Audio-visual signals and distraction of perceived pain

PhD thesis

Bo Bentsen

Royal Dental College, Faculty of Health Sciences, University of Aarhus
Department of Oral Radiology and Department of Clinical Oral Physiology

2002

Content Page

Preface 2

Acknowledgements 3

1 Introduction 4

2 Pain physiology 8

2.1 Peripheral mechanisms 8

2.2 Neural pathways 10

2.3 Central processing 10

3 Distraction 11

3.1 Possible mechanisms 11

3.2 Studies on the effect of distraction on experimental pain 12

3.3 Non-dental studies on the effect of distraction on procedural pain 13

3.4 Dental studies on the effect of distraction on procedural pain 13

4 Nitrous oxide 16

5 Experimental pain models 16

5.1 Electrical stimulation 17

5.2 Chemical stimulation 18

5.3 Mechanical stimulation 18

5.4 Thermal stimulation 18

6 Dental, procedural pain models 19

7 Assessment of pain 21

7.1 Psychophysics 21

7.2 Scaling of a sensation 21

7.3 Pain scales 22

7.4 Dimensions of pain 23

8 Own studies I-IV 24

8.1 Aims 24

8.2 Designs and results 25

8.3 Discussion 31

8.4 Conclusions 39

9 Future aspects 40

10 English summary 41

11 Dansk sammenfatning/Danish summary 44

12 References 47

Preface

This Ph. D. thesis is based on the following four original papers and a review of the literature. The studies are referred to by their Roman numerals throughout the thesis.

I.

Bentsen B, Svensson P, Wenzel A. The effect of a new type of video glasses on the perceived intensity of pain and unpleasantness evoked by a cold pressor test. Anesth Prog 1999; 46: 113-117.

II.

Bentsen B, Svensson P, Wenzel A. The hypoalgesic effect of 3-D video glasses on cold pressor pain: Reproducibility and importance of information. Anesth Prog 2000; 47: 67-71.

III.

Bentsen B, Svensson P, Wenzel A. Evaluation of effect of 3D video glasses on perceived pain and unpleasantness induced by restorative dental treatment. Eur J Pain 2001; 5: 373-378.

IV.

Bentsen B, Wenzel A, Svensson P. Comparison of the effect of video glasses and nitrous oxide analgesia on the perceived intensity of pain and unpleasantness evoked by dental scaling. Eur J Pain 2003; 7: 49-53.

Acknowledgements

I want to express my sincere thanks to my supervisors and co-authors professor, Ph.D., dr. odont. Ann Wenzel and professor, Ph.D., dr. odont. Peter Svensson. Ann for having initiated and guided my approach towards the scientific world and both for their valuable support, help and knowledge that brought me to this point. They have been a constant support for me in all aspects and with a positive attitude and unlimited time for which I am indebted.

I also want to thank Erik Gotfredsen, Mette Agerbæk and Jane Pauli for assistance of high quality and spirit. Associate professor Morten Frydenberg, Department of Biostatistics is thanked for his guidance into the field of biostatistics. And last but not least the tried staff and colleagues at my dental clinic as well as Jens Erik Winther, Merethe Hørsted and Bodil Birn for giving me the opportunity to fit this work into my other duties during the years.

Finally an unrestricted thanks is dedicated to my loved family for having made this possible.

Moreover, I wish to acknowledge the financial support from The Danish Dental Association.

1 Introduction

The current definition of pain is ”an unpleasant sensory and emotional experience with actual or potential tissue damage or described in terms of such damage” (Merskey & Bogduk 1994). The complex experience of pain is a natural part of living and is a personal experience known to everyone.

Acute pain has a purpose of learning and guiding the individual to react in a manner that is non-destructive to the body. Thus, this is a normal physiological response and protective mechanism that warn us against potential tissue damage, and this mechanism is obviously beneficial to the individual. Children, who were born without the capability to feel pain hurt themselves more and repeatedly compared with normal children (Ozbarlas et al. 1993, Nolano et al. 2000). This rare disease is an example of the individual not learning how and when to avoid possible tissue trauma, and it often results in severe tissue damage over time. The same lack of protection due to sensory malfunction is seen in leprosy patients, who lose their pain perception in the extremities, and who typically lose toes and fingers due to heat, mechanical or other injuries, which are not avoided in due time (Soares & Desar 1995). Transient or acute pain in this way stimulates the organism to behave in a way that secures its survival. In contrast, persistent or chronic pain develops or persists long after the acute injury has healed or disappeared and has no obvious meaning with regard to the protection of the injured.

Persistent pain is often described as much more bothersome, giving rise to e.g. depressed mood, sleep disturbances and loss of energy (Sullivan 1992). Typical examples of persisting pain in the orofacial region are temporomandibular disorders, burning mouth syndrome and atypical facial pain, which covers a variety of diagnoses (Woda & Pionchon 2000, 2001). Transient pain in the orofacial region is well known to most individuals, and it is general knowledge that dental treatment possesses the risk of a transient pain experience, which can be termed procedural pain.

Pain has been classified in many ways. Duration has been used as a pragmatic way to divide pain into acute or chronic pain (i.e. > or < 6 months). Furthermore, an anatomical approach may be used to classify pain according to the parts of the body. The present classification systems of symptoms and signs have limitations, and recently a mechanism-based classification of pain has been suggested as a parallel taxonomy (Woolf et al. 1998). According to this taxonomy a distinction can be made between transient pain, which refers to the response to a noxious stimulus that does not produce long-term sequela, tissue injury pain, and nervous

system injury pain (Woolf et al. 1998). Transient pain can be divided into spontaneous and evoked pain and the evoked pain can again be divided into experimental and procedural pain (Fig. 1).

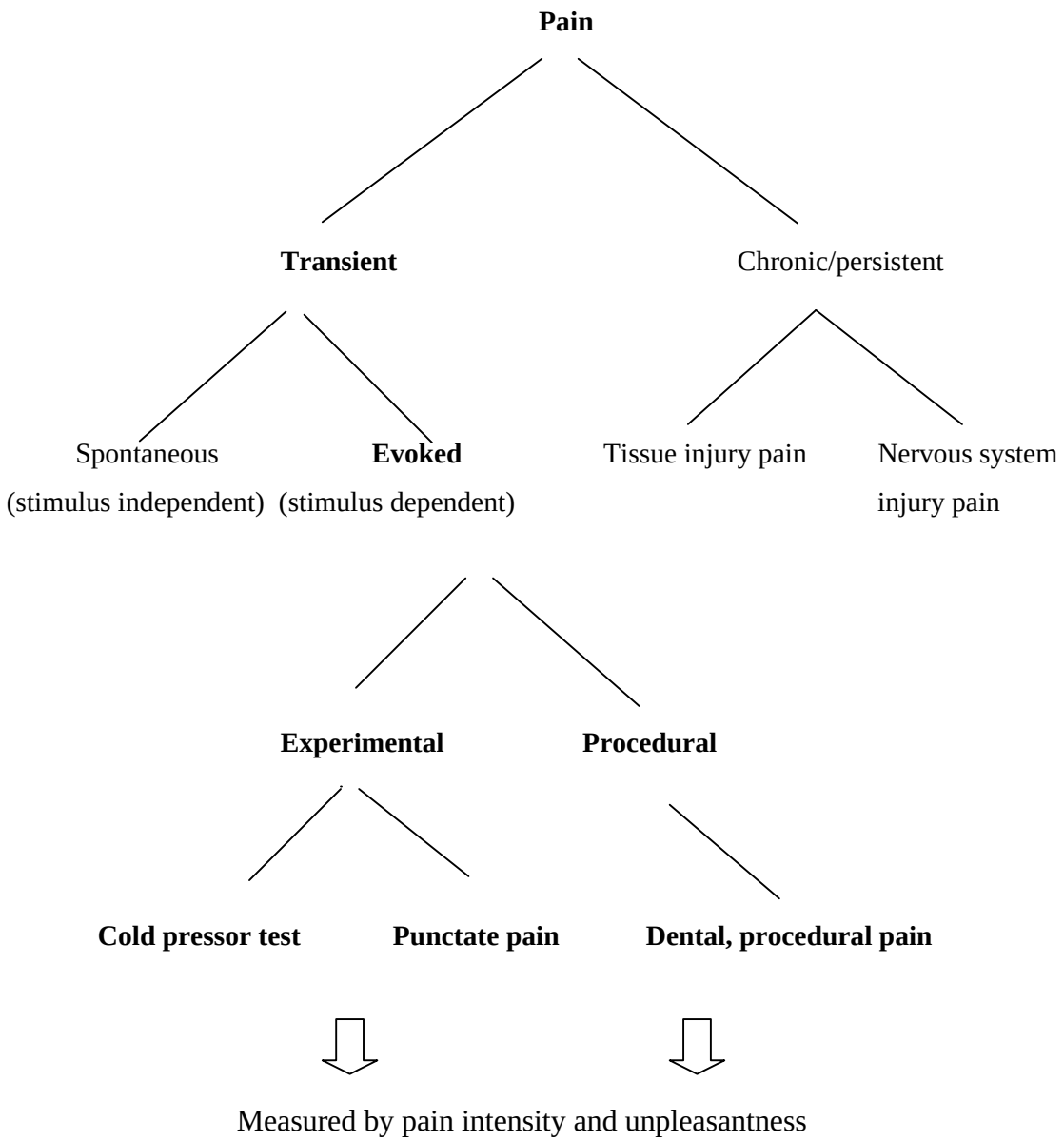


Fig. 1. Diagram showing the types of pain studied in this thesis (bold). The diagram follows the ideas of a mechanism-based classification (Woolf et al. 1998).

Management of dental, procedural pain covers an extensive spectrum of different interventions (Fig. 2). For a review, see *Petersen and Milgrom* (1989).

A broad range of pharmacological pain management procedures has been used, e.g. topical analgesics (Svensson et al. 1992, 1994), nitrous oxide (Dworkin et al. 1983), fentanyl (Gracely et al. 1979) and injection with local analgesics (Malamed et al. 2001). Two of the most common techniques for pain relief, nitrous oxide and injection with local analgesics are however, not without problems. Nitrous oxide has been shown to have serious side effects as studies have revealed a lower fertility (Rowland et al. 1992) and an increased frequency of spontaneous abortion (Rowland et al. 1995) among female dental assistants working in environments with high levels of nitrous oxide. Local analgesics, on the other hand, is regarded as safe in relation to environmental hazards, but is often disliked by the patients due to needle anxiety (Svensson et al. 1994).

In the group of non-pharmacological interventions, transcutaneous electrical nerve stimulation (TENS) has been used (Quarnstrom & Milgrom 1989, Oztas et al. 1997) together with acupuncture (Ernst & Pittler 1998, Sheng et al. 2000). Techniques involving cognitive psychological means of pain management include hypnosis (Barber & Mayer 1977), redefinition of the pain (Spanos et al. 1987), imagery (Chen 1991) and distraction.

Distraction is a way of reducing pain, which includes a large range of means, from video games (Corah et al. 1979, Seyrek et al. 1984) and sound (Carlin et al. 1962, Skjerve & Nedreås 1981, Corah et al. 1981) to watching video (Weisenberg et al. 1995a) and television (Seyrek et al. 1984). A recently proposed method of relieving pain and unpleasantness is audible and visual distraction with video glasses. Video glasses give the opportunity for the viewer to watch conventional or three-dimensional video with or without sound. The video glasses are lightweight and are easy for both patient and therapist to operate. For a schematic view over the management of procedural pain, see Fig. 2.

This thesis will focus on the possible distraction effect of video glasses on the perceived pain and unpleasantness evoked by transient experimentally induced painful stimuli and transient pain evoked by dental, procedural stimuli.

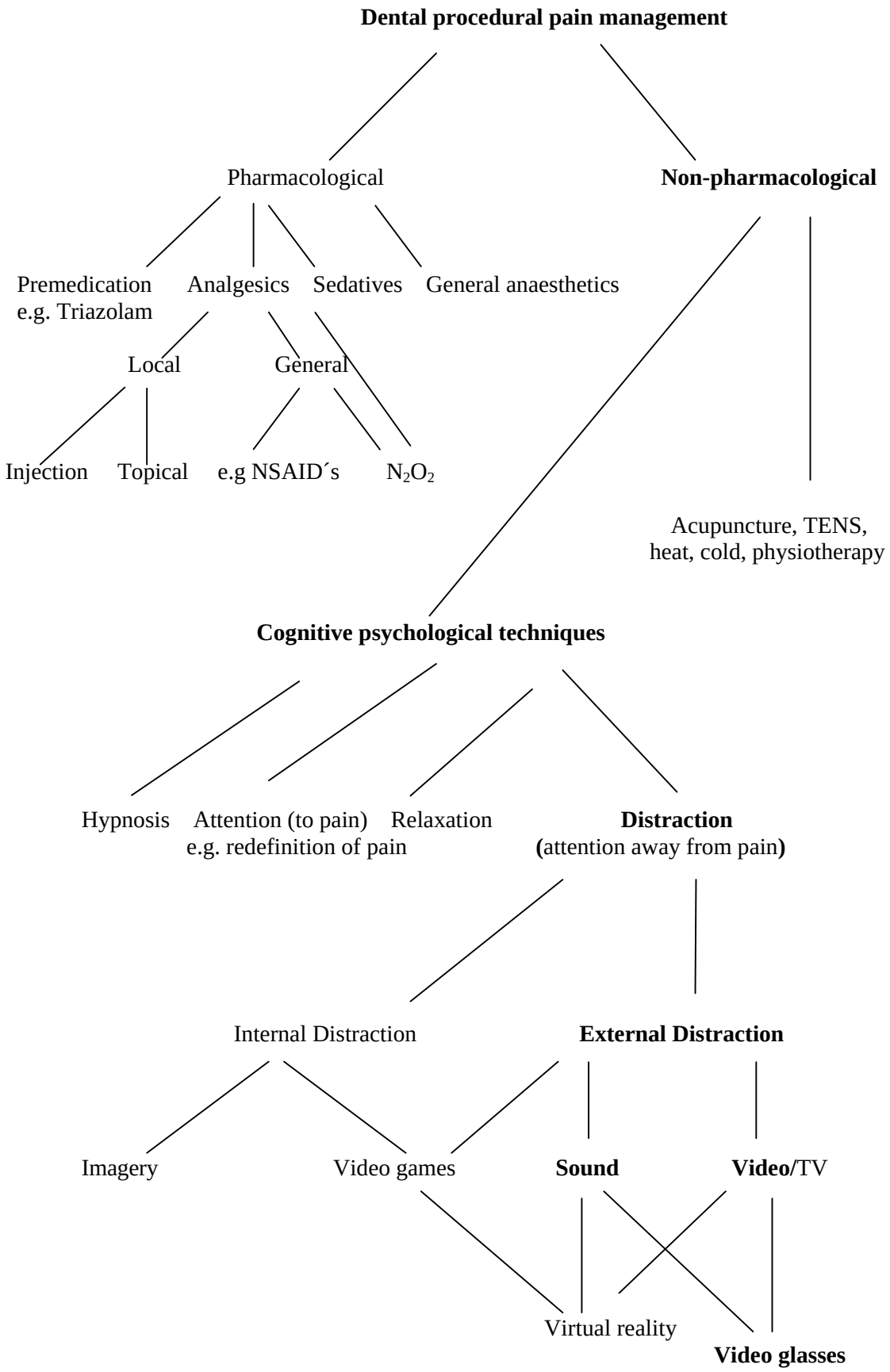


Fig. 2. Pathways of managing dental procedural pain and the position of video glasses in this hierarchy.

2 Pain physiology

The four major modalities of somatosensory sensibility according to a textbook (Gardner et al. 2000) are 1) touch sensation that mediates the shape, texture and size of items touching our surface 2) the proprioception that gives information about the position and movement of the body 3) sense of temperature that mediates the feeling of warm and cold, and finally 4) nociception that signals pain and itch.

The nociception of temperature and briefly, the touch sensation are the senses that will be focused on in this thesis. These senses are highly involved in the perception of pain evoked by cold stimuli and pain evoked by dental as well as sensations evoked by the Von Frey monofilament (for a description of Von Frey monofilament, see chapter 5). It must be emphasised that nociception and pain are two different terms, as nociception is defined as the neurophysiological / neuro-biological mechanisms evoked by a nociceptive stimulus whereas pain is the perceptual correlate to this nociceptive stimulus.

2.1 Peripheral mechanisms

Nociceptive and thermal inputs are mediated through a complex system of receptors and pathways. The nerve-fibres that mediate the sense of body temperature and pain are the fast conducting Ad-fibres, which are thin myelinated nerve fibres, and the slower conducting, unmyelinated C-fibres. C-fibres are often polymodal, meaning that they can transmit different types of nociceptive inputs, i.e. mechanical, thermal or chemical, but can also be classified into subgroups related to a single modality (Table 1).

Fibre	Name	Modality
C	CC	Low temperatures - cold
C	CM	Intense mechanical stimuli
C	CH	Intense heat
C	CMH	Intense mechanical, heat and chemical stimuli
C	CM_iH_i	Insensitive to heat and mechanical stimuli, but active during inflammation
Ad	AHM_{II} (short latency < 1sec)	Heat and mechanical stimuli
Ad	AHM_{I} (long latency >2 sec)	Heat and mechanical stimuli
Ad	HTM/AM	High-threshold mechano-receptor

Table 1. Subgroups of nociceptive fibres (Adapted from: Treede et al. 1995, Schmidt et al. 1995, Simone & Kajander 1997).

Thermal receptors in human skin are named cold and warm points and are unevenly distributed over the entire body surface with the highest density in the most temperature-sensitive regions, and generally with fewer warm points than cold points. In primates and mammals these point are small and only supplied by one or a few afferents fibres and maintain a constant firing when there is no change in skin temperature, whereas a dynamic response (rise or fall in discharge) is seen during changes in skin temperature. Cold and warm points are insensitive to other stimuli than thermal (Schmidt & Thews 1983). Responses to temperatures around and below 0°C are mainly mediated by Ad-fibres (Simone & Kajander 1997), and responses to temperatures above the freezing point are mediated by both Ad- and C-fibres. As more types of fibres often are activated at the same time, it can be difficult to determine which fibres are involved in the actual transmission of nociceptive signals. Pricking and localised pain are mediated by the fast myelinated Ad-fibres. The subjective response is a thermal first pain sensation that can be followed by a second and more diffuse and burning type of pain transmitted by the C-fibres. As can be seen from Table 2, there is no obvious single afferent fibre responsible for the mediation of the thermal stimuli/pain evoked by a cold pressor test (for detailed description of the cold pressor test, see chapter 5), since no fibres are at the peak discharge around 2°C. Furthermore, a study has shown that only approximately 30% of cold pain Ad-fibres are active around 0°C with a peak activity around -18°C (Simone & Kajander 1997). The nociceptive information from the cold pressor test is therefore most likely mediated by several afferent fibre types or by fibre types not yet described.

Fibre type	Modality	Activity interval °C	Conduction velocity m/s	Studies
Ad	Cold pain	-18 ? 14	2? 30	Simone & Kajander 1997
C (CC)	Cold pain	0 ? 19	1	Campero et al. 1996
Ad	Cold	20 ? 45	15	Darian-Smith et al. 1973
Ad (AHM_{II}) Ad (AHM_{I})	Heat/cold	> 46 and <0 > 53 and <0	15 25	Treede et al. 1995, Simone 1997
C (CMH)	Warm	> 38	1	Treede et al. 1995 Beitel & Dubner 1976

Table 2. Primary afferents involved in thermal and thermal pain sensations.

Nociceptive inputs are mediated by free nerve endings from the orofacial region. The nociceptors have been recognised in virtually all tissues including muscle, joints, tendons, fascia as well as in facial skin, oral mucosa, periodontium and tooth pulp. They are associated with Ad-mechano-thermal and polymodal C-fibres (Sessle 1987). The mechano-heat responsive fibres (CMH) from the C-fibre group are responsible for the mediation of punctate tactile skin stimulation (see chapter 5) with e.g. Von Frey hair (Weidner et al. 1999).

2.2 Neural pathways

From the periphery, the nociceptive signal is transmitted through the first order neuron via the dorsal root to a synapse in the spinal cord from where the second order neuron ascends through the spinothalamic tract. The main pathway ascends through the dorsal horn of the spinal cord, crosses the midline to the contralateral side of the spinal cord, and reaches thalamus through the anterolateral white matter. From the thalamus the signal is transmitted through the third order neuron to the somatosensory cortex.

In the major nociceptive pathway from the orofacial region, the nociceptive signal is transmitted via C- and Ad–fibres, and follows pathways much similar to that of the spinal nerve fibres. Through the first order neuron with cell body in the trigeminal ganglion (semilunar), the signal is mediated to a synapse with the second order neuron in the trigeminal brain stem sensory nucleus complex before projecting centrally to the thalamus and through the third order neuron to the cortex (Sessle 2000).

2.3 Central processing

Modern neuroimaging techniques like positron emission tomography (PET) have helped to outline cortical networks involved in processing of various somatosensory and nociceptive stimuli. For example *Petrovic et al.* (2000) showed that the activity in the periaqueductal grey matter (PAG)/midbrain increased during a cold pressor test. Also areas of the cortex have been shown to be active in e.g. thermal perception (Casey et al. 1996). During painful stimuli to the hand with 46°C hot water, a PET-scan of the cerebral cortex (contralateral side to the stimulus) was obtained (Rainville et al. 1997). This showed significantly increased regional cerebral blood flow in the primary somatosensory cortex (SI), in the secondary somatosensory cortex (SII), the anterior cingulate cortex (ACC) and the rostral insula (IC). This study also indicated that the ACC has a significant involvement in the processing of the affective component of pain (unpleasantness). Functional magnetic resonance imaging (fMRI) of the cerebral cortex has also revealed that cold pressor pain leads to increased ac-

tivity in ACC (Frankenstein et al. 2001). A PET study showed increased activity during cold pressor pain in the ACC, SII, SI and mid-insula areas of the cerebral cortex (Petrovic et al. 2000). During electrical stimulation of the dental pulp, an increased activity in recorded cerebral magnetic fields was shown in SII (Hari et al. 1983).
Thus, there is clear physiological evidence that a central processing of nociceptive inputs takes place and where this processing is located in distinct networks of the brain. Therefore, the possibility of a central modulation of this processing may exist, e.g. by distraction.

3 Distraction

Many different types of cognitive coping strategies have been suggested and studied with respect to their effect on the perceived pain. Generally, these strategies that use cognitive psychological techniques (focus attention, neutral imaging, pleasant imaging, distraction, etc.) have been shown to reduce the perceived pain (Fernandez & Turk 1989, Villemure & Bushnell 2002). As an example, distraction with mathematical tasks has been described to lower the perceived pain during a cold pressor test (Hodes et al. 1990).
In this thesis distraction will be defined as:
A state of mind that draws the attention away from painful or unpleasant stimuli.
Distraction and the basic, underlying idea that distraction has a pain-ameliorating effect, is the assumption that we have a limited capacity of attention. If a greater part of this attention can be caught by a distraction task, it will not be devoted to pain perception (McCaul & Malott 1984).

3.1 Possible mechanisms

Perceived pain and unpleasantness can be modulated by many different types of distraction and attention (review: Villemure & Bushnell 2002). At the peripheral level a painful sensation can be modulated in the dorsal horn of the spinal cord by interaction between different sensory inputs at the synapses with the second order neurons. This mechanism was basically proposed in the gate control theory by *Melzack & Wall* (1965). In a study on rats, it was shown that the activity in dorsal horn neurons could be inhibited by noxious stimuli to different parts of the body (Le Bars et al. 1979). The effect was only seen by nociceptive stimuli and was thus named diffuse noxious inhibitory control (DNIC). In humans, DNIC was shown to reduce heat pain stimuli to the face, when the volunteers also immersed their hand

in cold water (5 °C) (Talbot et al. 1989). DNIC is by definition only effective when the conditioning stimulus is noxious, which is not the case with video glasses. In an experimental pain model with recordings from neurons, a monkey was trained to perform tasks that required attention to heat stimuli or to a visual distraction (review: Villemure & Bushnell 2002). In a number of studies where this model was used, a reduction of nociceptive activity was seen in the medullary dorsal horn and the thalamus during distraction (review: Villemure & Bushnell 2002).

In a recent fMRI study, a significantly increased activity was seen in the periaquaductal grey matter (PAG) together with significantly lowered perceived pain when subjects distracted themselves from a painful stimulus (heat) (Tracey et al. 2002). In a PET study, the perception of the affective components (unpleasantness) of the perceived pain (heat) was significantly altered by the use of hypnosis (Rainville et al. 1997). This revealed a significant correlation between the perceived unpleasantness and the activity within ACC whereas the activity in SI and SII were unaltered, leading to the suggestion that pain-related activity is modulated in the ACC, and that this activity is strongly related to the perceived unpleasantness. The same research group performed a similar study (Hofbauer et al. 2001), only was the hypnotic modulation directed towards the perceived intensity and not the unpleasantness of the painful stimulus. Significant changes of the pain-evoked activity were seen within the SI area. These latter studies suggest that different areas of the central cortex are involved in the processing of unpleasantness and intensity of pain.

3.2 Studies on the effect of distraction on experimental pain

Music as distraction has been shown to have a hypoalgesic effect on cold pressor pain (Melzack et al. 1963) and experimental pain induced by electric stimulation of the dental pulp (Morosko & Simmons 1966). Studies on modulation of pain and unpleasantness have documented an effect of showing movies and demonstrated that humour, repulsive scenes as well as tragedy can increase pain tolerance (Weisenberg et al. 1995a, Zillmann et al. 1996). Volunteers that participated in studies on pain clearly stated an advantage of distraction and indicated that distracting oneself from pain stimulus (in this instance cold pressor pain) is a more efficient coping strategy than to attend to the painful stimulus (McCaul & Haugvedt 1982). *Johnson et al.* (1998) have interestingly shown that an external distraction with either non-painful heat stimuli or visual light stimuli was superior to a neutral imagery distraction when it comes to the effect on pain threshold. Imagery distraction in that study was induced by letting the volunteers imagine a lecture situation.

3.3 Non-dental studies on the effect of distraction on procedural pain

Visual distraction with the use of a kaleidoscope has been shown to reduce the perceived pain in children undergoing venipuncture (Vessey et al. 1994). Music has been shown to lower pain rating among patient during laceration repair (Menegazzi et al. 1991). Bubble blowing as distraction has been shown to lower pain rating among children during injection (Sparks 2001). It has also been shown that distraction by blowing a windmill was found to be a helpful coping technique during venipuncture (Lal et al. 2001) and the study suggested that this form of distraction is effective to children. This effect of distraction in children on perceived pain during venipuncture is debated. No effect on the perceived pain was found in a multisite study on distress, fear and self-reported pain in children who had venipuncture or intravenous injections (Carlson et al. 2000). These authors speculated that the difference between empirical reports of a pain reducing effect of distraction and their survey's inability to find a significant effect could be due to differences in the set-up of the studies. Furthermore, there could be methodological factors that may have obscured the chance of finding a difference between the experimental and control groups. When looking at more severe pain as seen in burn injuries, there was no differences on the children's distress during post burn dressing changes when they had a standardised analgesic medication combined with the presentation of a cartoon movie compared with medication alone (Landolt et al. 2002). In adult patients video and virtual reality has been shown to lower the pain ratings when used as distraction among patients with burn wound injuries (Hoffman et al. 2000a,b, 2001a, Miller et al. 1992) and patients undergoing endoscopy (Lembo et al. 1998).

3.4 Dental studies on the effect of distraction on procedural pain

It has been shown that distraction with a ping-pong video game lowered the discomfort rating among patients who had a tooth prepared for a filling (Corah et al. 1979). Further, in a study on the perceived pain and discomfort during preparation for a class II restoration, the use of video games and video-comedy programs has been shown to reduce the perceived pain and discomfort (Seyrek et al. 1984). *Anderson et al*. (1991) reported that patients listening to music experienced a stronger feeling of control of the pain than patients in a control group during dental treatment with music used as distraction and without any prior positive information, and without giving the patient the possibility to control the volume. In a clinical trial, it was demonstrated that showing video had no effect on pain during periodontal scaling, whereas a "virtual reality game" nearly eliminated pain with the same pain stimuli (Hoffman et al. 2001b). It was speculated that "virtual reality" is a distraction method,

which demand a higher degree of attention by the patient since it gives the possibility for the viewer to interact with the computer game. On the other hand, in a clinical trial a reduced unpleasantness/pain and anxiety was found during dental scaling when the volunteers were watching a movie through a pair of conventional audio/visual eyeglasses compared to a control situation (Frere et al. 2001).

Anxiety is common among dental patients and could be assumed to increase the perceived pain. There is evidence, however, that this may not be true as *Arntz et al.* (1991) have shown that anxiety is not correlated to the pain response. Finally, in a study using "virtual reality", there was no effect on children's anxiety and behaviour during restorative dental treatment (Sullivan et al. 2000).

There is a clear pattern in the results from these studies (Table 3) that support the hypothesis that distraction and attention can exert significant influences on the perceived intensity and unpleasantness of a painful stimulus. The results from the studies I-IV are described in chapter 8.

Study	Type of distraction	Stimuli: 1) Experimental 2) Procedural 3) Dental, procedural	Reported effect (perceived pain)	Reported effect (affective component of pain)
Morosko & Simmons 1966	sound/music	1) electrical stimuli of the dental pulp	pain threshold ?	pain tolerance?
Corah et al. 1979	video game (ping-pong)	3) dental preparation, class II	-	discomfort ?
Seyrek et al. 1984	audio (story) video TV game	3) dental restoration	pain intensity ? - -	discomfort ? discomfort ? discomfort ?
Anderson et al. 1991	music	3) dental restoration	pain intensity ?	discomfort ?
Menegazzi et al. 1991	music	2) laceration repair	pain intensity ?	-
Miller et al. 1992	video	2) burn wound care	pain intensity ?	pain quality ?
Weaver & Zillmann 1994	video	1) cold pressor test	-	discomfort ?
Vessey et al. 1994	kaleidoscope	2) venipuncture	pain intensity ?	-
Weisenberg et al. 1995a	humorous/ repulsive film	1) cold pressor test	-	pain tolerance ?
Lembo et al. 1998	video glasses	2) flexible sigmoidoscopy	-	discomfort ?
Bentsen et al. 1999, I	video glasses	1) cold pressor test	pain intensity ?	unpleasantness ?
Bentsen et al. 2000, II	video glasses	1) cold pressor test	pain intensity ?	unpleasantness ?
Carlson et al. 2000	kaleidoscope	2) venipuncture	pain intensity?	distress ?
Bentsen et al. 2001, III	video glasses	3) dental preparation, class I	pain intensity ?	unpleasantness ?
Hoffman et al. 2001a	virtual reality	2) burn wound care	pain intensity ?	unpleasantness ?
Frere et al. 2001	video glasses	3) dental scaling	-	discomfort ?
Sparks 2001	touch and bubbleblowing	2) immunisation	pain intensity ?	-
Bentsen et al. 2002, IV	video glasses	3) dental scaling	pain intensity ?	unpleasantness ?
Landolt et al. 2002	cartoon movies	2) burn wound care	-	distress ?

Table 3. Effect of distraction on perceived pain and unpleasantness. Studies are included if the stimuli are experimentally applied to the teeth or skin/mucosa and the distraction mode is visual and/or audible.

? = unaltered, ?= lowered, ?= increased, - = not examined.

4 Nitrous oxide

Nitrous oxide is a well-known and widely used (Petersen 1994) sedative in the dental clinic. It does not belong to the means of distraction, but is a pharmacological intervention. Sedation with nitrous oxide is an old remedy for reducing pain, first described in 1776 and a 100 years later introduced in the form we know today (Peretz et al. 1998). Nitrous oxide sedation is considered safe to the patient. In a recent study, no severe side effect was seen during 1025 administrations of a 50% nitrous oxide/oxygen mixture (Annequin et al. 2000). Nitrous oxide administered to a patient in concentrations between 15% and 45% has been shown to produce a statistically significant and subjectively meaningful decrease in pain sensation and to increase pain tolerance thresholds during painful, electric pulp stimulation (Dworkin et al. 1983). No effect of nitrous oxide on tactile threshold during stimulation with Von Frey hair on the chin was seen in a nitrous oxide group compared to a control group whereas the threshold for pressure pain was significantly increased compared with controls (Siiba et al. 1999). The central neural mechanisms that modulate the pain perception during sedation with nitrous oxide are not fully understood. However, in studies on rats it has been shown that a_2 –adrenoceptor antagonists injected intrathecally blocked the effect of nitrous oxide (Guo et al. 1996). Also opiate receptors in the periaqueductal grey are involved in mediating the hypoalgesics of nitrous oxide, and the effect can be blocked by direct injection of an antagonist (Naloxone). These findings indicate an activation of opiate receptors centrally and an influence on descending noradrenergic pathways (Fang et al. 1997).

5 Experimental pain models

To study a transient, evoked pain a multitude of experimental and clinical pain models have been developed (Gracely 1999), and in the following paragraphs the ones most relevant for this review will be described. The first question that occurs is of ethical nature - can it be justified to apply experimental painful stimuli to an animal or another human being? Moreover, which considerations should be taken into account if this experimental approach to pain is to be met with approval. It is obvious that no or minimal tissue damage should occur, and that the volunteer/patient must have the possibility to withdraw whenever in the process it is desired. This also requires the use of a painful stimulus with a rapid offset or that local anal-

gesics is ready. Furthermore, a stimulus with the smallest necessary magnitude of evoked pain and unpleasantness should be used.

Such ethical concerns on experimental pain models are offered by *Gracely* (1999), who considers it favourable that the ideal pain stimulus exhibits the following qualities: 1) results in minimal neurohistological variations between individuals, 2) provides minimal tissue damage, 3) shows direct relationship between stimulus and pain intensity, 4) provides information about discrimination between stimuli, 5) is repeatable without temporal interaction, 6) is easy to apply, 7) produces a distinct pain sensation, 8) allows a quantifiable determination of pain quality, 9) is sensitive to pain and changes in pain, 10) shows analgesic dose relation, 11) is applicable to humans and animals, 12) has a rapid onset, 13) has a rapid termination, 14) possesses natural quality, 15) has similar sensitivities in different individuals, 16) activates a limited range of afferents, 17) and is sensitive to manipulation. No single experimental pain stimulus possesses all these qualities, and the type of stimulus must therefore be chosen according to the aim of the experiment.

Experimental pain models can be classified in three main groups according to the stimulus modality, namely chemical, mechanical and thermal. Further, an additional, electrical, is often mentioned.

5.1 Electrical stimulation

Electrical stimulation has been used for many years to evoke a painful sensation in human subjects and animals in experimental studies (Bromm & Treede 1980, Carlin et al. 1962, Chudler et al. 1986, Drewes et al. 2002). A well-known method to evoke experimental pain is the electrical stimulation of the dental pulp (Carlin et al. 1962, Morosko & Simmons 1966, Dworkin & Chen 1982, Leavitt et al. 2002). This type of stimulation is easy to apply, has a fast onset and offset and shows a relation between the perceived pain and the magnitude of the electric stimulus (Fernandez de Lima et al. 1982). Electrical stimulation of the dental pulp is thought mainly to activate Ad- fibres at the periphery, and centrally the SII area (Chudler et al. 1986). Electrical stimulation of the dental pulp is modified by temporal summation in single Ad- and C-fibre experiments (Virtanen et al. 1987), and spatial summation was found in human subjects by stimulating two adjacent teeth independently and together (Brown et al. 1985). Electrical stimulation can also be adapted to the skin, e.g. with potassium ionophorese. In such a set-up, a potassium chloride gel is applied to the skin of the subject and K^+- ions pass through the skin when a current passes through the gel, thus giving

rise to a painful sensation. This method produces a linear relationship between the perceived pain and the magnitude of the current used (Johnson et al. 1998).

5.2 Chemical stimulation

Chemical stimulation is widely used and can produce very severe pain, e.g. with injection of capsaicin (Simone et al. 1989, Graven-Nielsen & Mense 2001, Arima et al. 2001, Witting et al. 2001). The injection of capsaicin, the active ingredient in red hot pepper responsible for the burning sensation, evokes a profound burning pain sensation with a dose dependent magnitude of the perceived pain (Simone et al. 1989).

Injections with hypertonic saline and potassium chloride solution have been used in an experimental pain model (Jensen & Norup 1992). Injection with hypertonic saline evokes a significant, deep localised pain (Svensson et al. 1998) and exhibits both temporal and spatial summation (Graven-Nielsen et al. 1997).

5.3 Mechanical stimulation

Mechanical stimulation (impact, punctate, brush and pressure) can be performed by e.g. a pressure algometer, brush or Von Frey filaments. A hand-held algometer has been used for measuring pain thresholds obtained from pressure at the temporal region (Jensen et al. 1986). The algometer gives a well-defined pressure at a constant rate and shows a small inter-individual variation (Jensen et al. 1986) and high reliability between and within examiners (Reeves et al. 1986). A widely used instrument for punctate stimulation, the Von Frey hair consists of a single, nylon fibre or monofilament. The end of this filament is pressed against the subject’s skin and thereby evokes a pressure sensation or pressure pain. When a certain point load is reached, the filament bends and the pressure stabilises and does not increase further. The method has good reliability and reproducibility between and within examiners (Bell-Krotoski & Tomancik 1987) and is a cheap, easy and reliable method if used in a standardised way (Voerman et al. 1999). The method has been used in both experimental studies (Costas et al. 1994, Schmidt et al. 1997, Siiba et al. 1999) and clinical pain studies (McGill et al. 1999).

5.4 Thermal stimulation

Thermal stimulation is either evoked by a heat pain or cold pain stimulus. Heat pain can be evoked by e.g. argon laser stimulation; this method is unique in the way that it is possible to activate nociceptive afferents without at the same time activating the mechano-sensitive af-

ferents (Arendt-Nielsen & Bjerring 1988). Argon laser has been used to evoke experimental pain in the oral mucosa (Svensson et al. 1991, 1992) and to study clinical persistent pain, the burning mouth syndrome (Svensson 1993). Other more special methods and devices for heat stimulation of the oesophagus have recently been developed (Drewes et al. 2002).
As a means to evoke cold pain, the cold pressor test is often used. With this method a limb (normally a hand) is submerged into ice-cold water (1-2°C) contained in a tank filled with water and crushed ice (Walsh et al. 1989). This method is considered safe, it shows no spatial summation and onset is rather slow. It takes 60 to 90 seconds before the perceived pain reaches its maximum followed by adaptation (Walsh et al. 1989). Offset is, on the other hand, fast. In the tank, the water is separated from the ice to avoid freezing injuries to the skin (Zachny et al. 1995), and the temperature is held constant by mechanical circulation of the water (Weisenberg et al. 1998). The model is used both in experimental pain studies (Weisenberg et al. 1995b, Zillmann et al. 1996) and in clinical trials (Zachny et al. 1995, Jones et al. 1988).

In the studies I-II focus was set on the following qualities of the experimental pain model chosen: 1) evoke light to moderate pain, 2) provide no tissue damage, 3) be easy to apply, 4) have fast onset/offset, 5) have natural quality and 6) allow for a quantifiable determination of pain quality.
On this background and because of the natural qualities and easy application, the cold pressor test was chosen as the main painful stimulus in studies I and II.

6 Dental, procedural pain models

Experimental, clinical pain is here defined as a painful sensation evoked by a specific dental treatment and some examples are given in the following (Table 4).
1) Removal of the mandibular third molar has been widely used as an experimental pain model in pharmacological studies on the effect of analgesic drugs. This surgical intervention evokes a strong painful sensation in most patients. The pain peaks just after the local analgesics have subsided (Nørholt 1998).
2) Needle penetration of the oral mucosa causes an initial moderate pain sensation (Bergius et al. 2002) and have been used as a means to provoke a painful sensation in studies on the effect of various topical analgesic ointments (Primosch & Rolland-Asensi 2001).

3) Orthodontic elastic separators are commonly used and can evoke dental pain. Prior to orthodontic treatment, separators are inserted between the molars to create space for the fixation of orthodontic appliances. This provokes a moderate pain that emerges after some hours and increases with time the first day and thereafter decreases to almost disappear after a week (Bergius et al. 2002).

4) It is well known to most dental patients that drilling in the tooth surface evokes a painful sensation, and drilling has been used to provoke pain (Anusavice & Kincheloe 1987, Harvey & Elliot 1995).

5) Scaling of dental pockets (removal of dental calculus) normally results in a mild pain from the gingiva and teeth and has been used to provoke experimental pain in studies on efficacy of topical analgesics (Svensson 1994).

6) As described earlier electrical pulp stimulation is a well-known method to evoke pain. This method is used as a diagnostic tool in dental practice to estimate the sensibility of the dental pulp and should be mentioned here as well (not included in Table 4).

Method	Mean peak, 100 mm VAS pain rating	Peak pain time	Studies
3rd molar removal	75	4-5 hours after surgery	Nørholt 1998
Needle penetration	44	initially	Bergius et al. 2002
Orthodontic separation	35	24 hours after insertion	Leavitt et al. 2002
Drilling	36	immediate	Bergius et al. 2002
Scaling	18	immediate	Svensson et al. 1994

Table 4. Properties of dental, procedural pain models (the VAS will be explained in the following).

Due to the simplicity of the treatments, their widespread use and primarily due to the fast onset/offset and the lack of sound tissue damage, patients in need of dental treatments, involving scaling (for study III) and drilling for (study IV) were chosen since such treatments would evoke mild to moderate pain.

7 Assessment of pain

7.1 Psychophysics

In the measurement of pain sensations, two qualitative descriptors of perceived pain are often operated, namely threshold and tolerance. Pain threshold is the lowest level at which the individual perceives the stimulation as painful, and tolerance is the highest level tolerated of a perceived painful stimulus (Weisenberg 1977).

Psychophysics is the part of neuroscience that studies and describes the relation between a stimulus and the evoked sensation. The first milestone in the work was set in the nineteenth century (review: Gescheider 1997) with the introduction of the equation: ? I/I = k, called Weber's law. Weber's law says that the change in stimulus intensity that can just be discriminated, ? I, is a constant fraction k of the starting intensity of the stimulus I.

In 1860, *Fechner* published the *Elements of Psychophysics* (review: Gescheider 1997) and introduced the just noticeable difference (JND) as a unit of sensation. He realised that it takes a greater change in stimulus to make a perceivable change in sensation if the stimulus intensity is already high. In 1957, *Stevens* (review: Gescheider 1997) described that the sensation of a JND was not the same at all stimulus intensities. Through series of experiments, he developed the equation: $S = k I^b$. Here, S is the perceived sensation, I the intensity of the stimulus, k an arbitrary constant determining the scale unit and ^{b} is a power constant, which depends on the stimulus condition and modality.

7.2 Scaling of a sensation

The two main groups of methods for relating the intensity of a painful stimulus to an evoked sensation are the "stimulus-dependent" and the "response-dependent" methods of scaling a sensation. The stimulus-dependent method is typically used to determine a "fixed" threshold (e.g. pain and tolerance). Here, the dependent variable is the stimulus altered either in time or intensity. An example of a stimulus-dependent method is the method of limits. This model uses rising intensities of stimuli from below an expected threshold, and decreasing intensities starting above this expected threshold, to approach the actual threshold (Gracely 1999). In the response-dependent method, the depending variable is the perceived sensation or response and the stimulus is fixed. This method is often used in evaluation of different interventions, e.g. efficacy of analgesic drugs (Jones et al. 1988, Zachny et al. 1995). Response-dependent methods are used in studies I-IV.

After having described the relationship between the intensity of a stimulus and the perceived sensation, the next question to arise is how to measure a change in perception.

7.3 Pain scales

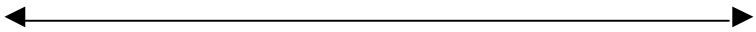
Many different types of pain scaling techniques have been developed, and they are normally divided into three groups, namely 1) nominal-, 2) ordinal-, 3) ratio/interval-scales (review: Gescheider 1997).

1) The nominal scale is a scale where the dependent variable only differs in quality, not in absolute order or relative size, e.g. pain/no pain as a way to determine threshold in response-dependent trials. This scale is very easy to use and easy to understand, but easily influenced by instruction, placebo effect and response bias (Price 1988).

2) The ordinal scale provides a ranking of scores, e.g. no/mild/moderate/severe pain. The ordinal scale is normally easy to understand for the subject/patient and easy to use for the examiner. The McGill Pain Questionnaire (MPQ) incorporates among other features an ordinal scale, i.e. the present pain intensity (Melzack 1975). Furthermore, the patients can choose descriptors from twenty word groups to specify their subjective pain experience. Descriptors are words or statements that describe a painful experience like jumping, flashing, shooting, nagging, nauseating, agonising, dreadful or torturing and are primarily divided into three subclasses that reflect the dimensions of the pain they describe (for dimensions of pain, see later in this section), namely sensory, affective and evaluative. Together, all the values can be added to give a value between 1 and 77, and thereby this part of the MPQ also possesses interval-scale qualities (see later). Due to the ranking of the descriptors in the MPQ, the quantitative information can be evaluated statistically by non-parametric tests (Melzack 1975). Another pain measure derived from the questionnaire is based on the number of descriptors chosen. The MPQ has been translated, among many other languages, into Danish (Helweg-Larsen et al. 1993). The MPQ has been applied to clinical dental pain as well (Grushka & Sessle 1984), and the MPQ was in that study sufficient to distinguish between two pain experiences caused by a reversibly inflamed tooth pulp and an irreversibly inflamed, necrotic tooth pulp.

The MPQ was incorporated in study IV to further explore the change in perceived pain during video use. Another reason for this was to minimise the risk of not getting appropriate answers from the older fraction of the patients as a previous study has shown that a significantly greater part of the patients, who did not complete the VAS (see later), belonged to this subgroup (Kremer et al. 1981).

3) Ratio-interval scales can measure the order, number, difference and ratio between scores. An example of this type of scale is the visual analogue scale (VAS). The VAS is widely used in pain studies (Chéry-Croze 1983, Chapman et al. 1985, Jones et al. 1988, Svensson et al. 1994, Zachny et al. 1995, Weisenberg et al. 1995a,b). The VAS consists of a line or scale, in each end labelled with statements appropriate for describing the extreme values of the sensation studied. For measures of pain intensity, the VAS is often labelled “no pain” and “most intense pain imaginable” in either end (Fig. 3). The subjects rate the perceived pain by placing a marker or simply tick the line in relation to the two extremes.



No pain Most intense pain imaginable

Fig. 3. Example of a 100-mm VAS for measuring pain intensity.

The length of the scale is often 100 mm as it has been shown that a length of 100 to 150 mm has the greatest sensitivity and is least vulnerable to biases and distortions (Stevens & Marks 1980, Seymour et al. 1985). The choice of end-phrase has been discussed and studied. In dental patients suffering from acute pulpitis or pericoronitis (Seymour et al. 1985), it was shown that too extreme end-phrases make too many patients score near 0; on the other hand, if the end-phrases are not extreme enough, the scores tend to cluster near 100. In this study, the best distribution of scores was found with the end-phrase “worst pain imaginable” (Seymour et al. 1985).

VAS scores, or at least calculated differences between VAS during treatment and baseline VAS, often show a Gaussian distribution allowing for the use of parametric statistical analysis. VAS has been shown be useful for separate measures of pain intensity and unpleasantness (Duncan et al. 1989), and VAS has been applicable in studies on dental pain (Seymour et al. 1985). Based on the above-mentioned properties together with its usefulness, the 100 mm VAS was used throughout the four studies (I-IV).

7.4 Dimensions of pain

Pain is not a single-dimensional experience, and there is evidence that the experience can be divided into at least two dimensions, the sensory-intensive and the affective component (Melzack & Casey 1968, Gracely et al. 1979, Rainville et al. 1997, Hofbauer et al. 2001). The sensory-intensive dimension of pain is a measure of how intensely the pain is perceived (perceived pain intensity), and the affective component describes how much the pain bothers

the subject (unpleasantness). The two dimensions of pain can successfully be quantified by the use of VAS (Duncan et al. 1989).

The affective component of the pain experience has recently been proposed divided into primary unpleasantness, which associated directly to the stimulus and a secondary unpleasantness linked with higher levels of activity and emotion (Fields 1999).

It has been demonstrated that the same painful stimulus is perceived differently in an experimental set-up compared with a clinical situation (Dworkin & Chen 1982). In that study, students were given an electrical, painful dental pulp stimulus from a pulp tester in a laboratory and in a true dental clinical situation. The group that received the painful stimulus in the dental clinic had significant lower thresholds and tolerance ratings than the laboratory group. Therefore, the present studies (I-IV) have assessed both pain intensity and unpleasantness and studied the effect of video glasses on the perceived pain and unpleasantness in both laboratory conditions (I and II) and in dental, clinical settings (III and IV).

8 Own studies I-IV

8.1 Aims

The overall aim of the present studies (I-IV) was to test the hypothesis that audio-visual signals through video glasses distract the perception of pain and unpleasantness in experimental and clinical settings. The studies represented by papers I-IV had the detailed aims listed below.

I. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during a cold pressor test.

II. To evaluate whether it is possible to manipulate the distraction effect induced by video glasses on the perceived pain and unpleasantness by giving the subjects different information about the expected effect and secondly, to determine the reproducibility of the effect in cold pressor tests.

III. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during a tooth preparation procedure.

IV. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during dental scaling and secondly, to compare a possible effect with the effect of nitrous oxide (N_2O) analgesics.

8.2 Designs and results

Video glasses (I-Glasses™, Virtual i-O™, Seattle, USA) is an audio-visual equipment, which has primarily been developed for virtual reality purposes (Front page picture). It has the capacity to show three-dimensional (3D) as well as traditional two-dimensional (2D) movies on two small monitors mounted in a headset with the sound transmitted through incorporated headphones. This gives a unique chance to distract a person with video and music simultaneously. In study I, the effect of 3D video, 2D video and no video was compared in two groups of healthy volunteers (13 males and 11 females) in a randomised, controlled trial. Posters on the university campus recruited the subjects, who prior to the experiment were randomly allocated to start with 3D, 2D or no video. The number of subjects needed in this paired cross-over design was calculated:

Power test:

$$N = \frac{s^2}{(\mu_0 - \mu_A)^2} ??(a,b) = \frac{250}{(0 - 13)^2} ?7.85 = 12$$

N= the number of volunteers needed in each group

s^2 = the expected variance in the material

μ_0 = the expected value under the null hypothesis (no change in VAS scores)

μ_A = the expected value under the alternative hypothesis (a change of VAS scores around 10-15 mm)

a,b= sum of type 1 and 2 errors (type 1 is the risk of getting a significant difference where there is no difference: false-positive result; type 2 is the probability of not detecting a significant difference: false-negative result).

The volunteer was placed in a comfortable chair beside the cold water tank with a water temperature of 1.5 ± 0.5°C (Front page picture). In the centre of the tank, a perforated cylinder was placed that separated the ice from the water inside the cylinder which allowed the water to circulate freely, but avoided direct skin contact with the ice. The 2D video shown was a sequence from the Beatles-video ”Help” and the 3D film featured youth roller-skating. A video recorder (NV-HD 660 Panasonic) was connected to the video glasses. The video glasses were mounted and tested for optimal perception of picture and sound. The volunteer immersed the left hand completely into the water tank, and after 3 minutes (or sooner if the sensation became unbearable) the volunteer withdrew the hand and was free to dry it with a

towel. After an inter-test period of more than 15 minutes during which the volunteer was allowed to exercise the hand, and after the volunteer indicated that the hand had its normal temperature, the next trial was performed (Fig. 4).

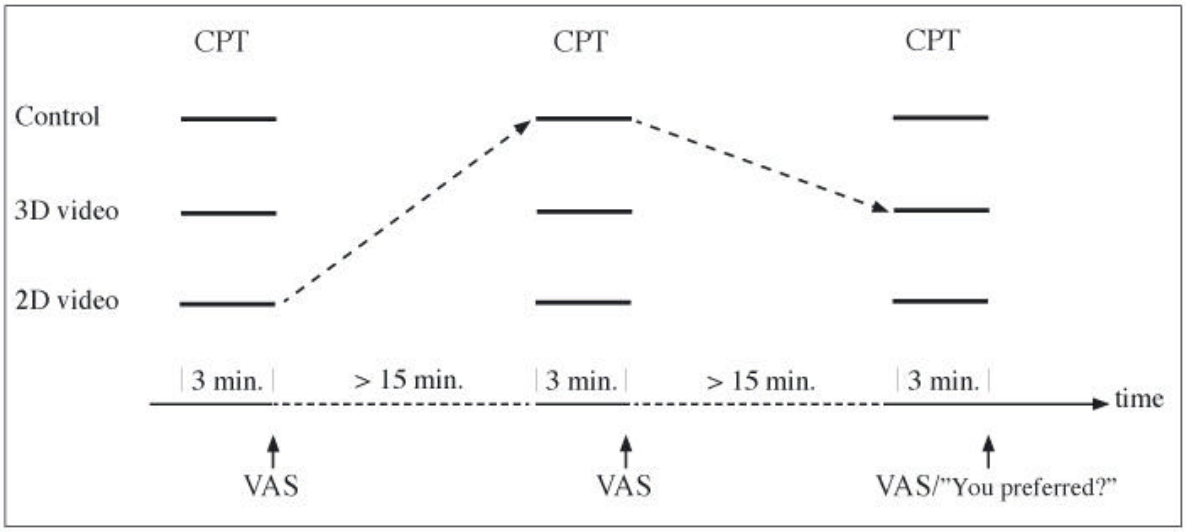


Fig. 4. Schematic view of the design in study I (the arrows show one of the 6 possible paths into which the volunteers were randomised).CPT=cold pressor test; VAS= visual analogue scale.

Immediately after each cold pressor test had been completed (Fig. 4), the volunteers scored their perceived pain intensity and unpleasantness on 100-mm VAS labelled with the statements “not at all painful” and “extremely painful” and, “not at all unpleasant” and “extremely unpleasant“ in either end. After the third trial, the volunteers were finally asked which of the three options: 3D video, 2D video, or no video they would prefer if they had to participate in another cold pressor test. Between the groups (males and females) there was a significant difference ($P<0.01$) in the rating of unpleasantness in the 3D video situation, while there were no significant differences between the genders in the other situations (2D, control). 3D video provided a significant reduction in both pain and unpleasantness ($P<0.01$) compared with the control situation in the male group. However, in the female group there was a significant reduction in unpleasantness with 2D video compared with the control ($P<0.05$). Seventy-five percent of the participants wanted to use video glasses if they were to repeat the cold pressor test.

In study I, it was documented that there was an effect of video glasses on pain, when using 3D video. We did not study if these findings could be due to a placebo effect or could be an outstanding result due to fascination of this new technique. In study II, the aim was to study

the placebo effect, and further to investigate if the effect obtained could be reproduced in the same experimental group after a period of time; in this case a time span of four weeks (Fig. 5). It is impossible to accomplish a true double blind study with video glasses as it is obvious to the volunteer whether he/she is wearing the glasses or not, and if the video is on or not. But a shortcut to the understanding of a possible placebo effect is to study the effect of video on volunteers manipulated to a pre-conceived opinion of the effect, positive or negative. Forty-five students enrolled in the study selected by the same means as in study I. The size of the groups was calculated in the same way as in study I, i.e. 39 students participated in the study since three groups were needed (15 males and 24 females). Thirty-seven students completed the study since two subjects did not show up for the second trial because they forgot the appointment. The participants were randomised into three groups, balanced with respect to age and gender, who received different information about the expected effect of 3D video on pain and unpleasantness. One group received positive information concerning “a very strong pain ameliorating effect”, the second group received neutral information and the third group received negative information about “an adverse effect coming from being blindfolded, etc”. Once assigned to a group, there was no cross-over between the groups. The students were strongly advised not to discuss their experiences during the test period.
A cold pressor test similar to the set up used in study I was used to induce experimental pain, and the volunteers rated the intensity of pain and unpleasantness on 100-mm VAS. The same set up of video glasses were used as in study I, and the 3D video sequence showing roller skating youth was the same in all cases. Each volunteer was exposed to the cold pressor test in two randomised trials (video and control) after the manipulated information was given, and the two trials were repeated in a second session after 4 weeks (Fig. 5).

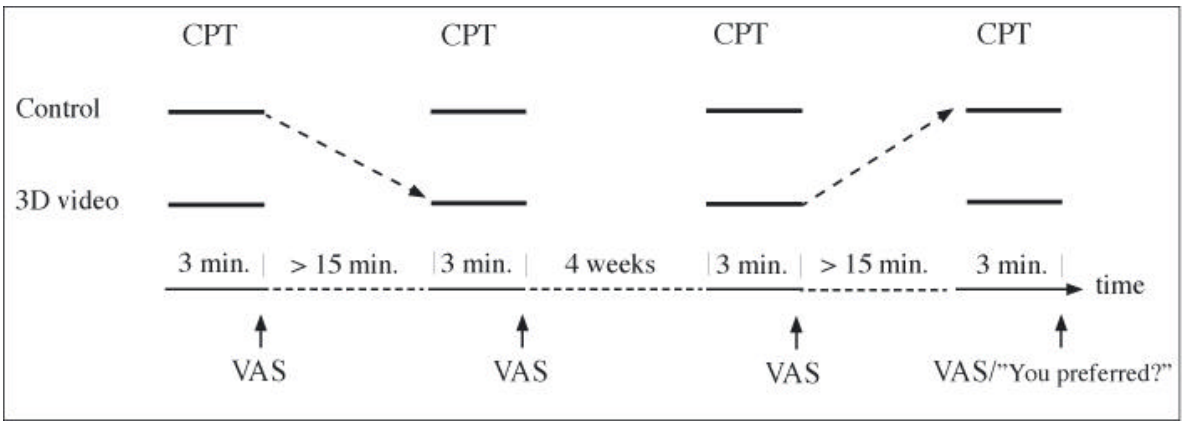


Fig. 5. Schematic view of the design in study II (the arrows show one of the 4 possible paths into which the volunteers were randomised); this design was identical for the three information groups. CPT=cold pressor test; VAS= visual analogue scale.

There was no significant difference in the effect of video glasses on perceived pain (P=0.74) or on the perceived unpleasantness (P=0.84) between the three information groups. The results of the pooled data from the three groups showed a significant effect of 3D video on perceived pain (P=0.03), but no effect on unpleasantness (P=0.18). After 4 weeks the study was repeated, and there were no significant changes in the obtained effect of video glasses. The median VAS scores were reduced in both the video and the control situations compared with the first session. Seventy-five percent of the participants wanted to use video glasses if they were to repeat the cold pressor test.

Study III was designed to evaluate whether distraction induced by video glasses also had an effect on the perceived intensity of pain and unpleasantness during dental treatment. Pain and unpleasantness was evoked by the preparation (drilling) for minor dental fillings (Class I). Poster information among the students at The Royal Dental College, Århus recruited twenty-three patients (17 female and 6 male, age range 20-49). The number of patients needed was calculated as previously, here with a reduction in VAS score of 10 set as the lowest clinically meaningful change.

$$N = \frac{s^2}{(\mu_0 - \mu_A)^2} ??(a,b) = \frac{250}{(0 - 10)^2} ?7.85 = 20$$

All patients had a need for an occlusal dental restoration in two homologous teeth. In this split-mouth design the patient received dental treatment wearing 3D video glasses and without video glasses (control situation) in a randomised order (Fig. 6). The 3D video was the same as used previously. After mounting and adjusting the video glasses, the tooth cavities were prepared in accordance with conventional techniques with a not previously used high-speed diamond burr. Immediately after finishing the tooth preparation, the patient rated the intensity of pain and unpleasantness on 100-mm VAS; hereafter the opposite tooth was prepared, and again the volunteer rated the intensity of pain and unpleasantness. The cavities were checked and filled using a routine composite technique. Eventually, the patient indicated whether she/he would prefer video glasses or not if she/he were to have another filling, and what the expectations of the effect had been.

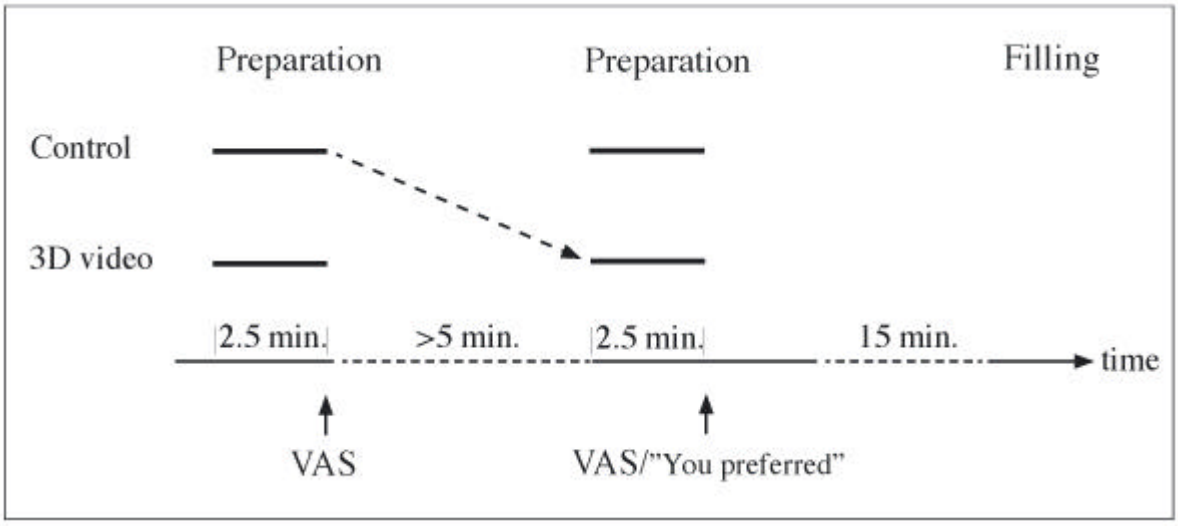


Fig. 6. Schematic views of the design in study III (the arrows show one of the possible paths through the study). The minutes indicated are average values.VAS= visual analogue scale.

There was no statistically significant effect on the perceived pain (P=0.90) or unpleasantness (P=0.39), but the majority (74%) of the patients would still prefer to wear video glasses if they were to have another filling, and 73% had expected a positive effect of the video glasses.

A reason for the lack of effect found in study III could originate in the fact that a pain stimulus of moderate to strong intensity was administered (tooth preparation). Therefore, study IV was carried out with the use of a pain stimulus of expected lower intensity (removal of calculus with a sonic scaler). A non-dental pain stimulus on the upper lip (Von Frey hair) was added to the study design. The commonly used nitrous oxide (N_2O) analgesics were included in the study to achieve a comparison of the effect on pain of video glasses with a well-known sedative as well as with the control situation.

Twenty-six patients with superficial chronic periodontitis recruited among the patients at the Dental Auxiliary Division, Royal Dental College, Århus enrolled in this randomised, controlled clinical study. The numbers needed were calculated as in study III. The effect of video glasses was compared with N_2O in one session and the effect of video glasses versus the control situation in another. Dental scaling was provided in two clinical sessions one week apart, which could have introduced a source of error if there were differences in the patients' level of anxiety between the two sessions (Fig. 7). The Corah anxiety scale was therefore used to determine any such differences in levels of dental anxiety in the patient between the two sessions.

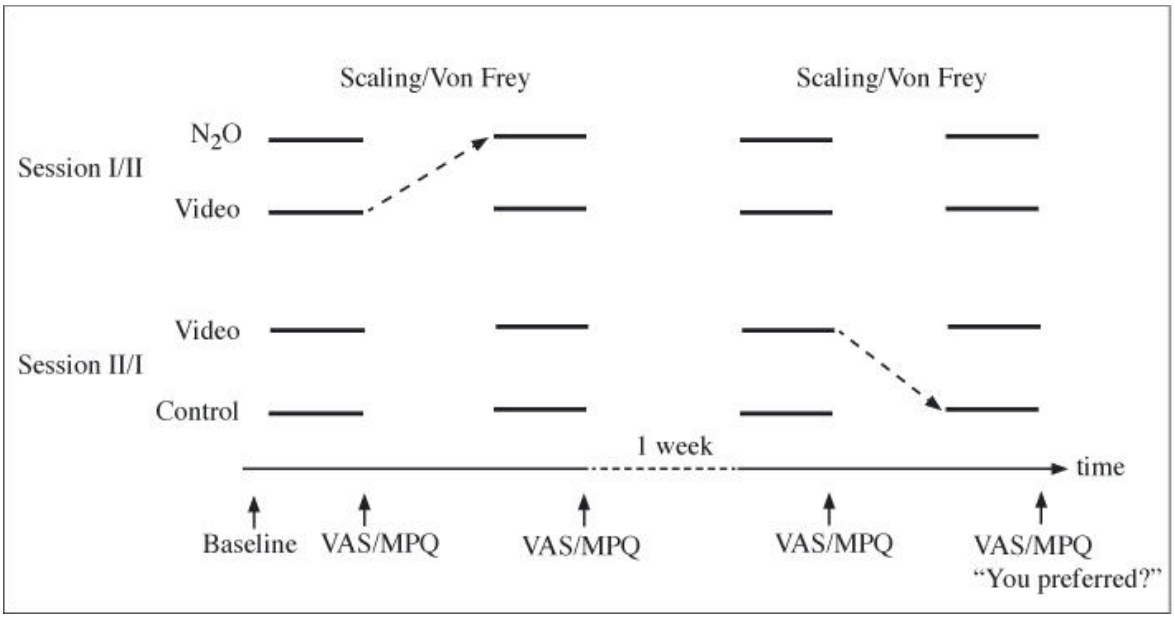


Fig. 7. Schematic view of the design in study IV (the arrows indicate one of 8 possible paths through the study). VAS= visual analogue scale.

The patients rated the intensity of pain and unpleasantness evoked by dental scaling and Von Frey filament stimulation on 100-mm VAS.

For dental scaling, there was no effect of video glasses on the perceived pain (P=0.85) or unpleasantness (P=0.73), nor of N_2O (P=0.69 and P=0.51, respectively) compared with the control situation. Similarly, no significant difference was found between VAS scores in the video glasses and N_2O situations (P=0.48, P=0.58). A significant effect of video glasses and N_2O (P<0.008) was found on the perceived pain intensity produced by Von Frey filament stimulation compared with the control situation, but no significant difference was seen between the video glasses and N_2O situations (P=0.07).

A MPQ score was obtained to investigate if this method of rating the pain could add information. The tendency was a reduction in pain scores, although a significant difference was only detected between the control and the N_2O situations (P=0.03) (Table 5).

Session	Video	N_2O	No distraction
Total mean (SD) MPQ (1-77) score during treatment	3.9 (4.5)	3.4 (2.9) #	6.3 (6.6)

Table 5. MPQ scores in the three situations, #:P=0.03.

Post-treatment interviews with the patients revealed that 81% of the patients in the video and 65% in the N_2O situation stated that this method had some beneficial effect on their overall experience of the treatment situation.

8.3 Discussion

Study designs

In the literature, various distraction techniques have been shown to raise the pain threshold (Weaver & Zillmann 1994, Zillmann et al. 1996, Vessey et al. 1994, Anderson et al. 1991, Morosko & Simmons 1966, Gardner et al. 1960, Skjerve & Nedreås 1981). That distraction of a painful stimulus can be demonstrated was shown in an experimental setting where the investigators were selected on the basis of their attractiveness (Levine & Simone 1991). Male volunteers rated significantly lower pain scores in front of a female investigator than in front of a male investigator during a cold pressor test. This could not be shown for the combination of female volunteers in front of male investigators. This should not have any implications on the present series of studies since the volunteers/patients always served as their own controls, and there has been no shift of investigators during a study.

Pain tolerance to the cold pressor test has been shown to increase after watching a humorous movie for 30 minutes before the pain stimulus started indicating a more complex interaction than just simple distraction (Weisenberg et al. 1998). When music was used as distraction, it has been indicated that it was essential for the hypoalgesic effect that firstly, the volunteer had a strong belief in the positive effect, and secondly, that she/he was allowed to control the volume thereby creating a feeling of controlling the pain (Melzack et al. 1963). The former of these conclusions was contradicted in study II as it was not possible to manipulate the volunteers' perception of the effect of the video glasses. The second statement was contradicted by a previous study (Anderson et al. 1991), which reported that patients listening to music during dental treatment experienced a stronger feeling of pain control than patients in the control group. This was found without any prior positive information and without giving the patient the possibility to control the volume. Based on these latter results the volunteers/patients in studies I-IV were only allowed to adjust the volume initially and were not informed about the possible effects of video glasses on the perceived pain and unpleasantness (except in study II where this was the purpose).

In a study on the perceived pain and discomfort during preparation for a class II restoration, the use of video games and video-comedy programs has been shown to reduce the perceived pain and discomfort (Seyrek et al. 1984). In another study (Frere et al. 2001) reduced discomfort and anxiety during dental scaling was demonstrated when the volunteers were watching a movie through a pair of conventional audio/visual eyeglasses compared to a control situation. On the other hand, in a clinical trial it was demonstrated that showing video had no effect on pain during periodontal scaling, whereas a "virtual reality game" nearly

eliminated pain with the same painful stimuli (Hoffman et al. 2001b). It was speculated that "virtual reality" is a distraction method, which demands a higher degree of attention by the patient since it gives the possibility for the viewer to interact with the computer game. This latter finding is in line with the findings in studies III and IV, where no effect of video glasses was observed on the perceived pain and unpleasantness during dental, procedural pain.

A recent study demonstrated that audio and video, transmitted through video glasses, reduced the intensity of symptoms during sigmoidoscopy while sound *per se* did not have a significant effect (Lembo et al. 1998). One interpretation of these results could be that the hypoalgesic effect is related to the intensity or diversity of the stimuli. Therefore, it was decided to include both conventional video and 3D video in study I. As the same video sequences were not available in both 2D and 3D, weight was put on their neutral contents in the selection of the two videos.

The content of the video has been shown to have a minor influence on the distraction effect, and no effect was found on the perceived cold pressor pain between humorous and documentary films (Nevo et al. 1993). In studies I-III, a standard 3D film showing youths rollerskating was used. In study IV, an exception was made as the patients were allowed to choose between more titles due to the large spread in age, and thereby presumed spread in interests. In studies I-II, the left hand was used for immersion in the cold pressor test every time since a previous study has shown that there is no difference in pain ratings using either the dominant or non-dominant hand during a cold pressor test (Chéry-Croze 1983).

The videos used in studies I-IV were of neutral content with the intention that it would not involve the patient emotionally. It might be expected that videos that involve the patient emotionally could have a positive effect on the perceived pain and unpleasantness. A previous cold pressor study (Weisenberg et al. 1995a) has shown a significant increase in pain tolerance in groups, who watched humorous and repulsive films compared to neutral films or no film. Despite the lack of effect when measured on VAS, three quarters of the patients in III and IV stated that if they were to have another filling or depuration, they would want to wear video glasses.

Anxiety is common amongst dental patients and could be assumed to increase the perceived pain. There is evidence however, that this may not be true since *Arntz et al.* (1991) have shown that anxiety is not correlated to the pain response. Finally, in a study using "virtual reality", there was no effect on children's anxiety and behaviour during restorative dental treatment (Sullivan et al. 2000). Since anxiety does not seem to influence the effect of dis-

traction on pain, the level of anxiety towards dental treatment was not taken into consideration when selecting patients and volunteers for the studies included in this thesis (I-III).
As the patients in study IV were seen in two separate sessions, differences in anxiety between these two appointments could be a confounding factor. No significant difference in the patients' dental anxiety levels was observed between the sessions, and the mean score was in line with the mean anxiety score of 7.2 on the Corah Dental Anxiety Scale recorded for 750 patients from dental school clinics, and far below the mean of 17 that was reported for a group of dental phobics (Corah et al. 1978). The influence of dental anxiety/phobia is therefore thought to be very low in this study.

Findings

The results in study I clearly demonstrated that the video glasses that transmitted 3D or 2D video and stereo sound reduced the perceived pain and/or unpleasantness evoked by the cold pressor stimulus. Another finding in study I was the gender difference in the effect of video glasses. 3D video produced a significant reduction in pain and unpleasantness in the male group compared to the control situation whereas there was no effect of 2D video. In the female group, there was a significant reduction only of unpleasantness of the 2D video compared to the control situation. The present results are in agreement with the findings in a study on relaxation and distraction during dental procedures, which suggested that relaxation in the form of instructions through earphones was more effective in women than in men, and that distraction in the form of a video game was more effective in men than in women (Corah et al. 1979). It must be emphasised that the male group consisted mainly of polytechnic students from Ålborg and the female group consisted of dental students from Århus, which could be confounding factors.
Other authors using the cold pressor test and other thermal test stimuli have observed gender differences (Weisenberg et al. 1995a, Weaver & Zillmannn 1994, Fillingim et al. 1998). Gender differences have also recently been demonstrated with glutamate used to evoke pain (Cairns et al. 2001, Svensson et al. in press). In a recent study gender effect of odors on pain perception was demonstrated, since pleasant odors significantly reduced pain perception in women but not in men (Marchand & Arsenault, 2002). Gender differences could also in fact be observed when combining results from the present studies. When the data from the experimental studies (I, II) were pooled, a significant difference between ratings of unpleasantness and pain intensity was found between genders in the video situation. A gender difference was also found in the pooled data from the dental, procedural pain studies (III, IV), al-

though only concerning unpleasantness. The gender difference regarding both pain intensity and unpleasantness re-emerged in an analysis of the pooled data from all the studies (I-IV) (Table 6). It may therefore be concluded that males rate the cold pressor pain as less painful and unpleasant than females when wearing video glasses.

Pain stimulus		Experimental N = 28 ? / 35 ?	Dental, procedural N = 21 ? / 32 ?	Experimental + dental, procedural N = 49 ? / 67 ?
Study		I + II	III + IV	I + II + III + IV
Control situation (baseline)	VAS pain ?	46.5 (24.3)	19.1 (14.1)	34.7 (24.6)
	VAS pain ?	53.7 (22.9)	27.2 (24.9)	41.0 (27.2)
	VAS unpleasantness ?	43.8 (21.1)	14.1 (12.1)	31.1 (23.0)
	VAS unpleasantness ?	51.7 (23.9)	23.2 (21.5)	38.1 (26.8)
3D video glass situation	VAS pain ?	36.1 (23.5) A	17.9 (17.3)	28.3 (22.8) D
	VAS pain ?	48.2 (20.5) A	27.1 (23.5)	38.1 (24.3) D
	VAS unpleasantness ?	34.8 (22.1) B	10.6 (13.3) C	24.4 (22.2) E
	VAS unpleasantness ?	50.2 (21.9) B	20.7 (22.2) C	36.1 (26.4) E
Effect (control – video)	VAS pain ?	10.3 (20.1)	1.2 (14.7)	6.4 (18.4)
	VAS pain ?	5.5 (18.1)	0.1 (18.5)	2.9 (18.4)
	VAS unpleasantness ?	9.0 (25.7)	3.5 (12.3)	6.7 (21.0)
	VAS unpleasantness ?	1.5 (16.2)	2.5 (18.0)	1.9 (17.0)

Table 6. Gender differences, mean and (standard deviation) in perceived pain and unpleasantness.When the data from the experimental studies were pooled, a significant difference was found between genders in the video situation. The difference also emerged in an analysis of the whole material (pooled data from I, II, III, IV). A: P=0.03, B: P=0.007, C: P=0.04, D: P=0.03, E: P=0.01.

Pain tolerance was not measured as no volunteers withdrew their hand before the fixed maximum period of three minutes. The fact that all volunteers in studies I and II did complete the 3 minutes cold pressor test is puzzling, since it has been shown that a given group of volunteers could be divided into a pain sensitive fraction and a pain tolerant fraction and that the pain sensitive fraction of the volunteers was only capable to endure the cold pressor

test for approx. 60 seconds (Chen et al. 1989). As the volunteers served as their own controls in the present design, this matter should be of little importance. An interesting finding was that everyone wanted to use video glasses, either 2D or 3D, if they were to repeat a cold pressor test, even if they had rated the lowest pain intensity in the situation without video glasses. Three-quarters of the volunteers, however, preferred the method in which they had rated the lowest pain intensity. It seems promising for the video glasses method that volunteers universally preferred it, and it seems that the individual is able to choose the method that gives the greatest relief of pain, and in this way optimise the effect.

The effect of 3D video on pain demonstrated in study I was maintained in study II with a larger group of volunteers including both sexes. It was not possible to manipulate the different groups to believe that the effect of the video glasses was either positive or negative. This tendency was not interpreted as a result of poor "manipulation", which maybe could have been clarified if it had been tested directly by asking the volunteers about their expectations after the manipulative lecture. Moreover, a significant effect may have been obtained by a huge increase in the sample size in each group. However, if many more individuals are needed to demonstrate a statistically significant effect, it is doubtful whether it would be clinically relevant. The most likely interpretation of the result is therefore that the effect of the video glasses on the perception of pain and unpleasantness is quite robust against pre-information and the “placebo” effect low. After four weeks, exactly the same trial was performed again, and at this time the volunteers scored generally lower on the VAS in both the video and control situation. This outcome may be speculated to be the result of the volunteers’ familiarity with the nature of the trial and the magnitude of the pain stimulus. Looking at the effect of video glasses, there were no changes over time; the difference between VAS scores for video and control was unaltered after 4 weeks.

In study III, a painful procedural stimulation was chosen, namely preparation (drilling) for a dental filling. The pain induced by preparation for a dental filling was of moderate intensity and is comparable to the magnitude of pain seen in previous cold pressor tests (I, II) (Table 7). The positive effect of 3D video on the perception of pain that was found in the previous studies I and II could however, not be repeated in this clinical study.

	study I, N=24	study II, N=39	study III, N=23	study IV, N=32
Pain	37.7 (21.8)	46.0 (22.7)	35.7 (23.6)	15.0 (14.7)
Unpleasantness	39.6 (21.9)	45.7 (23.8)	28.6 (20.9)	12.7 (13.6)

Table 7. Mean (SD) VAS values for pain intensity and unpleasantness in the control situations, studies I-IV.

In a recent study of the effect on anxiety during dental treatment of computer animated virtual reality shown through video head sets much similar to the video glasses used in studies I-IV, no effect was found (Sullivan et al. 2000). Others have been able to distract patients to some extent with video-comedy and -games in a dental filling situation (Seyrek et al. 1984) and in a clinical study on the discomfort during flexible sigmoidoscopy (Lembo et al. 1998). The latter showed a significant reduction in abdominal discomfort in the group that used video glasses during the examination. Genital examinations in children have been demonstrated to give rise to less anxiety when video glasses were provided during the examination (Berenson et al. 1998) and virtual reality equipment has recently been reported to significantly lower the pain intensity during burn wound care procedures (Hoffman et al. 2000a,b, 2001b).

We can only speculate on the reasons for the lack of distracting effect of the video glasses on the perceived pain and unpleasantness in the present clinical trials. In study III, a general aversion against video glasses as such can be ruled out since the vast majority of the patients (73%) did expect a positive effect of the video glasses and therefore were not negatively biased. The pain connected with the drilling in teeth is normally described by patients as sudden and sharp; it often occurs unpredictably and may as such be difficult to cope with. Another study has shown that pain predicted to be less painful than it actually was (under-predicted) was not perceived worse than the correctly predicted pain stimulus, but it disrupted the patients more (Arntz & Hopmans 1998). This could be an argument for postulating that the sudden and unpredicted pain, as dental pain often is, will compromise the effect of distraction due to the disruption. The major reason for the discrepancy between the results of the experimental studies (I, II) and the clinical, procedural studies (III, IV) could therefore be an emotional influence. It has also previously been shown that the patient response to a painful stimulus is larger in a clinical situation than it is to the same painful stimulus in a laboratory setting (Dworkin & Chen 1982).

A study comparing subjects with high and low hypnotic susceptibility showed only lower pain ratings to a cold pressor test among individuals highly susceptible to hypnosis (Tenenbaum et al. 1990). This was confirmed in a subsequent controlled clinical trial (Farthing et al. 1997) where it was shown that given four different types of distraction, these were only effective with respect to lowering the pain rating in a cold pressor test if the volunteers were highly hypnotisable. On this background it could be speculated whether the patients in study III could be divided into a sensitive and non-sensitive group regarding the effect of video. This was, however, not the case in study III (not investigated in I, II and IV) as there was no

correlation between the VAS pain rating and the patient's sensitivity to pain measured as the total VAS score of the video and the control situation (Fig. 8).

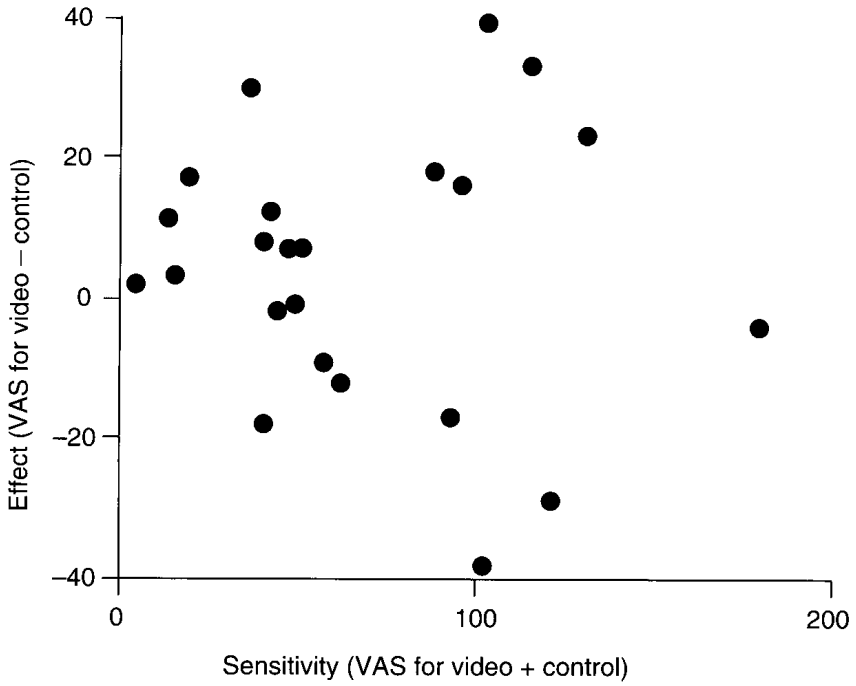


Fig. 8. No correlation was seen between pain sensitivity and the effect of video glasses in study III.

The Von Frey filaments were included in study IV to obtain a standardised, non-dental pain stimulus to the skin. The finding of a hypoalgesic effect of the video glasses and of N_2O to the painful skin stimuli evoked by the Von Frey filament is comparable to previous findings of an effect of video glasses on skin pain in cold pressor tests and burn wound care (Hoffman et al. 2000a,b, 2001a, I, II). These findings suggest that patients' sensitivity to cutaneous stimuli were modulated by this distraction method. The lack of effect of video and N_2O on the perceived pain and unpleasantness during ultrasonic scaling (IV) is, on the other hand, consistent with the lack of effect on the dental, procedural pain produced by tooth preparation found in study III.

Inhalation of N_2O in combination with oxygen has for a long time been known to provide pain relief, and a hypoalgesic effect of N_2O should therefore be expected. The pain perception during N_2O administration was, however, not significantly different from that seen under the influence of video glasses when measured on VAS. The MPQ scores found in study IV indicates that the use of VAS as the only way of measuring the unpleasantness and intensity of a perceived, dental procedural pain is not necessarily revealing the whole nature of the painful experience.

Previous studies have shown a significant effect of N_2O on pain tolerance and on pain threshold during electrical stimulation of the dental pulp (Dworkin & Chen 1982) and tactile stimulation with Von Frey filaments and pressure pain to the skin (Siiba et al. 1999), while others have failed to show a significant difference between compressed air and N_2O on labour pain (Carstoniu et al. 1994). As mentioned by *Sprehn et al*. (1994) there is only a limited number of controlled, clinical studies on the pain alleviating effect of N_2O, which is quite surprising taking the widespread use of the method into account.

The intensity of the pain could be thought to influence the effect of video glasses. Nevertheless, the pain induced by cavity preparation was of moderate intensity and the pain inflicted by dental ultrasonic scaling was of low intensity (Table 7). This should be compared with the experimental cold pressor pain in study II, where the pain perceived by the volunteers was considerably stronger, and where a significant reduction of the perceived pain was seen.

One can only speculate on the physiological mechanisms that no effect of video glasses was found on pain when the painful stimulus was dental scaling whilst an effect could be demonstrated on painful skin stimuli. A general aversion against video glasses can be ruled out again since none of the patients (studies I-IV) had any experience with video glasses. This was moreover supported by the fact that 81% of the patients in study IV felt that the video glasses had a positive effect on the total experience of the dental treatment situation. This finding is comparable with the findings in all three former studies I, II and III, in which about 75% of the volunteers/patients wished to use video glasses again if they were to have the painful stimuli repeated. The fraction of patients, who stated an overall positive effect on the treatment situation when wearing video glasses, was marginally higher than when N_2O was administered. The fact that three-quarters of the patients generally preferred distraction is in accordance with another cold pressor study (McCaul & Haugtved 1982) in which 73-92% of the volunteers stated that they preferred distraction to control and attention, although the distraction did not reduce the patients' pain intensity and unpleasantness.

This finding is in accordance with the findings in studies I and II where the volunteers rated a lower perceived pain during the cold pressor test when they were distracted by the audio-visual input from the video glasses.

A common belief would be, that the two perceptions (pain and unpleasantness) would be difficult to distinguish, but recent scientific work has revealed a possible physiological background for the division of disagreeable experiences in more dimensions (Rainville et al. 1997, Hofbauer et al. 2001). These studies show that different areas of the central cortex are involved in the perception of pain, and that a physiological distinction can be made between

the intensity and the unpleasantness of the painful stimulus. This is in accordance with the findings in studies III and IV where different responses regarding the two dimensions of the perceived pain were obtained (Table 8).

	Experimental studies I-II, N=63	Dental, procedural studies III-IV, N=53	Experimental and dental, procedural studies I-IV, N=116
Pain intensity	50.5 (23.4)	24.0 (21.5) A	38.4 (26.2) B
Unpleasantness	48.2 (22.8)	19.6 (18.8) A	35.1 (25.4) B

Table 8. A significant difference in VAS, mean and (SD) between the scores of pain and unpleasantness was seen in the pooled data from the dental, procedural studies (A: P=0.03) and in the pooled data from the experimental and dental, procedural pain studies I-IV (B: P=0.04) in the control situations.

8.4 Conclusions

I. ? Distraction induced by video glasses reduces the perceived intensity of pain and unpleasantness in the male subgroup when watching 3D video during an experimental pain stimulus provided by a cold pressor test.

? The reduction is only significant regarding unpleasantness in the female subgroup when watching 2D video.

? Three quarters of the volunteers would prefer distraction with video glasses again if they were to take another cold pressor test.

II. ? Distraction induced by video glasses reduces the perceived intensity of pain (but not unpleasantness) during an experimental pain stimulus provided by a cold pressor test in both sexes.

? It is not possible to manipulate the distraction effect induced by video glasses by giving the subjects different information about the expected effect.

? The effect of video glasses is reproducible after 4 weeks.

? Three quarters of the volunteers would prefer distraction with video glasses again if they were to take another cold pressor test.

III. ? Distraction induced by video glasses has no effect on the perceived intensity of pain and unpleasantness during a tooth preparation procedure.

? Three quarters of the patients would prefer to wear video glasses again if they were to have another tooth prepared.

IV. ? Distraction induced by video glasses has no effect on the perceived intensity of pain and unpleasantness during dental scaling.

? There is no significant difference in the effect of video glasses and nitrous oxide (N_2O) analgesics on the perceived intensity of pain and unpleasantness during dental scaling.

? Video glasses and N_2O reduce the perceived pain induced by Von Frey hair.

? 81% of the patients in the video situation and 65% in the N_2O situation stated that the methods have some beneficial effect on the perceived intensity of the evoked pain and unpleasantness.

9 Future aspects

Easy applicable, relatively cheap and non-invasive methods for reducing the perceived intensity and unpleasantness of painful stimuli will obviously always be of interest. The results of the studies in this thesis point out that this possibility exists for at least experimental pain induced by the cold pressor test. The method used combines an audio signal with a video signal in a pair of video glasses that transmit these signals to the volunteer/patient.

To fully explore this method it is necessary to furthermore conduct series of systematic studies where the different parameters that could possibly influence the effect of the video glasses on the perceived pain intensity and unpleasantness are explored. These parameters could be the type of painful stimulus, gender, video display method, sound type, film content and combinations hereof. The use of different brain imaging methods could possibly also lead to a better understanding of the neural mechanisms involved in the distraction of the perceived pain by video glasses. Virtual reality has been argued to have a stronger hypoalgesic effect than video and sound alone and than video games alone (Hoffman et al. 2000b, 2001b) and could therefore also be an interesting target for further controlled clinical studies. Other methods of rating the pain must be considered as well; it is puzzling that three quarters of the volunteers/patients in the present studies would prefer video glasses to nothing if they were to have another painful stimulus, even though they did not rate the pain intensity as lower in the video glasses situation.

The observed gender specific differences in the effect on pain and unpleasantness of distraction with video glasses are in line with other recent studies on gender specific reactions to pain and hypoalgesic drugs. Further studies on distraction should, as the development of new methods for reducing the perception of a painful stimulus continues, take the gender specific reactions to pain into consideration.

10 English summary

The present thesis is based on four studies (I-IV) with the main purpose to investigate the effect of an audio-visual input on the perception of a painful stimulus. As carrier of the audio-visual input video glasses (I-Glasses™, Virtual i-O™, Seattle, USA) were chosen in all four studies. The existing knowledge on this specific topic is limited and the two initial studies (I and II) were therefore focused on the effect of experimentally induced painful stimuli and the reproducibility of these findings. In I and II the cold pressor test (1-2°C chilled water) was used to induce experimental pain. Based on the results from the experimental studies the studies III and IV were targeted at dental, procedural pain. In III and IV the painful stimuli were preparation for a dental filling and dental scaling, respectively, which are some of the most common dental, procedural painful stimuli besides needle penetration. In study IV punctate stimuli with Von Frey hair was incorporated. In all four studies the volunteers/patients rated the intensity of pain and unpleasantness on 100-mm visual analogue scales (VAS).

The overall aim of the studies (I-IV) was to test the hypothesis that audio-visual signals through video glasses distract the perception of pain and unpleasantness in experimental and clinical settings.

The studies represented by papers I-IV had the detailed aims listed below.

I. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during a cold pressor test.

II. To evaluate whether it is possible to manipulate the distraction effect induced by video glasses on the perceived pain and unpleasantness by giving the subjects different information about the expected effect and secondly, to determine the reproducibility of the effect in cold pressor tests.

III. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during a tooth preparation procedure.

IV. To evaluate whether distraction induced by video glasses has an effect on the perceived intensity of pain and unpleasantness during dental scaling and secondly, to compare a possible effect with the effect of nitrous oxide (N_2O) analgesics.

Study I

The effect of 3D video, 2D video and no video glasses was compared in two groups of healthy volunteers (13 males and 11 females) in a randomized, controlled trial. The VAS ratings were statistically compared using the Wilcoxon-Signed-Rank test. Between the groups (males and females) there was a significant difference ($P<0.01$) in the rating of unpleasantness in the 3D video condition, while there were no significant differences between the genders in the other conditions (2D, control). 3D video provided a significant reduction in both pain and unpleasantness compared with the control situation in the male group ($P<0.01$). However, in the female group there was a significant reduction in unpleasantness with 2D video compared with the control situation ($P<0.05$).

Study II

Thirty-nine student participated in the study (24 females and 15 males, median age 23 years, range 19-28). They were randomised into three groups balanced with respect to age and gender, who received different information about the effect of 3D video on pain and unpleasantness: one group received positive information, the second group received neutral information and the third group received negative information. There was no significant difference in the effect of video glasses on perceived pain ($P=0.74$) or unpleasantness ($P=0.84$) between the three information groups. The data were therefore pooled. The results of the pooled data showed a significant effect of 3D video on perceived pain ($P=0.03$), but not on unpleasantness ($P=0.18$). After 4 weeks the study was repeated, and there were no significant changes in the effect of video glasses. The median VAS scores decreased in both the video and the control situations compared with the first session.

Study III

Twenty-three patients (17 female and 6 male, age range 20-49) with a need for occlusal dental restorations participated in the study. Differences in VAS ratings in the video and control situation were tested by Student’s t-test. There was no statistically significant effect on the perceived pain ($P=0.90$) or unpleasantness ($P=0.39$).

Study IV

Twenty-six patients (12 female and 14 male, age range 29 – 92) with superficial chronic periodontitis were enrolled in this randomized, controlled clinical study. For dental scaling, there was no effect of video glasses on the perceived pain ($P=0.85$), unpleasantness ($P=0.73$)

or of N_2O (P=0.69 and P=0.51, respectively) compared with the control situation. Similarly, no significant difference was found between VAS scores in the video glasses and N_2O situations (P=0.48, P=0.58). A significant effect of video glasses and N_2O (P<0.008) was found on the perceived pain intensity produced by Von Frey filament compared with the control situation, but no significant difference was seen between these methods (P=0.07).

Conclusions

I. Distraction induced by video glasses reduces the perceived intensity of pain and unpleasantness in the male subgroup when watching 3D video during an experimental, thermal pain stimulus provided by a cold pressor test.

The reduction is only significant regarding unpleasantness in the female subgroup when watching 2D video.

Three quarters of the volunteers would prefer distraction with video glasses again if they were to take another cold pressor test.

II. Distraction induced by video glasses reduces the perceived intensity of pain but nor unpleasantness during an experimental, thermal pain stimulus provided by a cold pressor test in both sexes.

It is not possible to manipulate the distraction effect induced by video glasses by giving the subjects different information about the expected effect.

The effect of video glasses is reproducible after 4 weeks.

Three quarters of the volunteers would prefer distraction with video glasses again if they were to take another cold pressor test.

III. Distraction induced by video glasses has no effect on the perceived intensity of pain and unpleasantness during a tooth preparation procedure.

Three quarters of the patients would prefer to wear video glasses again if they were to have another tooth prepared.

IV. Distraction induced by video glasses has no effect on the perceived intensity of pain and unpleasantness during dental scaling.

There is no significant difference in the effect of video glasses and nitrous oxide (N_2O) analgesics on the perceived intensity of pain and unpleasantness during dental scaling.

Video glasses and N_2O reduce the perceived pain induced by Von Frey filaments.

81% of the patients in the video situation and 65% in the N_2O situation stated that the methods have some beneficial effect on the perceived intensity of the evoked pain and unpleasantness.

11 Dansk Sammenfatning/Danish Summary

Denne afhandling er baseret på fire undersøgelser (I-IV) med det hovedsigte at undersøge effekten af et audio-visuelt signal på oplevelsen af et smertestimulus. Til transmission af signalet anvendtes videobriller (I-Glasses✍, Virtual i-O✍, Seattle, USA) i alle fire undersøgelser. Den eksisterende viden om dette emne er begrænset, og de første to undersøgelser (I, II) blev derfor rettet mod at undersøge om signalet fra videobrillerne kunne distrahere forsøgspersoners oplevelse af en eksperimentielt induceret smerte (isvand). Baseret på de lovende resultater af disse undersøgelser (I, II) blev de to følgende undersøgelser (III, IV) rettet mod klinisk tandsmerte. Der blev i disse undersøgelse (III, IV) som smertestimuli anvendt henholdvis præparation (udboring) til en fyldning i undersøgelse III og depuration (tandrensning) i undersøgelse IV. Disse behandlinger blev valgt, da de sammen med lokalbedøvelse hører til de mest udførte behandlinger hos tandlægen og generelt opfattets som smertevoldende. I undersøgelse IV blev der suppleret med et ikke-odontologisk trykstimulus med Von Frey hår. I alle undersøgelserne angav patienterne/forsøgspersonerne smerteintensiteten henholdsvis ubehaget af de påførte stimulus på en ”visual analogue scale” (VAS).
Det overordnede formål med undersøgelserne (I-IV) var at teste hypotesen, at audio-visuelle signaler transmitteret gennem videobriller påvirker oplevelsen af smerteintensitet og ubehag i såvel eksperimentielle som kliniske situationer.

De enkelte undersøgelser havde detaljerede formål, som beskrevet nedenfor:
I. At evaluere om distraktion med videobriller har en effekt på oplevelsen af smerte og ubehag under en eksperimentiel smertepåvirkning med kulde.
II. At evaluere om det er muligt at manipulere effekten af distraktion med videobriller på smerteoplevelsen ved at give forsøgspersonerne forskellig information om den forventede effekt. Yderligere, at undersøge om effekten er reproducerbar.
III. At evaluere om distraktion med videobriller har en effekt på oplevelsen af smerte og ubehag under preparation af en tand til fyldning.
IV. At evaluere om distraktion med videobriller har en effekt på oplevelsen af smerte og ubehag, når det smertevoldende stimulus er depuration, og yderligere at sammenligne den mulige effekt med effekten af lattergas.

Undersøgelse I

Effekten af 3D-video, 2D-video og ingen videobrille blev sammenlignet i to grupper af raske forsøgspersoner (13 mænd og 11 kvinder) i et randomiseret, kontrolleret forsøg. VAS angivelserne blev testet statistisk med Wilcoxon-Signed-rank test. Mellem kønnene sås en signifikant ($P<0.01$) forskel på oplevelsen af ubehag i 3D-situationen, mens der ikke fandtes kønsforskelle i kontrol og 2D-situationerne. Hos mændene sås en signifikant reduktion i oplevelsen af smertens intensitet og ubehag, når der blev anvendt 3D-video ($P<0.01$). Hos kvinderne sås en reduktion i oplevelsen af ubehaget udelukkende i 2D-situationen ($P<0.05$).

Undersøgelse II

39 studerende deltog i undersøgelsen (24 kvinder og 15 mænd). De blev tilfældigt fordelt i tre grupper med skyldig hensyntagen til alder og køn. Disse tre grupper modtog forskellig information om effekten af videobriller på oplevelsen af smerte og ubehag. En gruppe fik information om, at effekten var negativ; en gruppe fik information om, at effekten var positiv; og endeligt fik en gruppe besked om, at effekt af videobriller ikke var kendt. Der sås ingen signifikant forskel på effekten af videobriller mellem de tre grupper, hverken med hensyn til smerte ($P=0.74$) eller ubehag ($P=0.84$). Tallene fra de tre grupper blev derfor adderet til ét datamateriale, og resultaterne af dette samlede materiale viste en signifikant effekt af videobriller på oplevelsen af smerte ($P=0.03$), men ikke på ubehag ($P=0.18$). Forsøget blev gentaget efter fire uger, uden der kunne påvises en ændring i effekten.

Undersøgelse III

23 patienter (17 kvinder og 6 mænd) med behov for en okklusal fyldning i to homologe tænder deltog i denne kontrollerede, kliniske undersøgelse. Det smertevoldende stimulus var udboring af gammel klasse I/præparation til ny klasse I fyldning. Der sås ingen signifikant forskel på oplevelsen af smerte ($P=0.90$) eller ubehag ($P=0.39$) mellem video- og kontrolsituationerne.

Undersøgelse IV

26 patienter (12 kvinder og 14 mænd) med diagnosen parodontitis marginalis superficialis (mild parodontitis) deltog i dette randomiserede, kontrollerede kliniske forsøg. Med depuration som det smertevoldende stimulus sås ingen effekt af videobriller på oplevelsen af smerte ($P=0.85$) eller ubehag ($P=0.73$). Der sås tilvarende ingen effekt af lattergas (smerte: $P=0.69$,

ubehag: P=0.51). Der sås ingen forskel på oplevelsen af smerte mellem video- og lattergas-situationerne (smerte: P=0.48, ubehag: P=0.58). Ved anvendelse af Von Frey hår som smertevoldende stimulus sås en signifikant effekt på smerteoplevelsen i både video- og lattergas-situationerne sammenlignet med kontrolsituationen (P< 0.008), mens der ikke fandtes nogen forskel i effekten mellem de to situationer (P=0.07).

Konklusioner

I. Distraktion med 3D-videobriller reducerer oplevelsen af smertens intensitet og ubehaget hos mænd, når det eksperimentielle smertestimulus er isvand. En tilsvarende reduktion ses kun hos kvinder, når der var tale om 2D-video og kun på oplevelsen af ubehag. Tre-fjerdedele af forsøgspersonerne ville anvende videobriller igen, hvis de skulle igennem en ny isvands-test.

II. Distraktion med videobriller reducerer oplevelsen af smertens intensitet, men ikke ubehaget, når det smertevoldende stimulus er isvand. Det er ikke muligt at manipulere effekten af videobriller, ved at give forsøgspersonerne en bestemt forhåndsviden om den forventede effekt. Effekten af videobriller på oplevelsen af smerte kan genfindes efter 4 uger. Tre-fjerdedele af forsøgspersonerne ville anvende videobriller igen, hvis de skulle igennem en ny isvands-test.

III. Distraktion med videobriller har ingen effekt på oplevelsen af smerte eller ubehag, når smertestimulus er præparation til en fyldning. Tre fjerdedele af forsøgspersonerne ville anvende video briller igen, hvis de pány skulle have præpareret til en fyldning.

IV. Distraktion med videobriller har ingen effekt på oplevelsen af smerte eller ubehag, når smertestimulus er depuration. Anvendelsen af lattergas har ligeledes ingen effekt på oplevelsen af smerte eller ubehag, når smertestimulus er depuration. Videobriller og lattergas reducerer oplevelsen af smertens intensitet, når denne er induceret af Von Frey hår. 65% i lattergassituationen og 81% i videosituationen oplevede en positiv effekt på behandlings-situationen.

12 References

Anderson RA, Baron RS, Logan H. Distraction, control, and dental stress. J Appl Soc Psychol 1991; 21: 156-171.

Annequin D, Carbajal R, Chauvin P, Gall O, Tourniaire B, Murat I. Fixed 50% nitrous oxide oxygen mixture for painful procedures: A french survey. Pediatrics 2000; 105 (E47): 1-6.

Anusavice KJ, Kincheloe JE. Comparison of pain associated with mechanical and chemomechanical removal of caries. J Dent Res 1987; 66: 1680-1683.

Arendt-Nielsen L, Bjerring P. Reaction times to painless and painful CO_2 and argon laser stimulation. Eur J Appl Physiol Occup Physiol 1988; 58: 266-273.

Arntz A, Dreessen L, Merckelbach H. Attention, not anxiety, influences pain. Beh Res Ther 1991; 29: 41-50.

Arntz A, Hopmans M. Underpredicted pain disrupts more than correctly predicted pain, but does not hurt more. Behav Res Ther 1998; 36: 1121-1129.

Arima T, Arendt-Nielsen L, Svensson P. Effect of jaw muscle pain and soreness evoked by capsaicin before sleep on orofacial motor activity during sleep. J Orofacial Pain 2001; 15: 245-256.

Barber J, Mayer D. Evaluation of the efficacy and neural mechanism of a hypnotic analgesia produced in experimental and clinical dental pain. Pain 1977; 4: 41-48.

Beitel RE, Dubner R. Response of unmyelinated polymodal nociceptors to thermal stimuli applied to monkey’s face. J Neurophysiol 1976; 39: 1160-75.

Bell-Krotoski J, Tomancik E. The repeatability of testing with Semmes-Weinstein monofil. J Hand Surg (Am) 1987; 12: 155-161.

Bentsen B, Svensson P, Wenzel A. The effect of a new type of video glasses on the perceived intensity of pain and unpleasantness evoked by a cold pressor test. Anesth Prog 1999; 46: 113-117.

Bentsen B, Svensson P, Wenzel A. The hypoalgesic effect of 3-D video glasses on cold pressor pain: Reproducibility and importance of information. Anesth Prog 2000; 47: 67-71.

Bentsen B, Svensson P, Wenzel A. Evaluation of effect of 3D video glasses on perceived pain and unpleasantness induced by restorative dental treatment. Eur J Pain 2001; 5: 373-378.

Bentsen B, Wenzel A, Svensson P. Comparison of the effect of video glasses and nitrous oxide analgesia on the perceived intensity of pain and unpleasantness evoked by dental scaling. Eur J Pain 2003; 7: 49-53.

Berenson AB, Wiemann CM, Rickert VI. Use of videoglasses to decrease anxiety among children undergoing genital examinations. Am J Obstet Gynecol 1998; 178: 1341-1345.

Bergius M, Berggren U, Kiliaridis S. Experience of pain during an orthodontic procedure. Eur J Oral Sci 2002; 110: 92-98.

Bromm B, Treede RD. Withdrawal reflex, skin resistance reaction and pain ratings due to electrical stimuli in man. Pain 1980; 9: 339-354.

Brown AC, Beeler WJ, Kloka AC, Fields RW. Spatial summation of pre-pain and pain in human teeth. Pain 1985; 21: 1-16.

Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P. Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2001; 86: 782-791.

Carlin S, Ward WD, Gershon A, Ingraham R. Sound stimulation and its effect on dental sensation threshold. Science 1962; 138: 1258-1259.

Carlson KL, Broome M, Vessey JA. Using distraction to reduce reported pain, fear and behavioral distress in children and adolescent: a multisite study. J Soc Pediatr Nurs 2000; 5: 75-85.

Campero M, Serra J, Ochoa JL. C-polymodal nociceptors activated by noxious low temperature in human skin. J Physiol 1996; 497: 565-572.

Carstoniu J, Levytam S, Norman P, Daley D, Katz J, Sandler AN. Nitrous oxide in early labour. Safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. Anesthesiology 1994; 80: 30-35.

Casey KL, Minoshima S, Morrow TJ, Koeppe RA. Comparison of human cerebral activation patterns during cutaneous warmth, heat pain, and deep cold pain. J Neurophysiol 1996; 76: 571-581.

Chapman CR, Casey KL, Dubner R, Foley KM, Gracely RH, Reading AE. Pain measurement: An overview. Pain 1985; 22: 1-31.

Chen ACN, Dworkin SF, Haug J, Gehrig J. Human pain responsivity in a tonic pain model: Psycological determinants. Pain 1989; 37: 143-160.

Chen ACN. Cognitive neuropsychophysiology of thought imagery versus imagination imagery. Int J Neurosci 1991; 60: 65-77.

Chéry-Croze S. Relationship between noxious cold stimuli and the magnitude of pain sensation in man. Pain 1983; 15: 265-269.

Chudler EH, Dong WK, Kawakami Y. Cortical nociceptive responses and behavioral correlates in monkey. Brain Res 1986; 397: 47-60.

Corah NL, Gale EN, Illig SJ. Assessment of a dental anxiety scale. J Am Dent Assoc 1978; 97: 816-819.

Corah NL, Gale EN, Illig SJ. The use of relaxation and distraction to reduce psychological stress during dental procedures. J Am Dent Assoc 1979; 98: 390-394.

Corah NL, Gale EN, Pace LF, Seyrek SK. Relaxation and musical programming as means of reducing psycological stress during dental procedures. J Am Dent Assoc 1981; 103: 232-234.

Costas PD, Heatley G, Brooke RS. Normal sensation of the human face and neck. Plast Reconstr Surg 1994; 93: 1141-1145.

Darian-Smith I, Johnson KO, Dykes R. “Cold” fiber population innervating palmar and digital skin of the monkey: responses to cooling pulses. J Neurophysiol 1973; 36: 325-346.

Drewes AM, Schipper KP, Dimcevski G, Petersen P, Andersen OK, Gregersen H, Arendt-Nielsen L. Multimodal assessment of pain in the oesophagus: a new experimental model. Am J Physiol Gastrointest Liver Physiol 2002; 283: G95-G103.

Duncan CH, Bushnell MC, Lavigne GJ. Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. Pain 1989; 37: 295-303.

Dworkin SF, Chen ACN. Pain in clinical and laboratory contexts. J Dent Res 1982; 61: 772-774.

Dworkin SF, Chen AC, Schubert MM, Clark DW. Analgesic effects of nitrous oxide with controlled painful stimuli. J Am Dent Assoc 1983; 107: 581-585.

Ernst E, Pittler MH. Effectiveness of acupuncture in treating acute dental pain: a systematic review. Br Dent J 1998; 184: 443- 447.

Fang F, Guo TZ, Davies MF, Maze M. Opiate receptors in the periaqueductal gray mediate analgesic effect of nitrous oxide in rats. Eur J Pharmacol 1997; 336: 137-141.

Farthing GW, Venturino M, Brown SW, Lazar JD. Internal and external distraction in the control of cold-pressor pain as a function of hypnotizability. Int J Clin Exp Hypn 1997; 45: 433-446.

Fernandes de Lima VM, Chatrian GE, Lettich E, Canfield RC, Miller RC, Soso MJ. Electrical stimulation of tooth pulp in human. Relationships among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials. Pain 1982; 14: 207-232.

Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. Pain 1989; 38: 123-135.

Fields HL. Pain: an unpleasant topic. Pain 1999; 6: s61-s69.

Fillingim RB, Maixner W, Kincaid S, Silva S. Sex differences in temporal summation but not sensory-discriminative processing of thermal pain. Pain 1998; 75: 121-127.

Frankenstein UN, Richter W, McIntyre MC, Rémy F. Distraction modulates anterior cingulate gyrus activations during cold pressor test. Neuroimage 2001; 14: 827- 36.

Frere CL, Crout R, Yorty J, McNeil DW. Effects of audiovisual distraction during dental prophylaxis. J Am Dent Assoc 2001; 132: 1031-1038.

Gardner WJ, Licklider JCR, Weisz AZ. Suppression of pain by sound. Science 1960; 132: 32-33.

Gardner EP, Martin JH, Jessell TM. The Bodily senses. In: Principles of neural science. 2000, 4th ed., Kandel ER, Schwartz JH, Jessell TM edt., McGraw-Hill, USA.

Gescheider GA. Psychophysics: The fundamentals. 1997, 3rd ed., Lawrence Erlbaum Associates Inc., Mahwah, New Jersey, USA.

Gracely RH, Dubner R, McGrath PA. Narcotic Analgesia: Fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensation. Science 1979; 203: 1261-1263.

Gracely RH. Studies of pain in normal man. In: Textbook of Pain. 1999, 4th ed., Wall PD end Melzack R edt. Churchill Livingstone, London, UK.

Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Quantification of local and referred muscle pain in humans after sequential i.m. injections of hypertonic saline. Pain 1997; 69: 111-117.

Graven-Nielsen T, Mense S. The peripheral apparatus of muscle pain: evidence from animal and human studies. Clin J Pain 2001; 17: 2-10.

Grushka M, Sessle BJ. Applicability of the McGill Pain Questionnaire to the differentiation of "toothache" pain. Pain 1984; 19: 49-57.

Guo TZ, Poree L, Golden W, Stein J, Fujinaga M, Maze M. Antinociceptive response to nitrous oxide is mediated by supraspinal opiate and spinal a_2-adrenergic receptors in rat. Anesthesiology 1996; 85: 846- 52.

Hari R, Kaukoranta E, Reinikainen T, Huopaniemie T, Mauno J. Neuromagnetic localization of cortical activity evoked by painful dental stimulation in man. Neuroscience Letters 1983; 42: 77-82.

Harvey M, Elliot M. Transcutaneous electrical nerve stimulation (TENS) for pain management during cavity preparations in pediatric patients. ASDC J Dent Child 1995; 62: 49-51.

Helweg-Larsen S, Drewes AM, Petersen P, Jensen TS, Brennum J. McGill Pain Questionnaire translated into Danish: experimental and clinical findings. Clin J Pain 1993; 9: 80-87.

Hodes RL, Howland EW, Lightfoot N, Cleeland CS. The effects of distraction on responses to cold pressor pain. Pain 1990; 41: 109-114.

Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. J Neurophysiol 2001; 86: 402-411.

Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness III TA. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. Pain 2000a; 85: 305-309.

Hoffman HG, Patterson DR, Carrougher GJ. Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: A controlled study. Clin J Pain 2000b; 16: 244-250.

Hoffman HG, Patterson DR, Carrougher GJ, Sharar SR. Effectiveness of virtual reality-based pain control with multiple treatments. Clin J Pain 2001a; 17: 229-235.

Hoffman HG, Garcia-Palacios A, Patterson DR, Jensen M, Furness III T, Ammons WF Jr. The effectiveness of virtual reality for dental patients: a controlled study. Cyberpsychol Behav 2001b; 4: 527-535.

Jensen K, Andersen HO, Olesen J, Lindblom U. Pressure-pain threshold in human temporal region. Evaluation of a new pressure algometer. Pain 1986; 25: 313-323.

Jensen K, Norup M. Experimental pain in human temporal muscle induced by hypertonic saline, potassium and acidity. Cephalalgia 1992; 12: 101-106.

Johnson MH, Breakwell G, Douglas W. The effect of imagery and sensory detection distractors on different measures of pain: How does distraction work? Br J Clin Psychol 1998; 37: 141-154.

Jones SF, McQuay HJ, Moore RA, Hand CW. Morphine and ibuprofen compared using the cold pressor test. Pain 1988; 34: 117-122.

Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain measurement. Pain 1981; 10: 241-248.

Lal MK, McClelland J, Phillips J, Taub NA, Beatti RM. Comparison of EMLA cream versus placebo on children receiving distraction therapy for venepuncture. Acta Paediatr 2001; 90: 154-159.

Landolt MA, Marti D, Widmer J, Meuli M. Does cartoon movie distraction decrease burned children’s pain behaviour. J Burn Care Rehabil 2002; 23: 61-65.

Leavitt AH, King GJ, Ramsay DS, Jackson DL. A longitudinal evaluation of pulpal pain during orthodontic tooth movement. Orthod Craniofac Res 2002; 5: 29-37.

Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effect on dorsal horn convergent neurons in the rat. Pain 1979; 6: 283-304.

Lembo T, Fitzgerald L, Matin K, Woo K, Mayer EA, Naliboff BD. Audio and visual stimulation reduces patient discomfort during screening flexible sigmoidoscopy. Am J Gastroenterol 1998; 93: 1113-1116.

Levine FM, De Simone LL. The effects of experimenter gender on pain report in male and female subjects. Pain 1991; 44: 69-72.

Marchand S, Arsenault P. Odors modulate pain perception a gender-specific effect. Physiol Behav 2002; 76: 251-256.

McCaul KD, Haugtvedt C. Attention, distraction, and cold-pressor pain. J Pers Soc Psychol 1982; 43: 154-162.

McCaul KD, Malott JM. Distraction and coping with pain. Psychol Bull 1984; 95: 516-533.

McGill M, Molyneaux L, Spencer R, Heng LF, Yue DK. Possible source of discrepancies in the use of Semmes-Weinstein monofilament. Diabetes Care 1999; 22: 598-602.

Malamed SF, Gagnon S, Leblanc D. Articain hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc 2001; 132: 177-185.

Melzack R, Weisz AZ, Sprague LT. Stratagems for controlling pain: contributions of auditory stimulation and suggestion. Exp Neurol 1963; 8: 239-247.

Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150: 971-979.
Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain: a new conceptual model. In: The skin senses. 1968, Kenshalo D edt., CC Thomas, Springfield, Ill.

Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975; 1: 277-299.

Menegazzi JJ, Paris PM, Kersteen CH, Flynn B, Trautman DE. A randomized, controlled trial of the use of music during laceration repair. Ann Emerg Med 1991; 20: 348-350.

Merskey H, Bogduk N (eds). Classification of chronic pain. 1994, IASP Press, Seattle, USA.

Miller AC, Hickman LC, Lemaster GK. A distraction technique for control of burn pain. J Burn Care Rehabil 1992; 13: 576-580.

Morosko TE, Simmons FF. The effect of audio-analgesia on pain threshold and pain tolerance. J Dent Res 1966; 45: 1608-1617.

Nevo O, Keinan G, Teshimovsky-Arditi M. Humor and pain tolerance. Humor 1993; 6: 71-88.

Nolano M, Crisci C, Santoro L, Barbieri F, Cascal Kennedy WR, Wendelschafer-Crabb G, Provitera Lorenzo N, Caruso G. Absent innervation of skin and sweat glands in congenital insensitivity to pain with anhidrosis. Clin Neurophysiol 2000; 111: 1596-1601.

Nørholt SE. Treatment of acute pain following removal of mandibular third molars. Use of the dental pain model in pharmalogical research and development of a comparable animal model. Int J Oral Maxillofac Surg 1998; 27: 1-41.

Ozbarlas N, Sarikayalar F, Kale G. Congenital insensitivity to pain with anhidrosis. Cutis 1993; 51: 373-374.

Oztas N, Olmez A, Yel B. Clinical evaluation of transcutaneous electronic nerve stimulation for pain control during tooth preparation. Quintessence Int 1997; 9: 603-608.

Peretz B, Katz J, Zilburg I, Shemer J. Response to nitrous-oxide and oxygen among dental phobic patients. Int Dent J 1998; 48: 17-23.

Petersen JK, Milgrom P. Pain relief in the orofacial regions. 1989, Munksgaard, Copenhagen, Denmark.

Petersen JK. Nitrous oxide analgesia in dental practice. Acta Anaesthesiol Scand 1994; 38: 773-774.

Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 2000; 85: 19-30.

Price DD. Psychological and neural mechanisms of pain. 1988, Raven Press, New York, USA.

Primosch RE, Rolland-Asensi G. Comparison of topical EMLA 5% oral adhesive to benzocaine 20% on the pain experienced during palatal anesthetic infiltration in children. Pediatr Dent 2001; 23: 11-14.

Quarnstrom FD, Milgrom P. Clinical experience with TENS and TENS combined with nitrous oxide-oxygen. Anesth Prog 1989; 23: 66-69.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997; 277: 968-971.

Reeves JL, Jaeger B, Graff-Radford SB. Reliability of the pressure algometer as a measure of myofascial triggerpoint sensitity. Pain 1986; 24: 313-321.

Rowland AS, Baird DD, Shore DL, Weinberg CL, Savitz DA, Willcox AJ. Nitrous oxide and spontaneous abortion in female dental assistants. Am J Epidemiol 1995; 141: 531-538.

Rowland AS, Baird DD, Weinberg CL, Shore DL, Shy CM, Willcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous gasses. N Eng J Med 1992; 327: 993-997.

Schmidt RF, Thews G (edt.). Human Physiology. 1983, Springer Verlag, Berlin, Heiselberg New York.

Schmidt RF, Schmelz M, Forster C, Ringkamp M, Torebjörk E, Handwerker H. Novel classes of responsive and unresponsive C nociceptors in human skin. J Neurosci 1995; 15: 333-341.

Schmidt R, Schmelz M, Ringkamp M, Handwerker HO, Torebjörk HE. Innervation of territories of mechanically activated C nociceptor units in human skin. J Neurophysiol 1997; 78: 2641-2648.

Sessle BJ. The neurobiology of facial and dental pain: Present knowledge, future directions. J Dent Res 1987; 66: 962-981.

Sessle BJ. Acute and chronic craniofacial pain: Brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit Rev Oral Biol Med 2000; 11: 57-91.

Seymour RA, Simpson JM, Charlton JE, Phillips ME. An evaluation of length and end-phrase of visual analogue scales in dental pain. Pain 1985; 21: 177-185.

Seyrek SK, Corah NL, Pace LF. Comparison of three distraction techniques in reducing stress in dental patients. J Am Dent Assoc 1984; 108: 327-329.

Sheng LL, Nishiyama K, Honda T, Sugiura M, Yaginuma H, Sugiura Y. Suppressive effects of Neiting acupuncture on toothache: an experimental analysis on Fos expression evoked by tooth pulp stimulation in the trigeminal subnucleus pars caudalis and the periaquaductal gray of rats. Neurosci Res 2000; 38: 331-339.

Skjerve J, Nedreås S. Musikk brukt for å berolige ved tannbehandling av psykisk utviklingshemmede. Nor Tannlaegeforen Tid 1981; 91: 49-51.

Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 1989; 38: 99-107.
Simone DA, Kajander KC. Responses of cutaneous A-fiber nociceptors to noxious cold. J Neurophysiol 1997; 77: 2049-2060.

Siiba S, Nakanishi O, Ishikawa T, Hirakawa T, Kawahara H, Imamura Y. Increase in the threshold of pain and touch sensation in the human face with clonidine plus 30% nitrous oxide. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87: 294-298.

Soares D, Desar N. Hand wounds in leprosy patients. Lepr Rev 1995; 66: 235-238.

Spanos NP, Coss WP, Watson E. Expectancy, redefinition and reported pain. Percept Mot Skills 1987; 64: 355-358.

Sparks L. Taking the “ouch” out of injections for children. Using distraction to decrease pain. Am J Matern Child Nurs 2001; 26: 72-78.

Sprehn M, Trautner S, Wiingaard S, Sørensen MB, Dahl JB. Præhospital smertebehandling med kvælstofforilte (Entonox). Ugeskr Læger 1994; 156: 5830-5835.

Stevens JC, Marks LE. Cross-modality maching functions generated by magnitude estimation. Percept Psychophys 1980; 27: 379-389.

Sullivan C, Schneider PE, Musselman RJ, Dummett JCO, Gardiner D. The effect of virtual reality during dental treatment on child anxiety and behaviour. J Dent Child 2000; 67: 193-196.

Sullivan MJ, Reesor K, Mikail S, Fisher R. The treatment of depression in chronic low back pain: review and recommendations. Pain 1992; 50: 5-13.

Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S. Variability of argon laser-induced sensory and pain thresholds on human oral mucosa and skin. Anesth Prog 1991; 38: 79-83.

Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S. Hypoalgesic effect of EMLA and Lidocaine gel applied on human oral mucosa: Quantitative evaluation by sensory and pain threshold to argon laser stimulation. Anesth Prog 1992; 39: 4-8.

Svensson P, Bjerring P, Arendt-Nielsen L, Kaaber S. Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. Clin Pain 1993; 9: 207-215.

Svensson P, Koelsen JP, Svensson H. Efficacy of a topical anesthetic on pain and unpleasantness during scaling of gingival pockets. Anesth Prog 1994; 41: 35-39.

Svensson P, Arendt-Nielsen L, Houe L. Muscle pain modulates mastication: an experimental study in humans. J Orofac Pain 1998; 12: 7-16.

Svensson P, Cairns BE, Wang K, Hu JW, Graven-Nielsen T, Arendt-Nielsen L, Sessle BJ. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain, in press.

Talbot JD, Duncan GH, Buchnell MC. Effects of diffuse noxious inhibitory controls (DNICs) on the sensory-discriminative dimension of pain perception. Pain 1989; 36: 231-238.

Tenenbaum SJ, Kurtz RM, Bienias JL. Hypnotic susceptibility and experimental pain reduction. Am J Clin Hypn 1990; 33: 40-49.

Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci 2002; 22: 2748-2752.

Treede RD, Meyer RA, Raja SN, Cambell JN. Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. J Physiol 1995; 483: 747-758.

Vessey JA, Carlson KL, McGill J. Use of distraction with children during an acute pain experience. Nurs Res 1994; 43: 369-372.

Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain 2002; 95: 195-199.

Virtanen ASJ, Huopaniemi T, Närhi MVO, Pertovaara A, Wallgren K. The effect of temporal parameters on subjective sensations evoked by electrical tooth stimulation. Pain 1987; 30: 361-371.

Voerman VF, Egmond van J, Crul BJ. Normal values for sensory threshold in cervical dermatomes: a critical note on the use of Semmes-Weinstein monofilaments. Am J Phys Med Rehab 1999; 78: 24-29.

Walsh NE, Schoenfeld L, Ramamurthy S, Hoffmann J. Normative model for cold pressor test. Am J Phys Med Rehabil 1989; 68: 6-11.

Weaver J, Zillmann D. Effect of humor and tragedy on discomfort tolerance. Percept Mott Skills 1994; 78: 632-634.

Weidner C, Schmeltz M, Schmidt R, Hansson B, Handwerker HO, Torebjörk HE. Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. J Neurosci 1999; 19: 10184-10190.

Weisenberg M. Pain and pain control. Psychol Bull 1977; 84: 1008-1044.

Weisenberg M, Tepper I, Schwarzwald J. Humor as a cognitive technique for increasing pain tolerance. Pain 1995a; 63: 207-212.

Weisenberg M, Schwarzwald J, Tepper I. The influence of warning signal timing and cognitive preparation on the aversiveness of cold-pressor pain. Pain 1995b; 64: 379-385.

Weisenberg M, Raz T, Hener T. The influence of film-induced mood on pain perception. Pain 1998; 76: 365-375.

Witting N, Kupers RC, Svensson P, Arendt-Nielsen L, Gjedde A, Jensen TS. Neurol 2001; 57: 1817-1824.

Woda A, Pionchon P. Algies oro-faciales idiopathiques: sèmiologie, causes et mécanismes. Rev Neurol 2001; 157: 265-283.

Woda A, Pionchon P. A unified concept of idiopathic orofacial pain: pathophysiologic features. J Orofac Pain 2000; 14: 196-212.

Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Kolzenburg M, Lipton R, Loeser JD, Payne R, Torebjörk E. Towards a mechanism-based classification of pain. Pain 1998; 77: 227-229.

Zacny JP, Coalson D, Young C, Klafta J, Rupani G, Thapar P, Choi M, Apfelbaum JL. A dose-response study of the effects of intravenous midazolam on cold pressor-induced pain. Anesth Analg 1995; 80: 521-525.

Zillmann D, Wied DM, King-Jablonski C, Jenzowsky S. Drama-induced affect and pain sensitivity. Psychosom Med 1996; 58: 333-341.