Long-term consequences of Pain in Infancy

K. J. S. Anand, MBBS, D.Phil.
St. Jude Endowed Chair of Critical Care Medicine
Professor of Pediatrics, Anesthesiology, Anatomy & Neurobiology
Division Chief, Pediatric Critical Care Medicine
University of Tennessee Health Science Center, Memphis, TN
Editorial

New perspectives on the definition of pain

K.J.S. Anand* and Kenneth D. Craig

*Department of Pediatrics, Anesthesia and Psychiatry, Emory University School of Medicine, Egleston Children's Hospital at Emory University, 1405 Clifton Road, NE, Atlanta, Georgia 30322 (USA) and bDepartment of Psychology, University of British Columbia, Vancouver, British Columbia (Canada)

A new view of pain as a homeostatic emotion

A.D. (Bud) Craig

Atkinson Pain Research Laboratory, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA
Pain processing, the bare bones

- Different types of pain: tissue injury, inflammation, nerve damage, visceral origin
- Unique receptors / mechanisms: specialized nociceptors, nerve fibers, DRG cells, processing in spinal & supraspinal areas
- Sequential neurobiological changes: activation $\rightarrow$ modulation $\rightarrow$ modification of the pain system
- Pain is a multi-layered phenomenon: primary and secondary hyperalgesia, allodynia, temporal or spatial summation, sympathetically maintained pain, referred pain, central pain states
Pain activates cortical areas in the preterm newborn brain

Marco Bartocci a,b,*, Lena L. Bergqvist a,c, Hugo Lagercrantz a, K.J.S. Anand d

a Neonatal Research Unit, Astrid Lindgren’s Children’s Hospital, Karolinska University Hospital, Karolinska Institute, SE-17176 Stockholm, Sweden
b Department of Pediatrics, Neonatal Intensive Care, University of Genoa, Gaslini Institute, I-16147 Genoa, Italy
c Research and Development Unit, Department of Internal Medicine, Östersund Hospital, Jämtland County Council, SE 831 25 Östersund, Sweden
d Departments of Pediatrics, Anesthesiology, Pharmacology, Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, and Pain Neurobiology Laboratory, Arkansas Children’s Hospital Research Institute, Little Rock, AR 72202-3591, USA
**Contralateral Somatosensory vs. Visual Cortex**

- Baseline Tactile Venipuncture
- 

![Graph showing baseline, tactile, and venipuncture conditions with [Hb O2] levels.](image)

- Bilateral Somatosensory Cortex
- 

![Graph showing bilateral somatosensory cortex conditions with [Hb O2] levels.](image)
Cortical Pain Responses in Human Infants

Rebecca Slater,1 Anne Cantarella,2 Shiromi Gallella,2 Alan Worley,3 Stewart Boyd,3 Judith Meek,2 Maria Fitzgerald1

The Journal of Neuroscience, April 5, 2006 • 26(14):3662–3666

Figure 3.  Hemodynamic response in the youngest infant. A sample trace in the youngest infant in our sample (25 + 5 weeks PMA) is shown, demonstrating the evoked change in [HbT] in the contralateral and ipsilateral somatosensory cortex after a painful stimuli given at t = 20 s.
Cortical responses are greater on the Left than in Right Cortex (Bartocci, Bergqvist, Lagercrantz, Anand. Pain 2006)
Cortical function in preterm neonates

Responses in the preterm neonate varied by:

- Intensity of stimulation (tactile vs. pain)
- Gender (male vs. female)
- Laterality (left vs. right cortical hemisphere)
- Behavioral state (awake vs. asleep neonates)*
- Gestational age (more vs. less immature)
- Postnatal age (early differences, maturational changes*)

*Slater et al, 2006

What does this mean?
Consciousness, cortical function, and pain perception in nonverbal humans

DOI: 10.1017/S0140525X0700091X

K. J. S. Anand

Departments of Pediatrics, Anesthesiology, Neurobiology & Developmental Sciences, University of Arkansas for Medical Sciences, College of Medicine, and Pain Neurobiology Laboratory, Arkansas Children's Hospital Research Institute, Little Rock, AR 72202.
anandsunny@uams.edu
Criteria for Consciousness

- States of wakefulness
- Self-aware
- Express emotions
- Response to the environment
- Memory & learning
- Stream of consciousness

Are neonates more sensitive to pain?

Conditioning and Hyperalgesia in Newborns Exposed to Repeated Heel Lances

Anna Taddio, PhD
Vibhuti Shah, MD
Cheryl Gilbert-MacLeod, PhD
Joel Katz, PhD

Context
Hospitalized infants undergo repeated invasive procedures. It is unknown whether cumulative experiences with pain lead to anticipatory pain behaviors and hyperalgesia.

Objectives
To determine whether newborns who are born to mothers with diabetes and undergo repeated pain learn to anticipate pain and exhibit more pain during a painful procedure than normal infants.
Even routine painful procedures can be harmful for the newborn

C.V. Bellieni, L. Iantorno, S. Perrone, A. Rodriguez, M. Longini, S. Capitani, G. Buonocore

**Changes in markers of free radical production.**

<table>
<thead>
<tr>
<th></th>
<th>AOPP</th>
<th>TH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total group (n = 64)</strong></td>
<td>53.1</td>
<td>221.0</td>
</tr>
<tr>
<td></td>
<td>(SD = 47.3)</td>
<td>(SD = 93.5)</td>
</tr>
<tr>
<td></td>
<td>p = 0.2</td>
<td>p = 0.9</td>
</tr>
<tr>
<td><strong>Babies with pain score ≥ 4 (n = 34)</strong></td>
<td>53.5</td>
<td>218.3</td>
</tr>
<tr>
<td></td>
<td>(SD = 41.6)</td>
<td>(SD = 89.2)</td>
</tr>
<tr>
<td></td>
<td>p = 0.02</td>
<td>p = 0.36</td>
</tr>
<tr>
<td><strong>Babies with pain &lt; 4</strong></td>
<td>53.8</td>
<td>221.4</td>
</tr>
<tr>
<td></td>
<td>(SD = 55.3)</td>
<td>(SD = 97.3)</td>
</tr>
<tr>
<td></td>
<td>p = 0.5</td>
<td>p = 0.59</td>
</tr>
</tbody>
</table>

Blood advanced oxidative protein products (AOPP) and total hydroperoxides (TH) at the beginning (A) and at the end (B) of a heel prick in a group of neonates.
Can Adverse Neonatal Experiences Alter Brain Development and Subsequent Behavior?

*K. J. S. Anand*  Frank M. Scalzo

Department of Pediatrics, University of Arkansas for Medical Sciences, and Pain Neurobiology Laboratory, Arkansas Children’s Hospital Research Institute, Little Rock, Ark., USA

Pain, plasticity, and premature birth: a prescription for permanent suffering?

A collection of clinical and animal studies suggest that exposure to pain during the neonatal period leads to long-term changes in neural circuitry and behavior, contradicting the theory that infants don’t ‘remember’ painful experiences.

About 11,000 newborn infants are receiving intensive care in the U.S. today.
Maternal Separation 
(isolation, neglect, lack of tactile / social stimulation)

- Decreased Afferent Input
- Lack of NMDA Activity
- Increased Apoptosis
- Increased Anxiety
- Hyper-responsive HPA Axis
- Increased Pain Sensitivity
- Decreased Exploration

Normal Neonate
Maternal Infant Interaction
Increased Pain Sensitivity
Plasticity in the Neonatal Brain
Developmental apoptosis, neuronal differentiation

- Normal Childhood
  Behavioral Development
  Cognitive Abilities
  Adolescent/Adult Behavior
  Childhood pain

Cognitive Impairment
Behavioral problems
Poor Socialization Skills

Repetitive Pain
(inflammation, procedures, prolonged ventilation)

- Hyperexcitability, windup
- Excessive NMDA activation

Excitotoxic Damage
(altered EAA receptor structure and function)

- Decreased Pain Sensitivity
- Increased anxiety
- Hyperactivity
- Attention Deficit disorder

PET scans of Romanian orphans

Emotions vs. Executive functions

- Normal cognitive functions
- Developmental goals
- Coping strategies, memory

- Impaired cognitive function
- Atypical development
- Loss of control, learning

Preterm children show greater activations of thalamus, anterior cingulate cortex, cerebellum, basal ganglia, periaqueductal gray, vs. term or controls. Preterms show greater activation in the primary somatosensory cortex, anterior cingulate cortex, insula. Preterm children's continuous pain ratings show increased sensitization within and a lack of habituation across trials.
Developmental Origins of Adult Disease

(Gluckman & Hanson, Science, 305: 1733-1736, 2004)
Supraspinal effects of neonatal pain: changes in adult behavior (Anand et al. Physiology & Behavior, 1999)

- Increased anxiety, defensive withdrawal
- Hypervigilance, increased alcohol preference
Expression of Fos at 30 min. after hot plate exposure

Noxious Stim Group
Tactile Stim Group

- Noxious stimulation
- Tactile stimulation

Number of Fos positive cells (mean, SD)

- N4: p=0.0002
- T4: p=0.0006
- N4: p=0.0003

Noxious (N4) and tactile (T4) stimulation groups
Neonatal responses to single inflammatory pain

- Rat pups (n=112) at P1, P7, P14
- 4% formalin Rt forepaw vs. undisturbed
- Anesthetized, perfused at 1 hr or 4 hrs
- Cryostat sections (20μm) Fos protein immunohistochemistry or FluoroJade-B stain
- Cell counts made using MCID (Imaging Research Inc., St. Catharines, Ont., Canada)
- Counts verified by two blinded observers
Cell death following single inflammatory pain

Cell Death: Left side

Cell Death: Right side
Supraspinal responses to repetitive inflammatory pain

- Long-Evans rat pups (n=62), cross-fostered at P0, stimulated daily from P1 to P4
- Randomly assigned to Control gr. vs. 4% formalin vs. Ketamine (5mg/kg) vs. Ketamine + formalin
- Sacrificed on P5, perfused with 4% PFA (0-4°C)
- Cryostat sections (20µm) immunostained with FluoroJade-B, a specific marker for cell death
- Cell counts were made using MCID software (Imaging Research Inc., St. Catharines, Ont., Canada)
- Counts verified by two blinded observers
Neuronal Cell Death in selected brain regions

- Control
- Ketamine
- Ketamine&Formalin
- Formalin

Habenula: p = 0.4363
Cortex: p > 0.0001
Hippocampus: p < 0.0001
Amygdala: p < 0.0001
Hypothalamus: p < 0.0001
Thalamus: p = 0.0495
Cell Death (FJB)

- Undisturbed Control Group
- 4% Formalin Group
- Ketamine & 4% Formalin Group
- Ketamine Group

Neuronal activation (Fos)

- Anterior sections
- Intermediate sections
- Posterior sections
Cytokine Expression in Brain Tissue

- **Pro Inflammatory**
  - IL-1α (1.6-fold)
  - IL-1β (1.5-fold)
  - IL-2 (1.6-fold)
  - IL-9 (1.8-fold)
  - IL-12P70 (1.8-fold)
  - IL-18 (1.5-fold)

- **Anti-Inflammatory**
  - IL-4
  - IL-6
  - IL-13
  - IL-10 (1.5-fold)

- **Chemokines**
  - RANTES
  - MCP-1
  - EOTAXIN
Thermal pain thresholds in adult rats

[Graph showing Latency in Seconds with comparisons for Males, Females, and Males and Females with statistical significance levels indicated by * and **.]
Impaired long-term visual-spatial memory following Repetitive Neonatal Pain

Time required for bait consumption in an 8-arm Radial Maze Test

- **Control**
- **Ketamine**
- **Ket.+Formalin**
- **Formalin**

Duration (seconds)

- **25% bait**
- **50% bait**
- **75% bait**
- **100% bait**

Significance levels:
- p=0.009
- p=0.002
- p=0.002
- p=0.020
Startle response to paired auditory clicks

Control Group

Formalin injection Group
Startle response to paired auditory clicks

Inter-Stimulus Interval in Seconds

**SR Amplitude in µV**

- Formalin
- Control

* p<0.05
Anxiety Testing in Adult Rats

- Reduced time spent in the Open arms
- ANOVA p=0.016
- K > F, KF > F: p<0.05

- Decreased number of entries
- ANOVA p=0.0104
- K > F: p<0.01
Conclusions

Injury/inflammation in neonatal rats:
- Increases cell death in cortical (~3.3-fold) and subcortical (~1.6-fold) areas
- NMDA receptor-mediated excitotoxicity blocked by Ketamine analgesia
- No change in apoptotic mediators

Long-term behavioral changes in adult rats:
- Higher pain thresholds
- Impaired spatial learning
- Exaggerated startle response
- Increased anxiety

Ketamine Reduces the Cell Death Following Inflammatory Pain in Newborn Rat Brain

KANWALJEET J.S. ANAND, SARITA GARG, CYNTHIA R. ROVNAGHI, UMESH NARSINGHANI, ADNAN T. BHUTTA, AND RICHARD W. HALL

Pain Neurobiology Lab, AR Children’s Hospital Research Institute, Little Rock, Arkansas 72202; Department of Pediatrics, University of Arkansas for Medical Sciences, College of Medicine, Little Rock, Arkansas 72205
Long-term effects of Pain: human infants


- Altered cardiac autonomic responses during recovery from pain (Oberlander et al, 1999, 2000, 2002; Morison et al, 2001; Hatfield, 2008)

- Number of skin breaking procedures in preterm infants predict:
  - Poorer cognition & motor function (Grunau et al, May 2009)
  - Increased pain thresholds (Grunau et al, 1994)

  …independent of early illness severity, intravenous morphine, postnatal steroids, and other clinical factors

- Clinically significant somatization (4.5 yr) (Grunau et al, 1994)

- Greater affective responses (Grunau et al, 1998), lower mechanical (localized) & thermal sensitivity (generalized) (Walker et al, 2009)
Children undergoing 2nd surgery in the same dermatome required more anesthesia and postoperative analgesia, had higher pain scores, & greater catecholamine responses than matched controls undergoing their 1st surgery or those undergoing their 2nd surgery in a different dermatome.
Multivariate logistic regression analyses showed that gastric suction at birth was associated with functional intestinal disorders during later life (odds ratio, 2.99; 95% confidence interval, 1.32–6.79; P = .009), whereas maternal, perinatal, or other confounding variables were not significant.

Noxious stimulation caused by gastric suction at birth may promote development of long-term visceral hypersensitivity and cognitive hypervigilance, leading to an increased prevalence of functional intestinal disorders in later life.
**Hypothesis:** IV Morphine will lower the incidence of poor neurologic outcomes in ventilated preterm neonates from 25% in the placebo control group to 17.5% in the treatment group

**Poor Neurologic Outcomes:**
- Death at <28 days in the NICU
- Severe IVH (grade III or IV)
- Periventricular leukomalacia

**Morphine loading dose:** 0.1 mg/kg infused over 1 hour

**Continuous infusions by GA:**
- 23-26 weeks - 10 mcg/kg/hr
- 27-29 weeks - 20 mcg/kg/hr
- 30-32 weeks - 30 mcg/kg/hr

Total patients screened (N=4,254)
Not eligible or excluded (N=2,018)
Eligible for Enrollment (N=2,236)
Enrolled and Randomized (N=898)
- Morphine Group (N=449)
- Placebo Group (N=449)
Primary Outcomes

- Overall: p=0.578
- 23-26 weeks: p=0.700
- 27-29 weeks: p=0.053
- 30-32 weeks: p=0.314

Percentage of patients

- Placebo
- Morphine
Follow-up of NEOPAIN-enrolled subjects at 5-7 years age

Placebo (N=5) and Morphine groups (N=14, n=13 with AA)

Neuropsychological tests (Stanford-Binet, WRAT4, NSS), morphometrics (height, weight, HC), adaptive behavior (VABS), parent-rated behavior (CBCL, Conner’s CBRS), operant tests: motivation (PR), short-term memory (DMTS)
Follow-up of NEOPAIN patients

- Neuropsychological outcomes $\rightarrow$ no differences in Stanford-Binet, WRAT4, or NSS scores or subscales.
- Morphometrics $\rightarrow$ decreased body weight and head circumference in the Morphine group (Cohen’s d effect sizes 0.81 and 2.83, respectively).
- Adaptive behavior (VABS): reduced Socialization domain and Adaptive Behavior Composite Scores in Morphine group.
- Conner’s CBRS: increased social problems in Morphine group.
- Operant testing (PR): no differences in motivation.
- Short-term memory (DMTS): longer choice response latencies (3.86 vs. 2.71 sec) and 27% less task completion occurred in the Morphine group.
Follow-up at 5 years age; Placebo (N=41); Morphine (N=49)

- Cognitive testing (Revision Amsterdam Child Intelligence Test, RAKIT), morphometrics (height, weight), visual motor integration (Beery-Buktenica VMI), parent- and teacher-rated behavior (CBCL)
- Prevalence of chronic pain, Health Utility Index (HUI-15)
Follow-up of Dutch Morphine Trial
(de Graaf, Anand, et al. 2011)

- Morphometrics → decreased height for age in the Morphine group (p=0.02); likely due to SGA (Morphine 26.5%, Placebo 12.2%)

- Cognitive outcome: Morphine (94 ± 14.5) vs. Placebo (99.8 ± 12.9) (p=0.049); no difference when adjusted for open-label morphine, neonatal ventilation, and other clinical factors

- “Visual analysis” subtest of the RAKIT test showed significant negative effects for Morphine group (p=0.02), open-label morphine

- Visual-Motor Integration: lower Beery-Buktenica VMI scores in the Morphine group; + significant effect for open-label morphine

- No differences in CBCL (parent- or teacher-rated), prevalence of chronic pain, or health-related quality of life (HUI-15)
Cognitive outcomes in Ex-preterm Children

- Smaller brain volumes correlated with cognitive / behavioral outcomes: most prominent changes in the Somatosensory cortex, Thalamus, Hypothalamus (Peterson et al., 2000)

- Meta-analysis of cognitive outcomes WMD = 10.9 favors term neonates (Test of WMD: z= 15.89, p< 0.001) (Bhutta, Casey, Cleves, Anand, 2002)

- Present value per IQ point estimated $16,300 (Grosse et al., 2002)
Proposed mechanisms...

- Repetitive neonatal pain $\rightarrow$ cortical and hippocampal excitotoxic cell death $\rightarrow$ altered pre-attentional processes $\rightarrow$ attention deficit disorder $\rightarrow$ poor memory encoding $\rightarrow$ “hidden” learning disabilities $\rightarrow$ poor cognitive outcomes

- Prolonged drug exposure $\rightarrow$ altered neurogenesis, apoptotic cell death of mature neurons $\rightarrow$ reduced cellular density $\rightarrow$ impaired synaptogenesis $\rightarrow$ reduced visual-spatial processing $\rightarrow$ poor cognitive outcomes

How do we reverse this trend?
“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy”

Philippus Aureolus Theophrastus Bombastus von Hohenheim

“Paracelsus”
Role of Love in NICU care…

- Effects of tactile-kinesthetic stimuli (only if nurse focuses on baby) (Fields et al. 1988, 1993)
- “Kangaroo care” and its effects (more growth, less instability, less pain) (Ludington-Hoe 1996; Folie 2000)
- Rocking: maternal vs. simulated (no effects on the response to pain) (Johnston et al. 1997)
- Sensorial saturation (blocks pain) (Bellini, 2003, 2005)
Repetitive pain may lead to:

- Poor neurologic outcomes in premature babies
- Increased cell death in the immature brain
- Abnormal behavior during adulthood
- Increased vulnerability to stress, anxiety, other psychological disorders

Loving care may lead to:
Love, Pain, and Intensive Care

K. J. S. Anand, MBBS, DPhil\textsuperscript{a}, Richard W. Hall, MD\textsuperscript{b}

\textsuperscript{a}Departments of Pediatrics, Anesthesiology, Pharmacology, Neurobiology, and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas

The authors have indicated they have no financial relationships relevant to this article to disclose.

No activity can give you the joy that service does. . . . You should yearn for the chance to console, comfort, encourage, heal. See yourself as another, feel his joy to be yours, his sorrow to be yours.

—Sri Sathya Sai Baba\textsuperscript{1}
Conclusions

- Newborns and infants are frequently exposed to acute repetitive pain or prolonged pain.
- All infants are capable of consciously processing pain.
- Pain activates the cortex, hippocampus, hypothalamus, amygdala, other areas of the developing brain.
- Repetitive pain → excitotoxic or apoptotic cell death → altered development of brain, behavior, stress responses → vulnerability to pain / stress disorders, chronic pain.
- Blocking early pain can reduce / prevent the long-term sequelae of infant pain.
- Analgesia in the absence of pain alters brain development.