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Pain in premature infants

- Pain reactions and possible consequences in later life

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Description

Out of all newborns, approximately 6% are born prematurely in Finland. Preterm infants receive care in the Neonatal Intensive Care Unit where they undergo a variety of painful procedures daily. Pain in prematurely born infants continues to receive inadequate attention, which is why pain reactions should be recognized and taken into account by the health care professionals. Compared to children born full-term, premature infants are more likely to suffer from delays and disabilities in development.

The aim of the study was to determine how prematurely born infants react to pain and what kind of consequences this pain might have in later life. The purpose of the study was to conduct a literature review and collect up-to-date information for health care professionals and students in order for them to develop their professional expertise in neonatal nursing and pain management in preterm infants.

Data was searched and obtained from multiple databases such as the Academic Search Elite, Cinahl, Cochrane Library, Elsevier ScienceDirect and PubMed. Overall, fifteen articles were reviewed and selected. The data was analyzed by using thematic analysis.

Preterm infants react to pain by means of various physiological, behavioral and hormonal changes. These changes are not specific to pain and might be related to other kinds of distress or agitation. Preterm infants are more sensitive to pain than full-term infants, and discrimination between touch and pain is difficult for them. Pain experienced as a preterm infant affects the developing brain and might cause alterations in cognitive development, later pain perception, the hormone system and in brain structure. Nurses should have appropriate knowledge of pain in preterm infants so that the negative consequences of pain could be minimized. A suggestion for future research could be examining the connection between premature infants' pain-related stress exposure and cognitive and motor functioning at school age as well as whether the child's gender has an impact on the long-term consequences of pain experienced as a premature infant.

Keywords (subjects)

preterm infant, prematurely born infant, pain reaction, consequence of pain, literature review

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Tiivistelmä

Noin kuusi prosenttia kaikista vastasyntyneistä Suomessa syntyy keskosina. Keskosia hoidetaan vastasyntyneiden teho-osastolla, jossa he kokevat päivittäin monia kivuliaita toimenpiteitä. Keskoslasten kipua huomioidaan edelleen riittämättömästi, jonka vuoksi kipureaktiot tulisi tunnistaa ja huomioida terveydenhuollon ammattilaisten toimesta. Verrattuna täysiaikaisina syntyneisiin lapsiin, keskoset kärsivät todennäköisemmin kehityksellisistä viiveistä ja vammoista.

Opinnäytetyön tavoitteena oli selvittää miten keskoset reagoivat kipuun ja mitä seurauksia keskosena koetulla kivulla voi olla lapsen myöhemmässä elämässä. Työn tarkoituksena oli koota päivitettyä tietoa terveydenhuollon ammattilaisille sekä opiskelijoille kirjallisuuskatsauksen muodossa, jotta he voisivat kehittää ammatillista osaamistaan vastasyntyneiden hoitotyössä sekä keskoslapsen kivun hoidossa.

Aineistoa kerättiin useasta artikkelitietokannasta mukaan lukien Academic Search Elite, Cinahl, Cochrane Library, Elsevier Science Direct ja PubMed. Kaikkiaan viisitoista artikkelia valittiin katsaukseen. Analyysimenetelmänä käytettiin teemoittelua.

Keskonen reagoi kipuun erilaisin fysiologisin, käytöksellisin sekä hormonaalisin muutoksin. Muutokset eivät ole kivulle spesifejä, ne saattavat liittyä myös muuhun ahdinkoon tai epämukavuuteen. Keskoset ovat herkempiä kivulle kuin täysiaikaset vastasyntyneet ja kosketuksen ja kivun toisistaan erottaminen on heille hankalaa. Keskosena koettu kipu vaikuttaa kehittyviin aivoihin ja saattaa aiheuttaa muutoksia kognitiivisessa kehityksessä, myöhemmässä kipukäsityksessä, hormonitoiminnassa sekä aivojen rakenteessa. Hoitajilla tulisi olla asianmukainen tieto keskosen kivusta jotta kivun negatiiviset seuraukset voitaisiin minimoida. Jatkotutkimusehdotuksina on tarkempi tutkimus liittyen keskosena koettuun kipuun suhteessa kognitiivisiin ja motorisiin toimintoihin kouluiässä, sekä lapsen sukupuolen mahdollinen vaikutus keskosena koetun kivun pitkäaikaisiin seurauksiin.

Avainsanat (asiasanat)

keskonen, keskoslapsi, kipureaktio, kivun seuraus, kirjallisuuskatsaus

Muut tiedot

Contents

1 Introduction **3**
2 Prematurely born infant **4**
2.1 Defining prematurely born infant 4
2.2 Prematurely born infants' care environment 5
3 Pain and neonatal pain **8**
3.1 Definition and physiology of pain 8
3.2 Neonatal pain 10
3.3 Physiology of neonatal pain 11
3.4 Pain reactions of neonates 12
3.5 Assessment of neonatal pain 14
4 Aim and purpose and research questions **17**
5 Methods and implementation of the thesis **17**
5.1 Qualitative research and literature review 17
5.2 Literature search 19
6 Data analysis **22**
7 Results **24**
7.1 Premature infants' reactions to pain 24
Physiological reactions 25
Behavioral reactions 26
Touch and pain discrimination 26
7.2 Consequences of pain experienced as a prematurely born infant 27
Cognitive consequences 27
Later pain perception 28
Physiological consequences 29
8 Discussion **31**
8.1 Ethical considerations, validity and reliability 31
8.2 Discussion of the results and suggestions for future studies 34
References **41**

Tables

Table 1. The comparison between the environments in womb and NICU (Korhonen 1999, 61) 7
Table 2. Most commonly used multidimensional pain assessment tools in newborns (Walden 2013, 573) 16
Table 3. Inclusion criteria 20
Table 4. Data search 21

Figures

Figure 1. Process of data analysis 23
Figure 2. The themes and subcategories of the results 24

Appendices

Appendix 1. 47

1 Introduction

Out of all births, the incidence of preterm birth (before 37th gestational week) is around 6% in Finland. (Fellman & Luukkainen 2016) Out of approximately 55 000 newborn each year, around 500 (<1%) are born with very low birth weight (<1500 grams). (Ennakkotieto: Perinataalitilasto – synnyttäjät, synnytykset ja vastasyntyneet 2015)

The clinical interest towards pain experienced by preterm and full-term infants did not exist until 1980's but has been increasing rapidly since. Clinicians and nurses should have the information of the pain experienced during early infancy due to the fact that preterm infants spend long periods of time receiving care at the neonatal intensive care unit (NICU) and undergoing a variety of painful procedures. According to one research NICU patients go through approximately 14 painful procedures per day (ranging from 0 to 53). (Vanhatalo 2009; Hamunen 2009, 446.) Badr, Abdallah, Hawari, Sidani, Kassar, Nakad, Braidi (2010, 129) state that exposure to pain in early life may cause even alterations in brain development and indicate severe difficulties in cognition in later childhood.

Despite growing scientific evidence, there still is a clear lack of unequivocal knowledge and researches concerning pain mechanisms in early infancy. (Vanhatalo 2009) The aim of this literature review is to determine how premature born infants react to pain, and what kind of consequences this pain might have later in life. The purpose of this study is to conduct a literature review and collect up-to-date information for health care professionals and students in order for them to develop their professional expertise in neonatal nursing and pain management in preterm infants.

2 Prematurely born infant

2.1 Defining prematurely born infant

Archiater Arvo Ylppö defined prematurity of newborn infant as "a child who weighs less than 2500g at birth" in 1921. His definition was later approved by World Health Organization. (Oivallus 09/05: Hengenpelastajamääritelmä 2005) According to another international definition, which was established later on, a newborn is premature if he/she is born before 37th gestational week. (Jumpponen 2006, 8.) Prematurely born infants are roughly categorized according to their birthweight. Infants weighing less than 1500g and/or born before 32nd gestational week are called very low birth weight infants (VLBW). Furthermore, if a child's birthweight is less than 1000g, he/she is considered as extremely low birth weight infant. (Halimaa 2001, 17.)

In Finland, nearly 6% of the neonates are born before 37th gestational week from which approximately 1,5% are born with very low birth weight. During the last decades mortality of VLBW infants has decreased while the neurological prognosis has improved. However, approximately 20% of the extremely low birthweight infants (<1000g) are diagnosed with severe neurological disability and at school-age suffer from learning difficulties. Most of the infants with very low birth weight (<1500g) live normal life as adults although they might have had deficits while developing their independency. (Mikkola, Tommiska, Hovi & Kajantie 2009.)

Prematurely born infants differ from full-term newborn in various ways other than the birthweight. Their appearance is different, fat layer under subcutaneous tissue is nearly nonexistent, the skin is covered by thin hair called lanugo and the skin is thin and translucent. Also internal organs are undeveloped, which causes them to be vulnerable for infections. Prematurely born infants are unable to maintain the balance in body temperature, which affects respiration and oxygen demand. (Jumpponen 2006, 8; Korhonen 1996, 24.)

From the child's point of view, being born prematurely is a risk factor affecting his/her whole life. (Korhonen 1999, 14) Infants born prematurely are in greater risk at suffering from developmental delays and disabilities. (Butler & Als 2008, 1173)

2.2 Prematurely born infants' care environment

Prematurely born infants are typically treated in a stress-filled acute environment called Neonatal Intensive Care Unit. (Jepsen & Martin 2006, 2) Neonatal Intensive Care Unit (NICU) as a technical care environment causes stress to the prematurely born infant as well as to the parents. Technical caring and follow-up devices emphasize the child's fragility and dependence of the technical equipment. Preterm infants confront various stressful stimuli including noxious sounds, bright lights, painful procedures and non-nurturing handling. In addition, bathing weighing and changing of diapers are considered as stressful events to the infant. Obviously stressful procedures and events should be minimized as much as possible. (Korhonen 1996, 44; Korhonen 2006, 26; Walden 2013, 722.)

Immaturity and neurological difficulties decrease the prematurely born infant's and unhealthy newborn's ability to separate environmental stimuli. The sound environment of the neonatal intensive care unit causes stress to the prematurely born infant due to the sudden changes of sound level. Continuous lighting is untypical compared to the maturity of sense system of the child. In addition, uninterrupted sleep is prohibited by the lack of circadian rhythm and different care procedures. The environment of NICU differs greatly from the environment of womb which appears particularly in child's ability to rest and therefore has an effect on general condition of the child. (Korhonen 1999, 60-61.)

Prematurely born infants are exposed to variations in temperature, touch, light, sound, olfaction, oxygen and nutrients which are completely different that the infants have experienced in the womb. The developing brain of prematurely born infant is extremely sensitive to stimuli and it is essential that background stimuli is kept at appropriate level. (Altimier & White 2013, 724-725.) Intrauterine environment and NICU environment differ greatly from each other. As a presented in the following table (Table 1) and according to Rodriguez and Pattini (2016, 361), while womb offers maternal protection, ongoing nutrition, stable temperature and circadian rhythm, NICU environment is characterized by inappropriate, unconditional and painful stimuli at a time of great functional and structural brain development.

Table 1. The comparison between the environments in womb and NICU (Korhonen 1999, 61)

Womb	**NICU**
Support of the womb in maintaining balance All-encompassing support and resistance to movements by the womb	Moro reflex and sensation of losing balance and due to flat platform
Fluctuation between rest and action depending on mother's lifestyle	Repetitive handling and painful local stimuli
Homeothermic liquid environment	Changes in temperature
Mother's voice present all the time	Sound environment differing from mother's voice, typically with sudden changes
Slight light or total darkness	Continuous lighting, the lack of circadian rhythm

3 Pain and neonatal pain

3.1 Definition and physiology of pain

International Association for the Study of pain (IASP) defines pain as following: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". (IASP Taxonomy 2012) In the nursing field another common definition of pain also exists, which was discovered by an American registered nurse Margo McCaffery in 1968. According to it: "Pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does. " (McCaffery & Beebe 1994, 15.)

Characteristics of pain are multidimensional. Although individual is unable to express the pain verbally does not exclude the fact he/she could not experience it or need pain-relieving methods. Pain is not only a physiological phenomenon but also an emotional and sensory experience. Tissue damage is not needed in order to experience and sense pain. Sensation of pain is always individual; people experience the intensity of pain differently. (Salanterä, Hagelberg, Kauppila & Närhi 2006, 7.)

Pain can be classified in various ways. According to most common classification pain can be categorized either acute or chronic, or in other words fast or slow. If the pain is considered to be fast it is typically described as sharp or pricking and is not felt in the deeper tissues of the body. The sensation of pain

occurs rapidly in less than 0.1 seconds due to pain impulse propagate via medium diameter, myelinated A-delta fibers whereas in slow pain, the pain impulse conducts via small-diameter, unmyelinated C fibers and the pain sensation occurs in a second or more after the stimulus and increases gradually. As stated in one definition, pain becomes chronic when its duration exceeds the usual healing time of tissues. Slow pain is typically described as burning, aching or throbbing and may even be excruciating. In addition to occurring in the skin level, slow pain can also occur in internal organs or in deeper tissues of the body. In human body the receptors of pain are called nociceptors (noci- stands for harmful) and they can be found in every other tissue of the body except the brain. Nociceptors are activated by different exquisite stimuli, which can be further classified as either thermal, mechanical or chemical. When trauma or tissue damage occurs, nociceptors are stimulated by the release of prostaglandins, kinins and K+ (potassium) ions. Due to the poor adaptation by nociceptors the sensation of pain may continue to linger on even if the stimulus causing pain is removed. (Vainio 2009, 150, 155-157; Tortora & Grabowski 2003, 504.)

Kalso & Kontinen (2009, 76-77) state that the chain of events causing the sensation of pain can be roughly divided in four different phase; transduction, transmission, modulation and perception. The chain of events starts when a stimulus is targeted into pain-sensing. Pain signal takes place in the nociceptors, primary afferents, nerve endings which are activated by either a mechanical, chemical or thermal stimulus which leads to arise of action potentials, in other words, the electrochemical activation of the nociceptor. Transmission also takes place in the primary afferents. In transmission phase, the pain signal conducts via nerve cells into those parts of the central nervous system whose activation leads to the perception of pain. Peripheral sensory nerves

transmit the pain impulses from the peripheral tissue to its nerve endings located in the spinal cord, which activates the network of projection neurons. The signal of pain is then transmitted onwards from spinal cord to brainstem and thalamus and furthermore to cerebral cortex.

Modulation stands for the modulation of the pain in the nervous system. Inhibitory tracts exist in central nervous system whose task is to prevent the action of pain transmitting nerve cells in the spinal cord. However, the central modulation may also increase the sensation of pain. Modulation may take place in each level of the conduction system is the reason behind the relationship between the injury and the perception of pain being unpredictable and nonlinear. The last phase, perception, stands for the subjective sensation following the activation of the neurons which transmit the sensation of pain. The activation of central nervous system, more specifically thalamus, leads to sensation of pain. (Serpell 2011, 9.; Kalso & Kontinen 2009, 76-77.)

3.2 Neonatal pain

Pain is always an individual experience applying also to children. The intensity and quality of child's pain can be evaluated only indirectly expressed by the child itself or interpreted by the caregiver based on the child's physiological or behavioral changes. Age, gender, cognitive and linguistic development, previous experiences regarding pain, learning and temper have an effect on child's pain experience and its expression. In addition, environment, separation from the parents and child's comprehension may have an impact on the pain experience. (Hamunen 2009, 442.)

Acute pain and its subjective experience, measuring the pain and the developmental effects of pain experience are the three main themes in the treatment and studies of neonatal pain. Particularly challenging part is to separate the subjective experience of pain (significant in adults' pain) from the development effects of pain (significant in neonates' pain). It is important to treat neonatal pain due to the multiple care and examination procedures which could be classified as extremely painful in adults. (Vanhatalo 2009, 436.) Even healthy neonates undergo different painful procedures for instance blood sampling or circumcision. Sick neonates are exposed to repetitive painful procedures during their stay in NICU such as continuous injections for blood samples, suctioning of the airways and catheterization. According to one research NICU patients go through approximately 14 procedures per day (range 0-53). (Hamunen 2009, 446.)

3.3 Physiology of neonatal pain

Nervous system evolves rapidly during infancy. During that time sensitivity to repeated experiences is developed and nervous system learns to perceive and respond to them. This kind of shaping the central nervous system by experience is referred to as *plasticity*. Based on previous evidence and researches, early experience of pain may boost pain pathways and produce structural and functional reorganization of developing nociceptive pathways thus possibly act as a cause to long-term modulation in processing of pain in both infancy and adulthood. (Bentley 2013, 32-33.)

Conduction of pain signal from peripheral nerves to central nervous system requires functional flow of information within anatomically developed pain regulation system. Sensing of pain occurs in the peripheral nerves, which start to develop already on the seventh gestational week around the fetus' mouth. By the 11th gestational week nerves have spread to the facial area, palms and soles and by the 20th gestational week, the outer layer of the fetus's skin and mucosa are throughout sensing. Incomplete myelination slows down the pain signal at some extent, however the anatomical distances in newborn are short and therefore the impulse conducts from the peripheral nerves to the brain as fast as in adults. (Halimaa 2001, 25.) Neural pathways from the spinal cord to the brain develop during 20-24 gestational weeks. However, descending neural pathways from brain to the spinal cord develop after the child has been born. As a result, neonates experience peripheral stimuli more powerful because the nerve system is not mature enough to soften the stimuli. (Korhonen 1996, 181; Haapio, Reen & Salonen 2000, 150.)

3.4 Pain reactions of neonates

Although a neonate is unable to verbalize the feeling of pain, they express it through physiological, hormonal and behavioral changes. (Haapio et al. 2000, 151) Presumption should be that even if the infant is not showing any behavioral or physiological signs of pain, it still exists in every situation where it is usual for adult or older child to feel pain. (Walden 2013, 571) The pain threshold of neonates is lower than older children's. Acute pain causes a response to stress which may have even life threatening consequences such as bleeding

caused by increase in intracranial pressure. Continuous painful stimuli might cause central sensitization and change the plasticity of central nervous system. Due to these processes functional and structural changes in developing central nervous system are possible. (Hamunen 2009, 446.)

Understanding the pain reactions and reacting to them depends on the knowledge, experience and attitudes of the receiver. It is essential to recognize pain reactions and the factors affecting the level of pain in order to treat neonatal pain appropriately despite the environmental circumstances. In addition, health care professionals should foresee and evaluate the necessity of painful procedures: are they really necessary, or just considered as routine procedures. Chronic pain experienced during infancy is a risk factor not just in infant's childhood (sleeping problems), but also in adulthood (attention and learning disorders, later pain perception and chronic pain syndromes). It is immoral for neonatal clinicians and other health care professionals not to assess, prevent and manage neonate's pain, for it is considered to be a traumatic experience in child's life. (Haapio et al. 2000, 151-153; Coughlin 2014, 103-107.)

Physiological changes caused by pain are objectively observable and specific. However, in neonates they are not necessarily specific for pain, also other factors might have an impact. Increase in heart rate and breathing frequency and decrease on pulse oximetry are examples of physiological changes as a reaction to pain. Infant may also be passive with decreases in heart and respiratory rates and oxygen consumption. All pain launches stress response, despite the fact that all stress may not be pain. Stress causes concentration of hormones, such as growth hormone, glucagon, cortisol, adrenalin and noradrenalin, to rise in blood. However, the secretion of insulin decreases, which leads

to prolonged periods of hyperglycemia. (Haapio et al. 2000, 151-153; Coughlin 2014, 103-107.)

As a behavioral reactions pain causes the neonate to cry, produce facial expressions and movements. Facial expressions are the first indicator of pain and the reaction should be recognized before the infant even starts to cry. It has been shown that crying as a response to pain is more high-pitched and powerful and a rhythm that differs from normal crying. Crying of a neonate who is under extreme pain is difficult to control or uncontrollable. The level of consciousness might decrease and the infant might suddenly be in shock. Newborn infant reacts to pain by squirming, stiffening the body and withdrawing limbs. When experiencing extreme pain, neonates strive to stay still and protect themselves with immobility and unnatural position. (Haapio et al. 2000, 151-153.)

3.5 Assessment of neonatal pain

Pain in adults is defined as an emotionally unpleasant experience. This definition regarding pain assessment cannot be used in neonates due to their inability to verbally express it. (Vanhatalo 2009, 440.) Haapio et al. (2000, 151-153) claim that the assessment of neonatal pain is based only on observation. As presented in the following table (Table 2), several indirect assessment tools have been developed combining varieties of physiological parameters, hormone levels and behavioral changes. The most common pain assessment scales are NIPS (Neonatal Infant Pain Scale) and PIPP (Premature Infant Pain

Profile). The Neonatal Infant Pain Scale (NIPS) has been developed to assess acute pain by observing facial expressions, crying, breathing, hand and leg movements and sleep-awake rhythm. It can be used before, during and after procedures. The Premature Infant Pain Profile (PIPP) is an assessment tool that has been developed particularly for assessing pain in preterm infants. It evaluates pain according to physiological changes (heart rate and pulse oximetry) and behavioral changes (facial expressions). This assessment tool also takes into account the age and clinical condition on the infant, which have a remarkable effect on the infant's pain reactions. (Halimaa 2001, 31-32.)

Observation of facial expressions such as crying, frowning, the gap between upper lip and nose, is considered almost as effective assessment method as usage of some pain scale in clinical work. The effectiveness of pain management should be assessed repeatedly both during procedures and without any external stimuli. (Fellman & Luukkainen 2010, 129.) The common and unresolved issue for all the assessment tools is that by using them it is impossible to separate the painfulness of a certain stimuli from the other stress reactions that the stimuli causes. (Vanhatalo 2009, 440)

Table 2. Most commonly used multidimensional pain assessment tools in newborns (Walden 2013, 573)

Pain instrument	**Population**	**Indicators**	**Forms of validity**	**Reliability data**
Premature Infant Pain Profile (PIPP)	Preterm and term neonates	Gestational Age Behavioral State Heart Rate Oxygen Saturation Brow Bulge Eye Squeeze Nasolabial Furrow	**Face** Content Construct	Inter- and intrarater reliability greater than 0.93
CRIES: Neonatal Postoperative Pain Assessment Score	Neonates from 32-60 weeks	Crying Requires oxygen to maintain saturation 95% Increased blood pressure and heart rate Expression Sleep state	Face Content Discriminant Concurrent	Interrater reliability greater than 0.72
Neonatal Infant Pain Scale (NIPS)	Preterm and term neonates	Facial expression Cry Breathing patterns Arm Movement Leg movement State of arousal	Face Construct Concurrent validity	Interrater reliability greater than 0.92
Neonatal Pain Agitation and Sedation Scale (N-PASS)	Preterm and term neonates	Crying/irritability Behavior/state Facial expression Extremities/tone Vital signs	Concurrent Discriminate	Interrater reliability greater than 0.90

4 Aim and purpose and research questions

The aim of this thesis is to determine how prematurely born infants react to pain, and what kind of consequences this pain might have later in life. The purpose of the study is to conduct a literature review and collect up-to-date information for health care professionals and students in order for them to develop their professional expertise in neonatal nursing and pain management in preterm infants.

Research questions:

- How prematurely born infants react to pain?
- What kind of consequences this pain might have in later life?

5 Methods and implementation of the thesis

5.1 Qualitative research and literature review

Qualitative research aims to a profound understanding of a phenomenon without statistical or other quantitative methods. It is based on words and sentences, whereas quantitative research utilizes numbers as a base for the research. Unlike quantitative research, qualitative research does not strive to generalization. (Kananen 2014, 18.)

Literature review is one type of qualitative research. It is based on previous studies and researches related to one specific topic. By gathering the previous researches it is possible to get a general view of how much research based

knowledge related to the topic exists and what are the main contents and research methods of the studies that have been made previously. (Johansson 2007, 3) Phases of literature review are research plan, data search, data analysis and reporting of the results. (Johansson 2007, 5.) This research was conducted as literature review due to the fact that qualitative research enables the comprehensive understanding of the phenomenon. Although the phenomenon of pain experienced by premature infants is not totally unknown, the researchers wanted to gather up-to-date information for health care professionals in order for them to have clear insight on the subject. (Kananen 2014, 71)

Literature review focuses on precisely defined and selected researches. Only studies that are relevant and meet the purpose of the research are included. In literature review all the phases are accurately defined and documented in order to enable the repeatability and minimize the errors. (Johansson 2007, 5)

The first phase of a literature review is to define the need for the review, examine the previous studies about the topic and make a research plan. Research plan includes one to three clearly defined research questions. (Johansson 2007, 6.) The research questions are the basis of the process and they enable the writer to focus on the literature which is required in order to answer the questions in the most appropriate way. (Aveyard 2010, 24) This literature review had two research questions which aim to find out how prematurely born infants react to pain and what are the possible consequences of pain experienced as a prematurely born infant in later life.

After defining the research questions, a searching strategy is done. It includes defining the search terms and choosing the databases that are used in the lit-

erature search. The aim of the searching strategy is to identify all the researches that are relevant for the literature review. Literature search is a critical phase when considering the successfulness of the literature review; errors in this phase lead to misleading results and give a false view of the existing studies. (Pudas-Tähkä & Axelin 2007, 49.) Furthermore, the writer must define specific inclusion and exclusion criteria which can be targeted at participants, intervention, outcomes or the design of the study. Clear inclusion and exclusion criteria enable the writer to find the relevant researches which address the research questions. (Johansson 2007, 6; Aveyard 2010, 70-71.)

5.2 Literature search

Literature search can produce hundreds, even thousands of results many of which are irrelevant for the review. However, all of the references produced by the search have to be processed. Literature search process should be done by at least two researchers in order to reduce errors. (Pudas-Tähkä & Axelin 2007, 51.) In this literature review, after defining the research questions, search terms and inclusion and exclusion criteria, the literature search was conducted in April 2016. First the results were processed based on the titles, abstracts and predetermined criteria. Table 3 demonstrates the inclusion criteria for this literature review. From the passed articles the full texts were read and therefore the final articles which answer the research questions and fulfill the inclusion criteria were chosen for this study. In the last phase of the literature review the results are analyzed and the conclusion is made. (Johansson 2007, 7.)

Table 3. Inclusion criteria

Inclusion criteria:

- Free full text access
- Scientific publication
- Research in English or Finnish
- Published between 2000-2016
- Answers the research questions

In this literature review the data was searched from following databases: Academic Search Elite (EBSCO), Cinahl, Cochrane Library, Elsevier ScienceDirect and PubMed. Chosen search terms were Premature infant AND Pain and Preterm infant AND Pain. Also additional search was done by using search terms Premature infant AND Pain AND Consequences in order to find studies that would answer more properly to the second research question, however the search did not produce results. Answers to the second research question about the consequences of pain were found from the chosen articles by using the original determined search terms. The data search is demonstrated in the following table (Table 4).

Table 4. Data search

Database	**Search terms**	**Results**	**Chosen based on the title**	**Chosen based on the abstract**	**Chosen based on full text**	**Relevant studies**
Academic Search Elite	Premature infant AND pain	104	63	24	9	5
Academic Search Elite	Preterm infant AND pain	97	61	22	7	0
Cinahl	Premature infant AND pain	58	31	17	7	1
Cinahl	Preterm infant AND pain	18	16	10	3	0
Cochrane Library	Premature infant AND pain	10	7	0	0	0
Cochrane Library	Preterm infant AND pain	31	6	0	0	0
Elsevier ScienceDirect	Premature infant AND pain	188	6	2	1	1
Elsevier ScienceDirect	Preterm infant AND pain	152	11	3	2	1
PubMed	Premature infant AND pain	180	127	30	9	6
PubMed	Preterm infant AND pain	215	152	32	10	1

Based on the inclusion criteria the data search was conducted and 1053 results were found. The literature search conducted duplicates, which were removed from the chosen articles. Overall 15 articles were chosen and listed based on their publishing year. (Appendix 1)

6 Data analysis

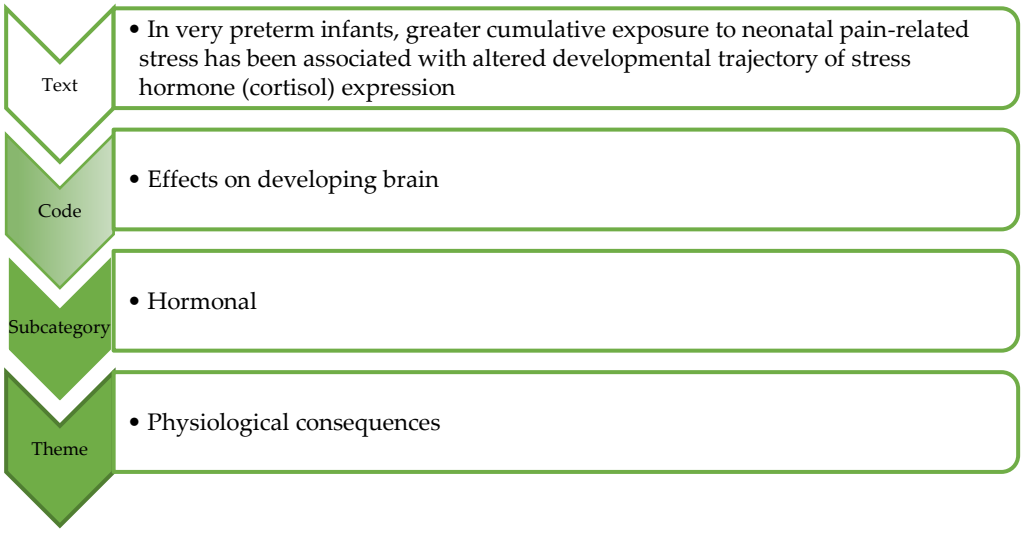
Content analysis is a basic analysis method which can be used in all qualitative researches. (Tuomi & Sarajärvi 2009,91) Through data analysis, the literature can be analyzed systematically and objectively. The purpose of data analysis is to summarize the findings and therefore produce results that are more substantive than the results from each individual research. (Tuomi & Sarajärvi 2009, 103; Aveyard 2010, 124.) Content analysis can be either inductive or deductive. Inductive content analysis is based on the data from the data search and the categories are reliant on the data and the research questions. The basis of a deductive content analysis is a theoretical concept or concepts which are now examined from a practical point of view. Analysis frame and the data classification are predetermined based on the previous knowledge and research. (Kankkunen & Vehviläinen-Julkunen 2009, 135.)

In this literature review inductive analysis was chosen for the analysis method due to the unpredictability of the results. Inductive content analysis is considered to be a three-phase-process; 1) reduction of the data 2) clustering of the data and 3) abstraction of the data. In the reduction of the data, the researcher

finds and highlights expressions which answer the research questions. When clustering the data, similarities and differences are searched from the coded expressions. Concepts that mean the same thing are classified as a subcategory and therefore themes and main categories. In the abstraction phase of the content analysis the relevant knowledge is separated and based on the chosen knowledge, theoretical concepts are formed. The researcher proceeds from original expressions to theoretical concepts and conclusion. Abstraction is continued by synthesizing categories as long as the content of the data allows. (Tuomi & Sarajärvi 2009, 108-111.)

In inductive content analysis concepts and categories are combined and therefore the answer to the research questions is found. Empiric data is connected to theoretical concepts and the concepts, themes and categories are presented in the results. (Tuomi & Sarajärvi 2009, 112-113.) Data analysis process is presented in Figure 1.

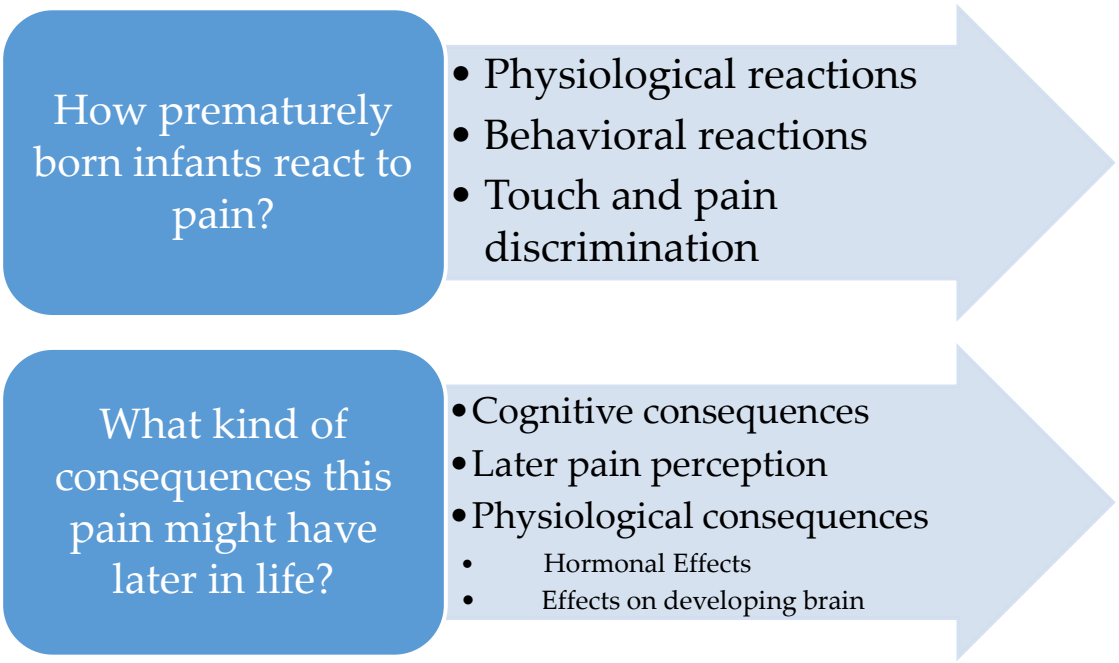
Figure 1. Process of data analysis



7 Results

The themes and subcategories of the results are presented in figure 2. Themes include physiological reactions, behavioral reactions, touch and pain discrimination, cognitive consequences, later pain perception and physiological consequences. The results are presented more closely in the text.

Figure 2. The themes and subcategories of the results



7.1 Premature infants' reactions to pain

Procedural pain in the NICU (neonatal intensive care unit) causes multiple physiological, behavioral and hormonal changes to infants born prematurely while their brain is immature and rapidly developing. (Grunau, Whitfield, Petrie-Thomas, Synnes, Cepeda, Keidar, Rogers, MacKay, Hubber-Richard & Johannesen 2009 138) The ability to express pain in preterm infants is limited.

(Korhonen, Haho & Pölkki 2013, 800) Various responses indicate pain, such as changes in facial expressions, body movements, cry, heart rate, respiratory rate, blood pressure and oxygen saturation. However, these changes are not specific only to pain, they can also be related to distress and/or agitation. (Vinall & Grunau 2014, 584.)

Premature infants react to pain differently and are more sensitive towards pain than full-term infants due to their immaturity in the developing brain. (Pölkki, Korhonen, Laukkala, Saarela, Vehviläinen-Julkunen & Pietilä 2010, 49; Donia & Tolba 2016, 77-78; Doesburg, Chau, Cheung, Moiseev, Ribary, Herdman, Miller, Cepeda, Synnes & Grunau 2013, 1946-1952.) In addition, even the day-to-day noninvasive nursing procedures are more stressful to prematurely born infants than to more maturely born infants. (Grunau, Weinberg & Whitfield 2004, 81) However, a study made by Grunau, Tu, Whitfield, Oberlander, Weinberg, Yu, Thiessen, Gosse & Scheifele (2010, 698) states that pain reactions indexed by behavior and heart rate do not seem to differ when comparing preterm and full-term infants.

Physiological reactions

Physiological reactions to pain in prematurely born infants might include decreased oxygen saturation, lower partial pressure of oxygen, increased heart rate and heart rate variability, rapid variations in intracranial pressure and increased levels of plasma cortisol, aldosterone, growth hormone, catecholamines and glucagon. (Hatfield 2014, 484) However, there are no specific physiological indicators that suggest the presence of pain in premature infants. In

fact, the reactions may be hardly noticeable or completely absent. (Pölkki et al. 2010, 49-50, 53.) According to Donia & Tolba (2016, 76) the physiological reaction to pain is greater after the procedure than during it. A few studies showed that prior pain exposure might contribute to the physiological responses by exaggerating them. (Grunau et al. 2004, 81; Donia & Tolba 2016, 79)

Behavioral reactions

Behavioral reactions to pain in neonatal pain assessment consist of facial actions, body movements and cry. (Vinall & Grunau 2014, 585) Preterm infants have an immature capability to express emotions, which is why it is difficult to perceive and confirm pain in preterm infants. (Korhonen et al. 2013, 798) In order to gather essential information about pain, the behavioral changes should be combined with the physiological changes and other situational factors. (Korhonen et al. 2013, 800)

Touch and pain discrimination

Due to their immature somatosensory system, discrimination between non-noxious and noxious stimuli is difficult in very preterm infants. In infants less than 35 gestational weeks the response to non-noxious and noxious stimuli is similar. (Ranger & Grunau 2014, 60; Fabrizi, Slater, Worley, Meek, Boyd, Olhede & Fitzgerald 2011, 1554.)

7.2 Consequences of pain experienced as a prematurely born infant

Cognitive consequences

Doesburg, Chau, Cheung, Moiseev, Ribary, Herdman, Miller, Cepesa, Synnes & Grunau (2013, 1953) state that neonatal pain-related stress may have an effect on the cortical oscillatory activity which has an important role in the cognition and perception generation. According to many researches (Grunau et al. 2009, 139; Ranger & Grunau 2014, 61; Grunauet al. 2004, 77) repeated and prolonged pain exposure is associated with altered development of cognition and learning in later childhood.

Children that have been born very prematurely, have a poorer cognition, more behavioral problems, poorer executive functions and a lower academic success compared to children born full-term. (Brummelte, Grunau, Chau, Poskitt, Brant, Vinall, Gover, Synnes & Miller 2012, 386) Even though infants born extremely preterm display broadly normal intelligence during childhood, they are at risk of having learning and behavioral disabilities at school age, such as getting distracted more easily, needing constant encouragement and being unable to complete unfamiliar tasks. In addition, they wanted to give up and terminate the tasks more easily. The difficulties in problem solving, poorer attention and self-regulation were associated especially with more cognitively challenging tasks. (Grunau et al. 2004, 77.) In one study, although

the neonatal pain exposure and cognitive outcomes had a clear relation, the researches took into account whether the relationship might be due to other neonatal factors. (Grunau et al. 2009, 143)

Later pain perception

Repeated and prolonged pain exposure during the vulnerable neonatal period modifies the infant's later pain processing, modulation and reactivity, long-term development, subsequent pain sensitivity and might contribute to the progression from acute to chronic pain. (Hatfield, 2014, 484) Long-term experiences of pain have negative effects on later pain behavior manifestation and pain sensations. (Korhonen et al. 2013, 800) The reason behind the long-term neurodevelopmental consequences and altered pain behavior in preterm infants is that the excess painful stimuli disrupts the normal formation of cortical circuits, which are essential for human brain to discriminate noxious from non-noxious stimuli. (Fabrizi et al. 2011, 1556) Brummelte et al. (2012, 390) state that a significantly larger neuronal activity as a response to a painful stimulus was observed in preterm infants compared to age-matched term infants. This might be an indicator of increased stimulation of vulnerable neurons. Therefore, pain-related overstimulation of the neurons may lead to neuronal damage and reduction of axonal connections in preterm infants which has an effect on later pain perception. Even though a human being may not preserve a conscious memory of an early painful experience, it is recorded elsewhere in the body. This supports the evidenced claims about early painful experiences having an effect on the infant development and pain perception later in life. (Page 2004, 15.)

Physiological consequences

Hormonal

Early exposure to procedural pain may cause long-term alterations in preterm infants' stress systems. (Grunau et al. 2004, 77) According to Ranger and Grunau (2014, 61) great exposure to neonatal pain-related stress is linked with modified developmental trajectory of cortisol (stress hormone) expression which has an effect on the hypothalamic-pituitary-adrenal (HPA) axis, the system behind cortisol production. While in the neonatal intensive care unit, prematurely born infants show significantly low basal and hair cortisol levels in response to pain-related stress, compared to full-term born infants. However, long after discharge, a shift in cortisol activity occurs and higher baseline cortisol levels can be predicted. The effects of procedural pain-related stress in the HPA axis during neonatal period in the NICU in children born prematurely persist to school age and might have an effect on the modulating immune function. (Brummelte et al. 2012, 391; Grunau et al. 2010, 703; Grunau et al. 2004, 80-81; Grunau, Cepeda, Chau, Brummelte, Weinberg, Lavoie, Ladd, Hirschfeld, Russell, Koren, Uum, Brant & Turvey 2013, 2, 5-6.)

Effects on brain structure

When considering the later consequences of pain experienced as a prematurely born infant, repeated and prolonged exposure to procedural pain or stress

is associated with long-term alterations to neuronal structure and function. (Brummelte et al. 2012; Ranger & Grunau 2014; Ranger, Chau, Garg, Woodward, Beg, Bjornson, Poskitt, Fitzpatrick, Synnes, Miller & Grunau 2013; Vinall & Grunau 2014; Hatfield 2014; Donia & Tolba 2016)

Ranger et al. (2013, 7) state that reduced brain size in the frontal and parietal regions in preterm neonates suggest significant exposure to stressful procedures in the NICU. Abnormalities in cortical thickness and reduction of cerebral white matter and subcortical gray matter are typical consequences of repeated pain-related stress in preterm infants on their developing and vulnerable brain. (Brummelte et al. 2012, 390; Donia & Tolba 2016, 79; Ranger & Grunau 2014, 59) Effects on white and gray matter are not limited only in infancy but may also be present during later childhood and adolescence. (Ranger & Grunau 2014, 59, 61) Greater neonatal pain-related stress may also be associated with lower cortical thickness at school age in children born very preterm. (Ranger et al. 2013, 6)

8 Discussion

8.1 Ethical considerations, validity and reliability

When conducting a research, the researcher's aim should be to produce valid and reliable knowledge in an ethical manner and the trustworthiness of the study should be measured. (Merriam 2009, 209-210; Tuomi & Sarajärvi 2002, 131) Trustworthiness, *rigour*, measures the quality of the research and stands for factors including credibility, confirmability, dependability, authencity and transferability. (Polit & Beck 2014, 72) Specific reporting of the implementation of the research is a great part of the trustworthiness of the study. Accurate reporting includes all phases of the study. (Tuomi & Sarajärvi 2002, 138.) Common issues where trustworthiness should be taken into account are data collection method, sampling strategy and the selection of a suitable unit of analysis. (Elo, Kääriäinen, Kanste, Pölkki, Utriainen & Kyngäs 2014, 2)

The trustworthiness of the research is usually measured with two concepts; validity and reliability. (Kananen 2015, 337) Reliability and validity can be measured through careful consideration to a study's conceptualization, the way the data is collected, analyzed, interpreted, and finally the way the results are presented. (Merriam 2009, 209-210.) Reliability, *dependability*, means that the research is persistent and repeatable. The study is reliable if the same result is achieved with a new sample. Validity, *creditability*, concerns the ability of the research method to measure what it is supposed to measure. The quality of evidence is another aspect of validity concerning dependent and independent variables and the relationship between them. For example, is a cer-

tain nursing intervention really the only cause for patient's condition's improvement or were there other confounding factors? Examination of the trustworthiness means that in different phases of the research process, right choices have been made and they are well justified. (Hirsjärvi, Remes & Sajavaara 2000, 213; Kananen 2015, 343; Polit & Beck 2014, 72.) The validity and reliability aspects are taken into consideration in this literature review. In order to increase research's trustworthiness for the reader, the titles, research methods and essential outcomes of the chosen researches were presented (Appendix 1). Other factor increasing research's trustworthiness was to choose as recent articles as possible and thus avoid bringing outdated information to the reader.

Ethical dilemmas of practical research include the choice of topic, treatment of the persons in the research group (informed consent) and demanding integrity → avoiding plagiation, thinking critically, and trustworthy reporting. (Tervakari 2005, 2) In this literature review, the factor confounding to the choice of topic was not just personal interest on the subject but also clear need for further research on pain in premature infants. According to ethical principle of integrity, the thoughts and writings of original authors in articles chosen to this research were not modified in any way to researchers' benefit in this literature review.

The data analysis process refers to a systematic organization and synthesis of research data. (Polit & Beck 2014, 378) In this literature review the data process was conducted by two independent researchers making it more trustworthy due to the fact that possibility of errors in data analysis reduces when it is done by at least two researchers. (Pudas-Tähkä & Axelin 2007, 51) In order to

repeat this literature review's data process, each step of it was documented thoroughly.

When conducting a literature review, it is preferable to use articles written also in other languages than English in order to avoid misconceptions. (Pudas-Tähkä & Axelin 2007, 53) In this research, only English written articles were used. Since this literature review is conducted in English, it was natural to choose key words in English as well. In addition, major part of the researches in the databases chosen for this literature review were written in English, and offered significantly more information than what would have been founded in our native language, Finnish. The chosen databases were PubMed, Cinahl, Academic Search Elite, Cochrane Library and Elsevier ScienceDirect. Multiple databases were chosen because after eliminating duplicates, each of those 5 databases had also some researches chosen for this literature review which others did not. Data search produced a few studies also in Chinese and Spanish, however they were excluded due to the inability to read and understand the articles. The reviewed studies were done in 5 different countries: Canada, USA, Finland, Egypt and Great Britain, giving insight from different areas all around the world, but also leaving major part uncovered. The researchers aimed to use as recent articles as possible, due to the fact that the specific medical field as a title for this literature review is rapidly developing with constant swifts and changes.

Most researches conducted in the field of nursing involve human subjects, which should be taken into consideration and researcher should develop procedures to ensure the fact that the research adheres to ethical principles. (Polit & Beck 2014, 51) Literature review is based on researches that already exist,

thus the presumption that the ethical principles are being followed already in the reviewed studies. This literature review is conducted by following good scientific practice which include honesty, meticulousness and accuracy in research process, recording and presenting results and in evaluation of the research and its results. (Finnish Advisory Board on Research Integrity 2012)

8.2 Discussion of the results and suggestions for future studies

Although every article chosen for this literature review offered information on pain experienced by premature infants, only few highlighted preterm pain reactions or the later consequences as the main theme of their study. This implicates the fact that this research topic is relatively new and not many studies have been made only from these points of view. The fact that really surprised the researchers while they were doing their background information research about neonatal pain, was the lack of textbooks on the subject written in their native language, Finnish. In fact, the last two proper Finnish textbooks specifically about premature infants in general and the care of premature infants were written in years 1996 and 1999. Another interesting fact was that while pediatric care textbooks focusing on childhood diseases were available in multiple editions in Finnish, only one textbook had neonatal pain as main theme and was written in year 2000. Still it seems that both neonatal pain and pain experienced by premature infants are not "trendy topics" deserving their own literature. Although several up-to-date textbooks from for example United States and Great Britain conducted in English were available and used as background information, the researchers wanted to include information on care provided specifically in Finland, due to the fact that it is the place where

this literature review is conducted. Thus, the reason why the researchers utilized 20-year old information as a reference for this research, is that newer textbooks on the subject were simply not available in their native language.

The researchers pondered the possible reason behind this extremely worrisome phenomenon: an obvious on-going lack of scientific interest considering the care of premature infants and the challenges involved in it. Why premature infants and their care is just a succinct subcategory in a care of pediatric and adolescent patients' textbook? Are a few pages of pain experienced by neonates and premature infants in a textbook about pain in general enough when we know that the premature infants who are being treated in NICU may experience up to 53 painful procedures every day? (Hamunen 2009, 446.)

Before the data analysis, only few sources of information about later consequences of neonatal pain was found from the literature used as this literature review's background knowledge. The researchers wondered what is the reason behind scientific lack of interest considering this topic? Is it perhaps still a taboo for society, and is it too difficult for health care professionals to admit their counterpart for underestimating premature infants' pain experiences with long-lasting consequences? The results of this research show that prolonged and repeated neonatal pain-related stress modulates the later pain perception, behavior and pain sensations. (Korhonen et al. 2013, 800) In addition it might have an effect on the progression of pain from acute to chronic pain. (Hatfield 2014, 484) Researchers found similar results while doing their background information search: Repetitive and chronic pain experiences in infancy increase the risk of health problems, disorders and deficits in both child- and adulthood. (Coughlin 2014, 103-107) In the Finnish references investigated for

background information, the focus was merely on the physiology of neonatal pain and not it's long-lasting consequences in infant's later life. This fact was surprising to the researchers.

Numerous articles stated that repeated and prolonged pain exposure is associated with altered development of cognitive abilities and learning in later childhood. (Grunau et al. 2009, 139; Ranger & Grunau 2014, 61; Grunau et al. 2004, 77) Furthermore, this might have an effect on the child's self-esteem and academic success. An interesting fact was that during childhood, prematurely born infants show normal intelligence, but in school age, they are at risk of having learning and behavioral difficulties. (Grunau et al. 2004, 77) One of the articles questioned the clear relation between pain-related stress experienced as a preterm infant and cognitive outcomes and pondered whether it is due to other neonatal factors. (Grunau et al. 2009, 143) The researchers feel that is important to take into account that prematurity itself can cause numerous problems regarding neurodevelopment and cognition and therefore the results might be the same without any consideration about pain.

Prematurely born infants react to pain by indicating physiological and behavioral changes. (Grunau et al. 2009, 138) Most of the changes were roughly the same as was described in the theoretical part when taking into account the characteristics of neonatal pain. Increase in heart rate and breathing frequency and decrease in pulse oximetry are common physiological changes as a reaction to pain. In addition, rise in hormonal levels such as cortisol, growth hormone and glucagon are a common physiological reaction to pain in preterm infants. (Hatfield 2014, 484) Researchers were surprised that they did not find information on infant's passivity and decreases in heart and respiratory rates

from the chosen articles as physiological reactions to pain, as these reactions were presented while looking up for background information on neonatal pain. (Coughlin 2014, 103-107)

Consequences on hormonal system and brain structure were studied carefully in some of the articles. Ranger & Grunau (2014, 16) state that there is an association between neonatal pain-related stress and cortisol expression, which affects the cortisol levels, and production. Six of the articles suggested that pain-related stress in preterm infants is associated with altered brain structure and function. Abnormalities in cortical thickness and reduction of cerebral white matter and subcortical grey matter were typical consequences of repeated pain-related stress in prematurely born infants. (Brummelte et al. 2012, 390; Donia & Tolba 2016, 79; Ranger & Grunau 2014, 59)

The difficulty in identifying pain reactions in preterm infants is that they can be related also to other distress the preterm infant is coping with and not only pain. (Pölkki et al. 2010, 49-50, 53) This might be one of the reasons why the assessment of preterm infants' pain continues to be a challenge for health care professionals. There are no specific signs whether the reactions are due to pain or for example environmental changes. Therefore, it is important that in addition to their own professional knowledge and experience, the health care professionals use different kinds of pain assessment scales in the care of prematurely born infants. On the researchers' opinion, it is not necessarily relevant for nurses to separate premature infants' pain reactions from other stress reactions such as those caused by environmental changes. The relevance lies on the management of pain or stress reaction and relieving the symptom regardless the cause behind it.

Another factor complicating the differentiation between pre- and full-term infants' reactions is that prematurely born infants can be more sensitive to pain and even normal routine non-painful procedures are more stressful for preterm than full-term infants. (Pölkki et al. 2010, 49; Donia & Tolba, 2016, 77-78; Doesburg et al. 2013, 1946-1952) Ranger & Grunau (2014, 60) and Fabrizi et al. (2011, 1554) emphasized in their study, that due to their immature nervous system, separating pain from normal touch is challenging for preterm infants. The researchers find this to be very important information when considering the care of preterm infants in neonatal intensive care unit. With the tiniest preterm infants, nurses might cause pain even by just touching them and therefore possible analgesia should be taken into account although the procedure itself does not necessarily cause pain. It is recommendable and justifiable to treat the infants by following the principle of "sparing care", meaning that nurses and other health care professionals should concentrate even the routine basic care with other possible procedures in order to give the infants the ability to rest without any stimuli as much as possible. The researchers were surprised by the lack of information on the principle of sparing care while they went through both background information and the articles chosen for this literature review. Information on sparing care can be found from many articles with pain management of premature infants as the main theme, but is absent from many articles considering premature infants' pain experiences.

The amount and the nature of possible later consequences came as a surprise to the researchers. It feels alarming, how much negative consequences pain can cause and researchers ponder how much of it could be avoided by proper management of neonatal pain in the NICU and pediatric ward environment.

Nurses have to be the voices, supporters and professionals taking the main responsibility of pain management during procedures for the premature infants, for they cannot express their emotions with words and thus form the most vulnerable group of patients. In addition, NICU surroundings do not always enable the presence of parents during painful procedures. An interesting point which came to the researchers' mind was whether the presence of parents have an effect on the recognition and management of the infant's pain? In case of the absence of parents, nurses are offering the parental support, protection and comfort for these infants. Researchers wonder whether it is too easy for health care professionals to think that because the premature infants/neonates cry just for a little while, they forget the whole thing soon after the procedure is done and the pain goes away. These infants may not have a clear memory about the pain in their minds, but roughly said, the pain lives on in their body memory.

The quality of medical and other care provided for these infants has developed with major steps during the last few decades, which is also the reason for their much improved life expectancy today. It is also known, that nurses have more and more ways and methods to alleviate these infants' suffering, both pharmacologically and non-pharmacologically. However, the more nurses are aware on the long-lasting consequences of pain on these infants, the more effort is put on trying to minimize those consequences by using pain relieving methods sufficiently. The more nurses know how to recognize premature infants' reactions to pain, the more they are able to reduce these infants' suffering.

Numerous articles chosen for this study pointed out that even though there were significant associations between neonatal pain and altered brain development later in childhood, many questions remain to be answered and more research is required to examine thoroughly and specifically how neonatal pain and stress exposure impacts neurodevelopment in immature infants. (Ranger & Grunau 2014, 64; Ranger et al. 2013, 10) In addition, according to the studies made, more research about the relation between pain-related stress exposure and cognitive and motor functioning at school age as well as sex differences concerning the long-term consequences should be made. (Ranger et al. 2013, 10; Grunau et al. 2009, 144)

As stated earlier, the researchers of this literature review also see a clear need for evidence-based textbooks with updated information, both in English but especially in Finnish, about premature infants and their care, premature infant's pain reactions and the importance of proper pain management in order to minimize these infants' suffering and the consequences of it in later life. This opinion is also supported by the results of this literature review: According to Brummelte et al. (2012, 361) comprehensive, up-to-date research about prematurely born infants' pain is needed in order to find effective ways to reduce pain in preterm infants and therefore avoid negative effects and consequences of it.

References

Altimier, L. & White, R. 2013. The Neonatal Intensive Care Unit (NICU) Environment. Comprehensive Neonatal Nursing. Ed. Kenner, C. & Lott, J. 5th Edition. Springer Publishing Company. Accessed 12.10.2016. https://janet.finna.fi, Ebrary.

Aveyard, H. 2010. Doing A Literature Review In Health And Social Care: A Practical Guide. Open University Press. Accessed 12.5.2016. https://janet.finna.fi/, Ebrary.

Badr, L., Abdallah, B., Hawari, M., Sidani, S., Kassar, M. Nakad, P. & Breidi, J. 2010. Determinants of Premature Infant Pain Responses to Heel Sticks. Pediatric Nursing May/Jun2010; 36(3): 129-137. Accessed 13.10.2016. https://janet.finna.fi

Bentley, J. 2013. Anatomy and Physiology of Pain. In Managing Pain in Children : A Clinical Guide for Nurses and Healthcare Professionals (2). Ed. Twycross, A., Dowden, S. & Stinson, J. Wiley-Blackwell. Accessed 11.10.2016. https://janet.finna.fi/, Ebrary.

Brummelte, S., Grunau, R.E., Chau, V., Poskitt, K.J., Brant, R., Vinall, J., Gover, A., Synnes, A. & Miller, S.P. 2012. Procedural pain and brain development in premature newborns. Ann Neurol. 71(3): 385-396. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Butler, S. & Als, H. 2008. Individualized developmental care improves the lives of infants born preterm. Acta Paediatrica. 97(9): 1173-1175. Accessed 15.5.2016. https://janet.finna.fi/, Academic Search Elite.

Coughlin, M. 2014. Prevention and Management of Pain and Stress. Transformative Nursing in the NICU: Trauma-Informed Age-Appropriate Care. Springer Publishing Company. Accessed 30.10.2016. https://janet.finna.fi, Ebrary.

Doesburg, S.M., Chau, C.M., Cheung, T.P.L., Moiseev, A., Ribary, U., Herdman, A.T., Miller, S.P., Cepeda, I.L., Synnes, A. & Grunau R.E. 2013. Neonatal

pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age. 154(10): 1946-1952. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Donia, A. & Tolba O. 2016. Effect of early procedural pain experience on subsequent pain responses among premature infants. Egyptian Pediatric Association Gazette. Accessed 29.4.2016. https://janet.finna.fi/, Elsevier ScienceDirect.

Elo, S., Kääriäinen, M., Kanste, O., Pölkki, T., Utriainen, K. & Kyngäs, H. 2014. Qualitative Content Analysis: A Focus on Trustworthiness. Sage Journals.

Fabrizi, L., Slater, R., Worley, A., Meek, J., Boyd, S., Olhede, S. & Fitzgerald, M. 2011. A Shift in Sensory Processing that Enables the Developing Human Brain to Discriminate Touch from Pain. Current biology. 21(18) :1552-1558. Accessed 29.4.2016. https://janet.finna.fi/, Elsevier ScienceDirect.

Fellman, V. & Luukkainen, P. 2010. Vastasyntyneen sairaudet. Lastentaudit. Ed. Rajantie, J., Mertsola, J. & Heikinheimo M. Helsinki: Kustannus Oy Duodecim.

Fellman, V. & Luukkainen, P. 2016. Vastasyntyneen sairaudet. Lastentaudit. Duodecim Oppiportti. Accessed 15.4.2016. https://janet.finna.fi/, Oppiportti.

Grunau, R.E., Cepeda, I.L., Chau, C.M.Y., Brummelte, S., Weinberg, J., Lavoie, P.M., Ladd, M., Hirschfeld, A.F., Russel, E., Koren, G., Van Uum, S., Brant, R. & Turvey, S.E. 2013. Neonatal Pain-Related Stress and NFKBIA Genotype Are Associated with Altered Cortisol Levels in Preterm Boys at School Age. PLoS ONE. 8(9): 1-10. Accessed 29.4.2016. https://janet.finna.fi/, Academic Search Elite.

Grunau, R.E., Thanh Tu, M., Whitfield, M.F., Oberlander, T.F., Weinberg, J., Yu, W., Thiessen, P., Gosse, G. & Scheifele, D. 2010. Cortisol, Behavior, and Heart Rate Reactivity to Immunization Pain at 4 months Corrected Age in Infants Born Very Preterm. The Clinical journal of pain. 26(8): 698-704. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Grunau, R.E., Whitfield, M.F., Petrie-Thomas, J., Synnes, A.R., Cepeda, I.L. Keidar, A., Rogers, M., MacKay, M., Hubber-Richard, P. & Johannesen, D. 2009. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain. 143(1-2): 138-146. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Grunau, R.E., Weinberg, J. & Whitfield, M.F. 2004. Neonatal Procedural Pain and Preterm Infant Cortisol Response to Novelty at 8 Months. Pediatrics. 114(1): 77-84. Accessed 29.4.2016. https://janet.finna.fi/, Academic Search Elite.

Haapio, M., Reen, E. & Salonen, A. 2000. Vastasyntyneen kivun hoito. Kivunhoito. Ed. Sailio E. & Vartti A-M. Tampere: Tammer-Paino Oy.

Halimaa, S-L. 2001. Hoidetaanko keskoslapsen kipua? Tutkimus hoitajien valmiuksista arvioida ja hoitaa keskoslapsen kipua. Doctoral thesis. The University of Eastern Finland. Kuopio: Yliopiston painatuskeskus.

Halimaa, S-L. 2003. Pain management in nursing procedures on premature babies. Accessed 27.4.2016. https://janet.finna.fi/, Cinahl.

Hamunen, K. 2009. Lasten kivun lääkehoito ja akuutti kipu. Kipu. Ed. Kalso, E., Haanpää, M. & Vainio, A. 3rd Edition. Helsinki: Kustannus Oy Duodecim.

Hatfield, L.A. 2014. Neonatal pain: What's age got to do with it? Surgical neurology international. 13;5(suppl 13): 479-89. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Hirsjärvi, S., Remes, P. & Sajavaara, P. 2000. Tutki ja kirjoita. Vantaa: Tummavuoren Kirjapaino Oy.

Johansson, K. 2007. Kirjallisuuskatsaukset - Huomio systemaattiseen kirjallisuuskatsaukseen. Systemaattinen kirjallisuuskatsaus ja sen tekeminen. Ed. Johansson, K., Axelin, A., Stolt, M. & Ääri, R-L. Turku: Digipaino.

Jumpponen, S. 2006. Keskosuuden määritelmät ja taustat. Kevyt pienokainen: tietoa keskosesta vanhemmille. Keskosvanhempien yhdistys Kevyt. Etelä-Savon kirjapaino Oy.

Kalso, E. & Kontinen, V. 2009. Kivun fysiologia ja mekanismit. Kipu. Ed. Kalso, E., Haanpää, M. & Vainio, A. 3rd Edition. Helsinki: Kustannus Oy Duodecim.

Kananen, J. 2014. Laadullinen tutkimus opinnäytetyönä. Miten kirjoitan kvalitatiivisen opinnäytetyön vaihe vaiheelta. Jyväskylän University of Applied Sciences.

Kankkunen, P. & Vehviläinen-Julkunen, K. 2009. Tutkimus hoitotieteessä. Helsinki: WSOYpro Oy.

Korhonen, A. 1996. Keskosen hoitotyö. Tampere: Tammer-Paino Oy.

Korhonen, A. 1999. Elämän ensitaidot- Erityisvauvan kehityksen tukeminen. Tampere: Tammer-Paino Oy.

Korhonen, A., Haho, A. & Pölkki, T. 2013. Nurses' perspectives on the suffering of preterm infants. Nursing Ethics. 20(7): 798-807. Accessed 29.4.2016. https://janet.finna.fi/, Academic Search Elite.

McCaffery, M. & Beebe, A. 1994. Pain: Clinical Manual for Nursing Practice. Mosby. Accessed 15.4.2016. https://janet.finna.fi/, Ebrary.

Merriam, S.B. 2009. Qualitative Research: A Guide to Design and Implementation. Jossey-Bass. Accessed 20.5.2016. https://janet.finna.fi/, Ebrary.

Mikkola, K., Tommiska, V., Hovi, P. & Kajantie, E. 2009. Keskosesta aikuiseksi. Lääketieteellinen aikakauskirja Duodecim 125(12): 1341-1347. Accessed 15.5.2016. https://janet.finna.fi/, Lääketieteellinen aikakauskirja Duodecim.

Oivallus 09/05: Hengenpelastajamääritelmä. 2005. The University of Helsinki. Viitattu 24.10.2016.
http://www.helsinki.fi/yliopistonhistoria/oivallukset/9_oivallus.htm

Page, G.G. 2004. Are There Long-Term Consequences of Pain in Newborn or Very Young Infants? The Journal of Perinatal Education. 13(3): 10-17. Accessed 29.4.2016. https://janet.finna.fi/, Cinahl.

Polit, D. & Beck, C. 2014. Essentials of Nursing Research - Appraising Evidence for Nursing Practice. 8th Edition. Wolters Kluwer Health / Lippincott Williams & Wilkins.

Pudas-Tähkä, S. & Axelin, A. 2007. Systemaattisen kirjallisuuskatsauksen aiheen rajaus, hakutermit ja abstraktien arviointi. Systemaattinen kirjallisuuskatsaus ja sen tekeminen. Ed. K. Johansson, A. Axelin, M. Stolt & R-L. Ääri. Turun yliopisto: Hoitotieteen laitoksen julkaisuja. Tutkimuksia ja raportteja. A:51/2007.

Pölkki, T., Korhonen, A., Laukkala, H., Saarela, T., Vehviläinen-Julkunen, K. & Pietilä, A-M. 2010. Nurses' attitudes and perceptions on pain assessment in neonatal intensive care. Scandinavian Journal of Caring Sciences. 24(1): 49-55. Accessed 29.4.2016. https://janet.finna.fi/, Academic Search Elite.

Ranger, M. & Grunau, R.E. 2014. Early repetitive pain in preterm infants in relation to the developing brain. Pain management. 4(1): 57-67. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Ranger, M., Chau, C.M.Y., Garg, A., Woodward T.S., Beg, M., Bjornson, B., Poskitt, K., Fitzpatrick, K., Synnes, A.R., Miller, S.P. & Grunau, R.E. 2013. Neonatal Pain-Related Stress Predicts Cortical Thickness at Age 7 Years in Children Born Very Preterm. PLoS ONE. 8(10): 1-12. Accessed 29.4.2016. https://janet.finna.fi/, Academic Search Elite.

Rodriguez, R. & Pattini, A. 2016. Neonatal intensive care unit lighting: update and recommendations. Archivos argentinos de pediatria. 114(4): 361-367. Accessed 15.9.2016. https://janet.finna.fi/, PubMed.

Salanterä, S., Hagelberg, N., Kauppila, M. & Närhi, M. 2006. Kivun hoitotyö. WSOY Oppimateriaalit Oy.

Serpell, M. 2011. Handbook of Pain Management. Springer Healthcare. Accessed 11.10.2016. https://janet.finna.fi/, Ebrary.

Tervakari, A-M. 2005. Hypermedian jatko-opintoseminaari. TTY/DMI/Hypermedialaboratorio. Accessed 13.10.2016. http://matwww.ee.tut.fi/hmopetus/hmjatkosems04/liitteet/JOS_hypermedia_Tervakari140105.pdf

Tortora, G. & Grabowski, S. 2003. Principles of Anatomy and Physiology. 10th Edition. John Wiley & Sons.

Tuomi, J. & Sarajärvi, A. 2009. Laadullinen tutkimus ja sisällönanalyysi. Kustannusosakeyhtiö Tammi.

Tutkimuseettinen neuvottelukunta. 2012. Hyvä tieteellinen käytäntö. Accessed 12.10.2016. http://www.tenk.fi/fi/htk-ohje/hyva-tieteellinen-kaytanto

Vainio, A. 2009. Kiputilojen luokittelu. Kipu. Ed. Kalso, E., Haanpää, M. & Vainio, A. 3rd Edition. Helsinki: Kustannus Oy Duodecim.

Vanhatalo, S. 2009. Kipujärjestelmän kehitys ja neonatologinen kipu. Kipu. Ed. Kalso, E., Haanpää, M. & Vainio, A. 3rd Edition. Helsinki: Kustannus Oy Duodecim.

Vanhatalo, S. 2009. Johdanto - Kipujärjestelmän kehitys ja neonataloginen kipu. Kipu. Duodecim oppiportti. Accessed 12.10.2016. https://janet.finna.fi, Oppiportti.

Vinall, J. & Grunau, R.E. 2014. Impact of repeated procedural pain-related stress in infants born very preterm. Pediatric Reasearch. 75(5): 584-587. Accessed 29.4.2016. https://janet.finna.fi/, PubMed.

Walden, M. 2013. Comprehensive Neonatal Nursing. Pain in the Newborn and Infant. 5th Edition. Springer Publishing Company. Accessed 15.4.2016. https://janet.finna.fi/, Ebrary.

Appendix 1.

Author, publishing year and place	*Title*	*Aim and purpose*	*Research method*	*Essential outcomes*
Donia, A. & Tolba, O. 2016. Egypt.	Effect of early procedural pain experience on subsequent pain responses among premature infants	To evaluate the short-term effects of early procedural pain exposure on subsequent behavioral and physiological responses among preterm infants; and to define possible contributing factors.	A prospective study which included 203 preterm newborn divided into two groups. Group 1 were exposed to painful procedures, group 2 were not exposed. NIPS was used as a measurement tool.	It was found that prior pain exposure and the number of procedures predict dampened behavioral and exaggerated physiological subsequent in pain responses.
Ranger, M. & Grunau, R.E. 2014. Canada.	Early repetitive pain in preterm infants in relation to the developing brain.	Discuss the short- and long-term effects of pain-related stress and associated treatments on brain maturation and neurodevelopmental outcomes in children born preterm.	Literature review	Altered brain development is evident in preterm children. During their NICU stay, preterm neonates are exposed to multiple factors that may alter the developing brain, and teasing out specific pain-related effects is challenging.
Vinall, J. & Grunau, R.E. 2014. Canada.	Impact of repeated procedural pain-related stress in infants born very preterm.		Scientific publication	

Hatfield, L.A. 2014. USA.	Neonatal pain: What's age got to do with it?	To present the seminal and current literature describing the unique physiological aspects of neonatal pain processing.	Literature review	The representation of neonatal pain physiology is described in three processes: local peripheral nervous system, spinal cord and supraspinal processing.
Ranger, M., Chau, C.M.Y., Garg, A., Woodward, T.S., Beg, M., Bjornson, B., Poskitt, K., Fitzpatrick, K., Synnes, A.R., Miller, S.P. & Grunau, R.E. 2013. Canada.	Neonatal Pain-Related Stress Predicts Cortical Thickness at Age 7 years in Children Born Very Preterm	To evaluate whether neonatal pain-related stress (adjusted for clinical confounders of prematurity) is associated with altered cortical thickness in very preterm children at school age.	42 right-handed children born very preterm (24-32 weeks gestational age) followed longitudinally from birth underwent 3-D T1 MRI neuroimaging at mean age 7,9 years.	In very preterm children without major sensory, motor or cognitive impairments, neonatal pain-related stress appears to be associated with thinner cortex in multiple regions at school age, independent of other neonatal risk factors.
Doesburg, S.M.,Chau, C.M., Cheung, T.P.L., Moiseev, A., Ribary, U., Herdman, A.T., Miller, S.P., Cepeda, I.L., Synnes, A. & Grunau, R.E. 2013. Canada.	Neonatal pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age	To demonstrate alterations in the spectral structure of spontaneous cortical oscillatory activity in ELGA children at school-age.	54 preterm children as part of a longitudinal study. 25 age-matched full-term control children were recruited from the longitudinal study.	There is a link between neonatal pain-related stress, functional brain activity, and school-age visual perceptual abilities in children born very prematurely. Associations between spontaneous neuromagnetic activity, neonatal pain, and visual-perceptual abilities are specific to children born at ELGA.

Grunau, R.E., Cepeda, I.L., Chau, C.M.Y., Brummelte, S., Weinberg, J., Lavoie, P.M., Ladd, M., Hirschfeld, A.F., Russel, E., Koren, G., Van Uum,S., Brant, R. & Turvey, S.E. 2013.Canada.	Neonatal Pain-Related Stress and NFKBIA Genotype Are Associated with Altered Cortisol Levels in Preterm Boys at School Age	To examine whether cortisol changes persist to school age, and if common genetic variants in the promoter region of the NFKBIA gene involved in regulation of immune and inflammatory responses, modify the association between early experience and later life stress as indexed by hair cortisol levels, which provide and integrated index of endogenous HPA axis activity.	91 preterm infants and 42 full-term infants	Hair cortisol levels were lower in preterm compared to term-born children. The etiology was gender-specific. In preterm boys lower hair cortisol was associated with greater neonatal pain.
Korhonen, A., Haho, A. & Pölkki, T. 2013. Finland.	Nurses' perspectives on the suffering of preterm infant**s**	To describe nurses' perceptions of the suffering of preterm infants	A descriptive qualitative approach which included 19 nurses working in the neonatal intensive care unit.	Suffering is individually determined among the preterm infants, thus requiring a sensitive approach to care.
Brummelte, S., Grunau, R.E., Chau, V., Poskitt, K.J., Brant, R., Vinall, J., Gover, A., Synnes, A. & Miller, S.P. 2012. Canada.	Procedural pain and brain development in premature newborns	To examine relationships between procedural pain in the NICU and early brain development in very preterm infants	86 infants born very preterm were followed prospectively from birth and studied with MRI, 3D MR spectroscopic imaging and diffusion tensor imaging (DTI)	Greater neonatal procedural pain was associated with reduced white matter FA and reduces subcortical grey matter NAA/choline. Reduced FA was predicted by early pain, whereas lower NAA/choline was predicted by pain exposure throughout the neonatal course, suggesting a primary and early effect on subcortical structures with secondary white matter changes.

Fabrizi, L., Slater, R., Worley, A., Meek, J., Boyd, S., Olhede, S. & Fitzgerald, M. 2011. UK.	A Shift in Sensory Processing that Enables the Developing Human Brain to Discriminate Touch from Pain	Understand how and when the circuitry required for touch and pain discrimination emerges in the human brain	EEG recording in infants aged 28-45 weeks gestation	Specific neural circuits necessary for discrimination between touch and nociception emerge from 35-37 weeks gestation in the human brain
Pölkki, T., Korhonen, A., Laukkala, H., Saarela, T., Vehviläinen-Julkunen, K. & Pietilä, A-M. 2010. Finland.	Nurses' attitudes and perceptions of pain assessment in neonatal intensive care	To describe nurses' attitudes towards and perceptions of pain assessment in neonatal intensive care and the demographic factors related to these attitudes and perceptions of pain	257 Finnish nurses. A Likert-type questionnaire.	On average nurses' attitudes were positive towards the pain assessment in neonatal intensive care. However, there were some gaps in the knowledge concerning the respondents' perceptions of the items, which is a challenge to nursing and nursing education.
Grunau, R.E., Thanh Tu, M., Whitfield, M.F., Oberlander, T.F., Weinberg, J., Yu, W., Thiessen, P., Gosse, G. & Scheifele, D. 2010. Canada.	Cortisol, Behavior, and Heart Rate Reactivity to Immunization pain at 4 Months Corrected Age in Infants Born Very Preterm	To examine reactivity and recovery to pain of immunization injections, in preterm compared with full-term infants at 4 months CCA.	A cohort study with participants a total of 138 infants (99 preterm and 39 full-term)	Cortisol, behavior, and heart rate increased during immunizations. Cortisol concentrations were lower in preterm ELGA and VLGA boys, compared with full-term boys. In contrast, facial and heart rate responses to immunization did not differ between preterm and full-term infants.

Grunau, R.E., Whitfield, M.F., Petrie-Thomas, J., Synnes, A., Cepeda, I.L., Keidar, A., Rogers, M., MacKay, M., Hubber-Richard, P. & Johannesen, D. 2009. Canada.	Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants	To examine relationships between cumulative procedural pain (number of skin-breaking procedures from birth to term, adjusted for early illness severity and overall intravenous morphine exposure), and later cognitive, motor abilities and behavior in very preterm infants at 8 and 18 months corrected chronological age (CCA), and further, to evaluate the extent to which parenting factors modulate these relationships over time.	A prospective follow-up of 211 infants (137 preterm and 74 full-term). In addition a questionnaire for parents.	Greater overall exposure to intravenous morphine was associated with poorer motor development at 8 months, but not at 18 months CCA, however, specific protocols for morphine administration were not evaluated. Lower parenting stress modulated effects of neonatal pain, only on cognitive outcome at 19 months.
Page, G.G. 2004. USA.	Are There Long-Term Consequences of Pain in Newborn or Very Young Infants?	To examine if significant and long-lasting physiological consequence may follow painful insults in the very young, including changes in the central nervous system and changes in responsiveness of the neuroendocrine and immune systems to stress at maturity.	Literature review	Long-lasting physiological consequence may follow painful insults in the very young, including changes in the central nervous system and changes in responsiveness of the neuroendocrine and immune systems to stress at maturity.
Grunau, R.E. Weinberg, J. & Whitfield, M.F. 2004. Canada.	Neonatal Procedural Pain and Preterm Infant Cortisol Response to Novelty at 8 Months	To examine the alteration of preterm infants stress systems after hospital discharge (cortisol levels at 8 months) in ELGA and VLGA infants.	76 infants (54 preterm and 22 term-born)	ELGA preterm infants show a different pattern of cortisol levels before and after positive stimulation of visual novelty than more maturely born, VLGA preterm and term-born infants. Exposure to high numbers of skin-breaking procedures may contribute to "resetting" basal arousal systems in preterm infants.