short and simplified description of the drug development cycle, but it gives an insight in the general process and helps to set the context for the work described in this thesis. For a full overview of drug discovery and development see the textbook ‘Drug discovery and development: technology in transition’ (Rang, 2006).

Before testing a new compound in a patient group, it can be useful to look for early indications of efficacy and proof of mechanism in healthy volunteers. A disease model in healthy volunteers can often be combined in phase I safety studies to save time and money and can provide a first indication for the efficacy of novel drugs. Such a model should be able to test certain aspects of the disease in healthy volunteers (for a short period of time) without doing any harm to the volunteer. Some examples are a glucose tolerance test for
diabetes medicine or the experimental pain models described in paragraph 1.7. Ideally the model that is used in humans will have an analogue model in animals in order to compare the data from pre-clinical studies. Within the drug development cycle, experimental pain models are sometimes seen as the missing link between pre-clinical animal research and efficacy studies in pain patients. These models can be seen as translational studies that enable us to compare results from the animal studies with human studies. Showing efficacy of an animal model will hopefully be a good predictor to find efficacy in a human pain model, which in turn, will be a good predictor to show efficacy in patients. In practice this is one of the most difficult issues that disease models are facing as different animal species (including humans) have different physiological properties that will react differently to the model and the new drug. Therefore, extrapolating findings from animal studies to human models and patient outcomes remains a challenge. There have been examples of new candidate analgesic compounds that showed great potential in animal studies but failed to find any effects in humans, for example the NK1-antagonist developed by Merck (Boyce & Hill, 2004; Lowe, 2005).

1.9 THESIS OUTLINE

The work presented in this thesis is focussed on the early phases of the drug development specifically on phase I human pain models for acute pain (chapters 2 and 3) and neuropathic pain (chapters 5 and 6) as well as testing somatosensory function and characterization for phase II studies of neuropathic pain patients (chapter 4). In all these different studies it is important that the measurements used in the study are well suited to detect the desired therapeutic (analgesic) effect. This is summarized under the term ‘assay sensitivity’, which is defined as: the ability of a trial to distinguish an effective treatment from a less effective or ineffective intervention. Without assay sensitivity, a trial is not internally valid and is not capable of comparing the efficacy of two interventions (Snapinn, 2000). Both human experimental pain models and somatosensory profiling of patients can play a vital role to improve the assay sensitivity of clinical trials for novel analgesics.

We have applied standardized measures from a QST battery in the experimental models for acute pain in chapter 2 and 3 as well as in the assessment of neuropathic pain patients and healthy controls subjects in chapter 4. The second part of the thesis (chapter 5 and 6) describes a newly developed topical capsaicin model that can be applied in early phase of drug development.

In chapter 2 we have tested the reliability of 10 QST parameters and 3 continuous pain measurements over a three week period on three different locations. In this chapter we investigated both the variability over time as well as between locations. We anticipated
the QST battery to be a highly reliable and objective measure to measure acute pain and somatosensory functions.

In chapter 3 we performed a pharmacological validation for acute pain measurements using QST measures as well as other tests for experimental acute pain in a double blind two-way cross-over design with the highly used analgesic remifentanil. We hypothesized that remifentanil would have an analgesic effect on a wide range of QST parameters. Furthermore, we discussed which measures can be regarded as most reliable and robust.

Chapter 4 describes the application of a standardized QST test protocol in a group of 100 neuropathic pain patients and 200 healthy controls. We showed that the comparison with a reference group of healthy control subjects can provide useful additional information about the sensory functioning of neuropathic pain patients. In this chapter we compare QST profiles from uni-lateral neuropathic pain patients at both the affected and contra-lateral healthy body side to reference values from age and gender matched healthy volunteers.

In the last two chapters we have described the development and pharmacological validation of the Heat Capsaicin Warmth (HCW) model. This is a newly adapted topical capsaicin model that mimics symptoms of neuropathic pain like alldynia, secondary hyperalgesia while continuous burning pain is present at the same time. Compared to previous capsaicin models this model shows more robust read outs for hyperalgesia and alldynia and the model induces a tonic state of continuous pain for up to two hours. In Chapter 5 the pilot study is described that was performed to decide on the final design of the Heat Capsaicin Warmth model. In the second part of chapter 5 we performed a direct comparison of our new capsaicin model with the existing heat capsaicin model described by Petersen & Rowbotham (1999). We tested both models for the extent of alldynia and hyperalgesia as well as the intensity and duration of the continuous pain throughout the model. In chapter 6 we performed a pharmacological validation study with the HCW model. For this purpose we administered a single dose of the anti-convulsive drug gabapentin, a first line treatment in neuropathic pain and a 45 minute infusion with the opioid remifentanil to healthy subjects.

All studies were performed within the framework of the Top Institute Pharma project which aimed to improve the assay sensitivity for studying novel analgesics in early phase clinical drug development. Our general hypothesis was that using standardized QST measures for acute and neuropathic pain in both healthy volunteers and patients would improve the reliability of the outcome measures in efficacy studies. Furthermore we aimed to develop a more robust topical capsaicin model for neuropathic pain to achieve reliable hyperalgesia and alldynia in combination with continuous tonic pain. We hope that these methods will lead to improved methods for testing the efficacy of novel analgesics.
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