Development of pain and touch in early life

K. J. S. Anand, MBBS, D.Phil., FCCM.
Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine
Stanford University School of Medicine, Palo Alto, CA.

Disclosures: Dr. Anand has no financial relationships with any commercial, pharmaceutical, or medical device companies related to this presentation; there are no conflicts of interest to disclose. As senior editor for the book “Pain in Neonates & Infants”, he receives royalty payments from Elsevier Science Publishers and Up-To-Date, Inc. He does not subscribe to Pro-Life or Pro-Choice viewpoints and does not receive any financial or non-financial benefits from any such organizations.
SPECIAL ARTICLE

PAIN AND ITS EFFECTS IN THE HUMAN NEONATE AND FETUS

K.J.S. Anand, M.B.B.S., D.Phil., and P.R. Hickey, M.D.

Reprinted from the New England Journal of Medicine
317:1321-1329 (November 19), 1987
What is pain?
Flawed definition of pain, relies on mostly on self report

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

*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)
Newborns are more sensitive to pain

Premature infants display increased noxious-evoked neuronal activity in the brain compared to healthy age-matched term-born infants

Rebecca Slater, Lorenzo Fabrizi, Alan Worley, Judith Meek, Stewart Boyd, Maria Fitzgerald

NeuroImage 52 (2010) 583-589

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/ynimg

NeuroImage

[References: Norman et al., 2008; Slater et al., 2010; Maimon et al., 2013]
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

* 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
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 $t = 20\text{ s}$. 
Somatosensory perception in preterm newborns

Responses in the preterm neonate varied by:

- Intensity of stimulation (tactile vs. acute 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, maturation changes*) (*Slater et al., J Neuroscience 2006)

What does this mean?
Abstract

While the network of pain processing is well described, the neural underpinnings in newborn infants remain unknown, meaning we have limited understanding of how pain is perceived in this age group. Using functional magnetic resonance imaging (fMRI) we identified pain processing centers in newborn infants, suggesting that the infant pain experience closely resembles that seen in adults. This highlights the importance of developing effective pain management strategies in this vulnerable population.

DOI: 10.7554/eLife.06356.001
Figure 2. Noxious-evoked brain activity in response to the maximal presented stimulus in adults (512 mN) and infants (128 mN). Red-yellow coloured areas represent active brain regions (threshold $z \geq 2.3$ with a corrected cluster significance level of $p < 0.05$). An image of a midline sagittal brain slice (right panel) identifies the location of each example slice in the horizontal plane. (A) Adult activity is overlaid onto a standard T1 weighted MNI template and (B) infant activity is overlaid onto a standard T2 weighted neonatal template, corresponding to a 40-week gestation infant.
Controversy about fetal pain: new or old?

Fetuses, Fentanyl, and the Stress Response: Signals from the Beginnings of Pain?
[Editorial Views]


*Professor of Pediatrics, Anesthesiology, and Neurobiology and Morris & Hettie Oakley Chair for Critical Care Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas. Director, Pain Neurobiology Laboratory, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas. anandsunny@uams.edu. +Professor of Anaesthetics, Sir Ivan Magill Department of Anaesthetics, Imperial College School of Medicine, London, United Kingdom. Accepted for publication June 2, 2001.
Fetal Pain
A Systematic Multidisciplinary Review of the Evidence

Context
Proposed federal legislation would require physicians to inform
seeking abortions at 20 or more weeks after fertilization that the fetus
and to offer anesthesia administered directly to the fetus. This article
e whether a fetus feels pain and if so, whether safe and effective techniques
and measures can be provided and are available at that time.

Table. Anatomical and Functional Development of Nociception and Pain Perception Pathways

<table>
<thead>
<tr>
<th>Anatomical/Functional Characteristic</th>
<th>Description</th>
<th>Gestational Age, wk</th>
<th>Source</th>
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<tr>
<td>Peripheral cutaneous sensory receptors</td>
<td>Perioral cutaneous sensory receptors</td>
<td>7.5</td>
<td>Humphrey, 13 1984</td>
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<td></td>
<td>Palmar cutaneous sensory receptors</td>
<td>10-10.5</td>
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<td>Abdominal cutaneous sensory receptors</td>
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<tr>
<td>Spinal cord</td>
<td>Spinal reflex arc in response to nonnoxious stimuli</td>
<td>8</td>
<td>Okado and Kojima, 14 1984</td>
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<td></td>
<td>Neurons for nociception in dorsal root ganglion</td>
<td>19</td>
<td>Konstantinidou et al, 15 1995</td>
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<tr>
<td>Thalamic afferents</td>
<td>Thalamic afferents reach subplate zone</td>
<td>20-22</td>
<td>Kostovic and Rakic, 16 1990</td>
</tr>
<tr>
<td></td>
<td>Thalamic afferents reach cortical plate</td>
<td>23-24</td>
<td>Kostovic and Rakic, 18 1984</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Kostovic and Goldman-Rakic, 19 1983</td>
</tr>
<tr>
<td>Cortical function*</td>
<td>Somatosensory evoked potentials with distinct, constant components</td>
<td>29</td>
<td>Klimach and Ciske, 20 1988</td>
</tr>
<tr>
<td></td>
<td>First electrocardiographic pattern denoting both wakefulness and active sleep</td>
<td>30</td>
<td>Hibek et al, 21 1973</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Clancy et al, 22 2003</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Torres and Anderson, 23 1985</td>
</tr>
</tbody>
</table>

*Earliest evidence of functional thalamocortical connections required for conscious perception of pain.
Fetal Pain reviews

Scientific rationale: 3 major flaws!

1. Pain is a hard-wired system
2. The structures and mechanisms used for adult pain perception are the same in fetuses & neonates
3. Cortical activation is required for pain perception

- Serious methodological problems
- Major financial conflicts of interest
Appearance of functional mesodiencephalon associated with maturation of the reticular formation of the brain stem,
Responses of the Fetal Pain System

Subcortical consciousness: Implications for fetal anesthesia and analgesia

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Roland R. Brusseau\textsuperscript{a} and George A. Mashour\textsuperscript{b}

\textsuperscript{a}Department of Anesthesia, Perioperative and Pain Medicine, Children's Hospital, Harvard Medical School, Boston, MA 02115; \textsuperscript{b}Division of Neurosurgical Anesthesia, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, MI 48109.

roland.brusseau@childrens.harvard.edu
gmashour@med.umich.edu
Consciousness, Behavior, and Clinical Impact of the Definition of Pain

K. J. S. Anand,* Cynthia Rovnaghi,† Marlene Walden,‡ and John Churchill§

From the *University of Arkansas for Medical Sciences, Little Rock, Arkansas; †Pain Neurobiology Laboratory, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas; ‡Nell Hodgson School of Nursing, Emory University, Atlanta, Georgia; and §Hendrix College, Conway, Arkansas.

Pain Forum 8(2): 64–73, 1999

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Antenatal Determination of Fetal Brain Activity in Response to an Acoustic Stimulus Using Functional Magnetic Resonance Imaging

R.J. Moore, S. Vadeyar, J. Fulford, D.J. Tyler, C. Gribben, P.N. Baker, D. James, and P.A. Gowland

1 Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, United Kingdom
2 School of Human Development, University of Nottingham, United Kingdom
Non-invasive detection and identification of brain activity patterns in the developing fetus

Hari Eswaran a,*, Naim I. Haddad b, Bashir S. Shihabuddin b, Hubert Preissl a,c, Eric R. Siegel d, Pam Murphy a, Curtis L. Lowery a

a Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, 4301 W. Markham Slot 518, Little Rock, AR 72205, USA
b Department of Neurology, University of Arkansas for Medical Sciences, 4301 W. Markham Slot 500, Little Rock, AR 72205, USA

4. Discussion

The fact that the spontaneous fetal brain activity can be recorded and identified without the application of electrodes or other invasive means is phenomenal. The poten-
Resting state networks in the newborn brain

A: Primary visual areas
B: Somatosensory and motor cortical areas
C: Temporal primary auditory cortex
D: Parietal association cortex
E: Anterior prefrontal cortex

(Fransson et al. Resting state networks in infant brain. *PNAS* 104 (39): 15531-6, 2009)
Self-awareness

- Newborns root more to external stimuli as compared to self-stimulation → they can differentiate the touch from self vs. non-self (P Rochat 2003)

Photograph Courtesy: Bjorn Westrup, MD, PhD
Subcortical Control of Consciousness

Multiple lines of evidence....

- Surgical removal of large areas of the cortex → no impairment of consciousness
- Electrical stimulation of cortical areas → separate perception of cortical stimulation
- Damage of the reticular activating system, but not the cortex, leads to loss of consciousness
- Absence epilepsy: transient lapse of consciousness → stimulated by the midline thalamus, but not the cortex
- Children with absent cerebral cortex (hydranencephaly) → show arousal and self-awareness
Saggittal and frontal MRI images of a child with hydranencephaly: occipital and midline cortical matter, but mostly disorganized glial elements, intact cerebellum and brainstem (Merker, Brain Behav. Sciences, 2007)
The reactions of a 3-year-old girl with hydranencephaly when her baby brother was placed in her arms by her parents, who face her attentively and help support the baby while taking these photographs

(reprinted from: Merker, Brain Behav. Sciences, 2007)
Conclusion: “The available scientific evidence makes it possible, even probable, that fetal pain perception occurs well before late gestation. Our current understanding of fetal development provides the anatomical structures, the physiological mechanisms, and the functional evidence for pain perception developing in the second trimester, certainly not in the first trimester, but well before the third trimester of human gestation.”
Subcortical control of consciousness & pain perception

Pain Perception does not have to depend on fetal development of the cortex.

Thalamus and Midbrain developed and functional by 18 weeks of gestation.

Fetal Pain?

The subcortical control of pain perception (Anand KJS, Pain - Clinical Updates, 2006)

- Young children without a cortex (hydranencephaly) show pain responses that are purposeful, coordinated, similar to those of normal children (Shewmon, et al., Developmental Medicine & Child Neurology, 1999)
- Preterm newborns or adolescents with massive cortical injury mount biological and behavioral pain responses that are indistinguishable from those of normal controls (Oberlander, et al., Pediatrics, 2002)

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Fetal awareness and fetal pain: the Emperor’s new clothes

Martin Ward Platt

Arch Dis Child Fetal Neonatal Ed published online February 3, 2011
doi: 10.1136/adc.2010.195966
Conclusions

- Touch perception develops just before 2nd trimester
- Pain develops later during the 2nd trimester of fetal life
- Human consciousness maybe manifested at that time
- Could a response to pain be a biomarker for the onset of human consciousness in the fetus?
How do pain exposures affect the child later in life?

K. J. S. Anand, MBBS, D.Phil., FCCM.
Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine
Stanford University School of Medicine, Palo Alto, CA.

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Epidemiology of Acute Pain in Infants

**Porter & Anand, 1998**
- 144 babies: 7,672 procedures
- 53 procedures/baby, 87% were heelsticks
- Pain relief for 3% procedures

**Simons, Anand, et al., 2003**
- 151 babies for 14 days in NICU
- Total 19,674 procedures, 31% repeats
- Procedures/baby/day: 14.3±4.0
- 60% neonates received some analgesia (continuous, episodic)

**Carbajal, Anand, et al., 2008**
- All ICUs in Paris = 430 babies
- Total 72,515 procedures: 52,779 painful, 19,736 stressful
- 115 procedures/baby; 16/day
- Pain relief for 20% procedures

**Roofthooft, Anand, et al., 2014**
- 175 babies for 14 days in NICU
- Total 21,076 procedures
- Higher number in newborns <29wk
- Procedures/baby/day: 11.4±5.7
- 37% neonates received some form of analgesia
The EuroPAIN Survey: 18 Countries, 243 NICUs

Data from 6,680 neonates were obtained by Nov 4\textsuperscript{th}, 2013

- 2691 in U.K.
- 916 in France
- 468 in Spain
- 455 in Greece
- 422 in Italy
- 334 in Norway
- 236 in Portugal
- 208 in Netherlands
- 201 in Finland
- 160 in Sweden
- 128 in Belgium
- 126 in Germany
- 84 in Cyprus
- 83 in Poland
- 73 in Austria
- 45 in Lithuania
- 28 in Malta
- 22 in Estonia

**Europain Survey Contacts**

**Principal Investigators:**

1. **Ricardo Carbajal**, MD, PhD  
   Armand Trousseau Hospital  
   26 av du Dr Nettar  
   75012 Paris, France

2. **Mats Eriksson**, RN, PhD  
   Centre for health care sciences  
   Örebro University Hospital,  
   S-701 85 Örebro, Sweden

3. **Anand, K.J.S.**,  
   Department of Pediatrics,  
   University of Tennessee Health Science Center,  
   Room 346R, 50 North Dunlap St., Memphis, TN, U.S.A.

**Study Coordinator:**  
Emilie Courtois, RN  
Armand Trousseau Hospital  
26 av du Dr Nettar  
75012 Paris, France  
emilie.courtois@trs.aphp.fr  
Tel + 33 144736451
Assessment of continuous pain in newborns admitted to NICUs in 18 European countries

Kanwaljeet J. S. Anand (anandam@stanford.edu)¹, Mats Eriksson², Elaine M. Boyle³, Alejandro Avila-Alvarez⁴, Randi Dovland Andersen⁵, Kosmas Sarafidis⁶, Tarja Polkki⁷, Cristina Matos⁸, Paola Lago⁹, Thalia Papadouri¹⁰, Simon Attard-Montalto¹¹, Mari-Liis Ilmoja¹², Sinno Simons¹³, Rasa Tameliene¹⁴, Bart van Overmeire¹⁵, Angelika Berger¹⁶, Anna Dobrzenska¹⁷, Michael Schrot¹⁸, Lena Bergqvist¹⁹, Emilie Courtois²⁰, Jessica Rousseau²⁰, Ricardo Carbajal²⁰ on behalf of the EUROPAIN survey working group of the NeoOpioid Consortium

Key notes

- Neonatal pain assessments have previously focused on acute pain associated with skin-breaking procedures, but the importance of assessing continuous pain remains unknown.
- Assessments of continuous pain varied 0–100% in neonatal intensive care units (NICUs), occurring daily in 10.4% of all neonates and at least once during their NICU stay in 31.8% neonates.
- Neonatal pain research, clinical guidelines and bedside practices should also focus on assessments of continuous pain in addition to the assessments for procedural pain.
Does repetitive pain alter the developing brain?

- Pain is developmentally unexpected
- Increased plasticity in immature brain
- Limited modulation of pain impulses
- Behavioral shut-down, Learned helplessness?
  - Greater sensitivity to heat pain (at P16, P22)
  - Increased anxiety & defensive withdrawal
  - Prolonged memory in social discrimination
  - Increased preference for alcohol
  - Fewer cells activated in adult cerebral cortex
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.

K.I.S. Anand  response to tactile or noxious stimuli. This led to an increase in pain response behav-
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

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

Cognitive Impairment
Behavioral problems
Poor Socialization Skills
Expression of Fos at 30 min. after hot plate exposure

Noxious Stim Group
- Neonatal rats exposed to 4 needlesticks each day P1-P7
- Allowed to grow to adult size (P60-P70)
- Exposed to thermal pain (hot plate)
- Sacrificed at 0 and 30 minutes
- Brain sections from matched pairs of rats stained for neuronal activity
Cell death after a single episode of inflammatory pain

Cell Death: Left side

Cell Death: Right side
Cell death following repetitive pain in selected brain regions

- **Control**
- **Ketamine**
- **Ketamine & Formalin**
- **Formalin**

**Habenua**: p = 0.4363

**Cortex**: p < 0.001

**Hippocampus**: p < 0.001

**Amygdala**: p < 0.001

**Hypothalamus**: p = 0.0495

**Thalamus**: p = 0.005
Impaired long-term visual-spatial memory in adult rats following Repetitive Neonatal Pain

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

- Control
- Ketamine
- Ket.+Formalin
- Formalin

*p-values: 0.002, 0.009, 0.002, 0.020*
Long-term effects of repetitive pain

Repetitive pain in newborn 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. Leads to altered long-term behavior in adult rats: higher pain thresholds, impaired spatial learning, exaggerated startle response, increased anxiety.

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

Department of Pediatrics, Obstetrics and Reproduction Medicine, University of Siena, Siena, Italy

Ketamine analgesia for inflammatory pain in neonatal rats: a factorial randomized trial examining long-term effects

Address: Pain Neurobiology Laboratory, Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas 72202, USA, 2Department of Surgery, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA, 3Department of Pediatrics and Center for Translational Neuroscience, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA, 4Department of Pediatrics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA, and 5Departments of Pediatrics, Anesthesiology, Pharmacology, Neurobiology & Developmental Sciences, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA
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 2\textsuperscript{nd} surgery in the same dermatome required \textit{more anesthesia and postoperative analgesia, had higher pain scores, & greater catecholamine responses} than matched controls undergoing their 1\textsuperscript{st} surgery or those undergoing their 2\textsuperscript{nd} surgery in a different dermatome.
Gastric suctioning at birth was associated with functional intestinal disorders during later life (odds ratio, 2.99; 95% confidence interval, 1.32–6.79; P = 0.009), 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.
Ex-preterm children show additional activations of thalamus, anterior cingulate cortex, cerebellum, basal ganglia, periaqueductal gray, vs. Term-NICU and Term-Normal children.

Ex-preterm children show markedly increased activation in the primary somatosensory cortex, anterior cingulate cortex, insula.

Continuous pain ratings of ex-preterm children show increased sensitization within and a lack of habituation across trials.
Greater neonatal pain predicted lower body weight (Wald $\chi^2=7.36$, $P=0.01$) and head circumference (Wald $\chi^2=4.36$, $P=0.04$) at 32 wks PCA, after adjusting for birth weight percentile, postnatal risk factors, severity of illness (SNAP-II), days of mechanical ventilation, infection, morphine and corticosteroid exposures.

Painful procedures at <32 weeks PCA accounted for 21% variance in early body growth and 12% variance in early head growth.
After comprehensively adjusting for multiple clinical factors, greater neonatal procedural pain was associated with reduced white matter FA ($\beta = 0.0002$, $p = 0.028$) and reduced subcortical gray matter NAA/choline ratio ($\beta = 0.0006$, $p = 0.004$). Reduced FA was predicted by early pain (before scan 1), 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.

**Objective:** Preterm infants are exposed to multiple painful procedures in the neonatal intensive care unit (NICU) during a period of rapid brain development. Our aim was to examine relationships between procedural pain in the NICU and early brain development in very preterm infants.

**Methods:** Infants born very preterm ($N = 86$; 24–32 weeks gestational age) were followed prospectively from birth, and studied with magnetic resonance imaging, 3-dimensional magnetic resonance spectroscopic imaging, and diffusion tensor imaging: scan 1 early in life (median, 32.1 weeks) and scan 2 at term-equivalent age (median, 40 weeks). We calculated N-acetylaspartate to choline ratios (NAA/choline), lactate to choline ratios, average diffusivity, and white matter fractional anisotropy (FA) from up to 7 white and 4 subcortical gray matter regions of interest. Procedural pain was quantified as the number of skin-breaking events from birth to term or scan 2. Data were analyzed using generalized estimating equation modeling adjusting for clinical confounders such as illness severity, morphine exposure, brain injury, and surgery.

**Results:** After comprehensively adjusting for multiple clinical factors, greater neonatal procedural pain was associated with reduced white matter FA ($\beta = -0.0002$, $p = 0.028$) and reduced subcortical gray matter NAA/choline ($\beta = -0.0006$, $p = 0.004$). Reduced FA was predicted by early pain (before scan 1), 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.

**Interpretation:** Early procedural pain in very preterm infants may contribute to impaired brain development.
After controlling for early illness severity, IV morphine exposure, and postnatal steroids, a higher number of skin-breaking procedures predicted lower cognitive & motor development at 8 and 18 months.

Greater overall exposure to intravenous morphine was associated with poorer motor development at 8 months, but not at 18 months.

Lower parenting stress modulated effects of neonatal pain, but only on their cognitive outcomes at 18 months.
Neonatal pain, functional cortical activity and school-age cognitive outcomes (Doesburg et al., *Pain* 2013)

ELGA children showed significantly reduced Full Scale IQ (P<0.0001) and lower WISC scores on the:
- Verbal Comprehension Index (P<0.0001),
- Perceptual Reasoning Index (P<0.007),
- Working Memory Index (P<0.003), and
- Processing Speed Index (P<0.004)

Generalized Linear Modeling showed that:
- Neonatal pain predicted higher γ/α MEG activity
- Adjusted for confounders (morphine, vent days, SNAP-II, surgery, postnatal steroids, midazolam)
Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm

Source
- Lloyd et al., 1998
- Portnoy et al., 1988
- McDonald et al., 1990
- Smith and Knight-Jones, 1991
- Teplin et al., 1993
- Sommerfelt et al., 1993
- Levy-Shiff et al., 1994
- Hall et al., 1995
  - Study 1
  - Study 2
- Sommerfelt et al., 1995
- Botting et al., 1996
- Stjernqvist and Svenning
  - Bolke and Meyer, 1996
- Seigel et al., 2000
- Taylor et al., 2000
  - Study 1
  - Study 2
- Rickards et al., 2001
- Overall

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<tr>
<th>Source</th>
<th>Relative Risk (95% CI)</th>
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<tr>
<td>Sciram et al., 1990</td>
<td>2.38 (1.10-4.79)</td>
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<tr>
<td>Ross et al., 1991</td>
<td>2.42 (1.00-6.09)</td>
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<tr>
<td>Botting et al., 1997</td>
<td>3.81 (1.89-7.70)</td>
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<tr>
<td>Stevenson, 1999</td>
<td>1.75 (0.52-5.87)</td>
</tr>
<tr>
<td>Stjernqvist and Svenning, 1999</td>
<td>2.40 (0.90-6.40)</td>
</tr>
<tr>
<td>Taylor et al., 2000</td>
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</tr>
</tbody>
</table>
- Study 1 | 1.34 (0.23-7.67) |
- Study 2 | 4.07 (0.94-17.77) |
| Overall | 2.64 (1.85-3.78) |
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
Translational studies identify long-term impact of prior neonatal pain experience

Suellen M. Walker

**NEONATAL EXPERIENCE**
- preterm birth
- intensive care
- pain and tissue injury
  - procedures / surgery
  - type / severity / frequency

**BIOLOGICAL FACTORS**
- gestational age / sensitive periods
- sex / genetic vulnerability
- stress
- intercurrent illness: type and severity
- drugs: beneficial → adverse effects

**PSYCHOSOCIAL FACTORS**
- NICU environment
- handling → skin-to-skin contact
- non-pharmacological pain interventions

**PAIN OUTCOMES IN LATER LIFE**
- persistent pain
  - risk / prevalence / severity
- pain related disability
- response to treatment
  - health care utilization

**BIOLOGICAL FACTORS**
- age / sex
- somatosensory function and sensitivity
- stress vulnerability → resilience
- epigenetic changes / neuroinflammation
- intercurrent illness

**PSYCHOSOCIAL FACTORS**
- gender
- cognitive function
- catastrophizing → adaptive coping
- anxiety → self-efficacy
- parental response / social support
Neurotoxicity of Anesthesia in the Newborn?

K. J. S. Anand, MBBS, D.Phil., FCCM.
Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine
Stanford University School of Medicine, Palo Alto, CA.

Disclosures: Dr. Anand has no financial relationships with any commercial, pharmaceutical, or medical device companies related to this presentation; there are no conflicts of interest to disclose. As senior editor for the book “Pain in Neonates & Infants”, he receives royalty payments from Elsevier Science Publishers and Up-To-Date, Inc. He does not subscribe to Pro-Life or Pro-Choice viewpoints and does not receive any financial or non-financial benefits from any such organizations.
Blockade of NMDA Receptors and Apoptotic Neurodegeneration in the Developing Brain

Chrysanthy Ikonomidou,* Friederike Bosch, Michael Miksa, Petra Bittigau, Jessica Vöckler, Krikor Dikranian, Tanya I. Tenkova, Vanya Stefovska, Lechoslaw Turski, John W. Olney

A-D: TUNEL staining PND7 MK801 0.5 mg/kg E: TUNEL staining PND7 PCP F-G: Electron micrographs of degenerating neurons

A: A single dose of MK801 (0.5, 0.75, or 1 mg/kg ip) on PND7, rat pups sacrificed at 4, 8, 12, 16, 24, or 48 hours
Ketamine neurotoxicity in the immature rat brain

- NMDA receptor blockade by MK801, PCP, or Ketamine (20 mg/kg x 7 doses = 140 mg/kg) was associated with apoptotic neurodegeneration in the brain of P7 rats (Ikonomidow C, 1999)

- Ketamine dose- and time-dependently induced neuronal cell death in different animal species (mice, rats, monkeys, guinea pigs, etc.) (Scallet AC, 2004; Fredriksson A, 2004; Young C, 2005; Rudin M, 2005)

Developmental windows for ketamine-induced neurotoxicity in rhesus monkeys

Slikker W, et al. 2007

20 mg/kg/hr ketamine (IV infusion x 24 hr)

→ Caspase-3 immunostaining of cortex

❖ Gestational Day 122 Prenatal monkey

❖ Posnatal Day 5 Neonatal monkey

❖ Postnatal Day 35 Infant monkey

Scale bar: 100 µm
Anesthetic Agents and the Immature Brain: Are These Toxic or Therapeutic?
Kanwajeet J.S. Anand, M.B.B.S., D. Phil.,* Sulpicio G. Soriano, M.D.†

Of Mice and Men: Should We Extrapolate Rodent Experimental Data to the Care of Human Neonates?

Anesthetic Neurotoxicity in Newborns
Should We Change Clinical Practice?
Ketamine and neurodegenerative mechanisms

A DIFFERENT VIEW

Anaesthetic neurotoxicity in rodents: is the ketamine controversy real?

Adnan T Bhutta¹, Ajay K Venkatesan², Cynthia R Rovnaghi², K J S Anand³
1. UAMS College of Medicine – Department of Pediatrics, Little Rock, Arkansas, USA
2. Arkansas Children’s Hospital Research Institute – Pain Neurobiology Laboratory, Little Rock, Arkansas, USA
3. University of Arkansas for Medical Sciences, and Pain Neurobiology Laboratory – Paediatrics, Little Rock, Arkansas, USA

Correspondence
K. J. S. Anand, University of Arkansas for Medical Sciences, and Pain Neurobiology Laboratory, 4301 W. Markham Street, Little Rock, AR 72205, USA.
Tel: 1-800-777-7700 |
Email: anandsunny@uams.edu

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Potential Neurotoxicity of Ketamine in the Developing Rat Brain

Xiaoju Zou,* Tucker A. Patterson,* Natalya Sadovova,† Nathan C. Twaddle,‡ Daniel R. Doerge,‡ Xuan Zhang,* Xin Fu,§ Joseph P. Hanig,¶ Merle G. Paule,* William Slikker,* and Cheng Wang*"1

*Division of Neurotoxicology, National Center for Toxicological Research, U.S. Food & Drug Administration, Jefferson, Arkansas 72079; †Toxicologic Pathology Associates, Jefferson, Arkansas 72079; ‡Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food & Drug Administration, Jefferson, Arkansas 72079; §Center for Devices and Radiological Health, U.S. Food & Drug Administration, Rockville, Maryland 20850; and ¶Center for Drug Evaluation and Research, U.S. Food & Drug Administration, Silver Spring, Maryland 20993
Neuroprotective effects of Ketamine
Repetitive pain in newborn 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 Leads to altered long-term behavior in adult rats: higher pain thresholds impaired spatial learning exaggerated startle response increased anxiety

Dual Effects of Ketamine: Neurotoxicity Versus Neuroprotection in Anesthesia for the Developing Brain
Jia Yan, MD and Hong Jiang, MD, PhD

Ketamine as a neuroprotective and anti-inflammatory agent in children undergoing surgery on cardiopulmonary bypass: A pilot randomized, double-blind, placebo-controlled trial
Adnan T. Bhutta, MBBS, FAAP; Michael L. Schmitz, MD; Christopher Swearingen, PhD; Laura P. James, MD; Wendy L. Wardbegnoche, PhD; Diana M. Lindquist, PhD; Charles M. Glasier, MD; Volkan Tuzcu, MD; Parthak Prodhan, MBBS; Umesh Dyamenahalli, MD; Michiaki Imamura, MD, PhD; Robert D. B. Jaquiss, MD; Kanwaljeet J. S. Anand, MBBS, DPhil
Pilot RCT: Hypothesis
(Bhutta, Anand, et al, PCCM, 2013)
- Ketamine (2 mg/kg), via NMDA receptor blockade and anti-inflammatory effects, will block excitotoxic neuronal cell death and inflammation, thereby offering neuroprotective effects during CPB

Pilot RCT: Methods
- Blinded, placebo-controlled RCT: age < 1 year, no chromosomal abnormalities, surgical VSD repair
- Ketamine 2 mg/kg pre-CPB (n=13) vs. Controls normal saline (n=11);
- Same anesthetic & surgical protocols, same postoperative ICU care
- Biomarkers of inflammation and CNS injury measured at the end of surgery, 6 hrs, 24 hrs, and 48 hrs after surgery
- MRI/MR-Spectroscopy before surgery and at hospital discharge
- Bayley Scales for Infant Development (BSID-II) assessed before surgery and about 3 weeks after surgery
C Reactive Protein

Pilot RCT: Effects on inflammation
(Bhutta, Anand, et al, PCCM, 2013)
Pilot RCT: Effects on Neuronal injury
(Bhutta, Anand, et al, PCCM, 2013)
Ketamine (2 mg/kg) prior to CPB may reduce CNS injury and inflammation following CPB in infants.

Infants receiving Ketamine show less glutamate release, lower choline (decreased neuronal metabolism) and creatine levels (less energy requirements) in postoperative MR Spectroscopy scans.

NIRS signal postop shows greater chaos/complexity in the Control group.

We propose a large, multicenter RCT to confirm the neuroprotective effects of Ketamine and to examine the safety of Ketamine use in infants.
Ketamine in neonates: the bottom line

Animal studies show that:
– Ketamine is neurotoxic in high doses, with repeated doses or prolonged exposures; in the absence of surgery / pain
– Ketamine is neuroprotective in the setting of prolonged pain, brain trauma, ischemia, seizures, etc.
– Neuroprotective effects occur with clinically relevant doses
– Ketamine blocks proliferation, alters neurogenesis of NSPCs

Clinical implications:
– No human studies reported for Ketamine-induced neurotoxicity
– Avoid prolonged exposures, in high doses, or during pregnancy
Neonatal rats (P1-P7) exposed to daily inflammation ± morphine

Adult rats exposed to repetitive neonatal pain had hypoalgesia to thermal pain (P = 0.013), reduced locomotor activity (P < 0.001), and decreased ethanol preference (P = 0.045)

Neonatal morphine pretreatment significantly reduced the long-term effects of repetitive neonatal pain on thermal hypoalgesia and locomotor activity, but did not alter reduced ethanol preference.
Neonatal morphine pretreatment attenuated neonatal injury-induced thermal and mechanical hypoalgesia in adolescent and adult rats.

- Neonatal morphine reduced the hyperalgesia and increased the rate of recovery after CFA-induced inflammation in adulthood.
- Neonatal morphine did not alter the dose-responses to morphine analgesia in adulthood.
- Neonatal injury markedly reduces morphine potency in adult rats.
RCTs of 87 children, given morphine vs. placebo as neonates

Morphine therapy associated with improved long-term outcomes (higher IQ scores, lower ABC & CBCL scores) at 5-6 years age

<table>
<thead>
<tr>
<th></th>
<th>Morphine Median (interquartile range)</th>
<th>Non-morphine Median (interquartile range)</th>
<th>Mann–Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at assessment (years)</td>
<td>5.9 (5.6–6.0)</td>
<td>5.7 (5.0–5.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Intelligence (IQ)</td>
<td>98 (85–112)</td>
<td>94 (81–109)</td>
<td>2.0</td>
</tr>
<tr>
<td>Motor impairment (ABC)</td>
<td>9 (5.3–21.5)</td>
<td>12 (6.9–22.8)</td>
<td>−2.0</td>
</tr>
<tr>
<td>Behaviour problems (CBCL)</td>
<td>24 (14–42)</td>
<td>29 (16–41)</td>
<td>−3.0</td>
</tr>
</tbody>
</table>
Magnetoencephalography Reveals Slowing of Resting Peak Oscillatory Frequency in Children Born Very Preterm

SAM M. DOESBURG, URS RIBARY, ANTHONY T. HERDMAN, ALEXANDER MOISEEV, TERESA CHEUNG, STEVEN P. MILLER, KENNETH J. POSKITT, HAL WEINBERG, MICHAEL F. WHITFIELD, ANNE SYNNES, AND RUTH E. GRUNAU

Department of Diagnostic Imaging [S.M.D.], The Hospital for Sick Children, Toronto M5G 1X8, Canada; Department of Psychology [U.R., H.W.], Department of Physics [T.C.], Simon Fraser University, Burnaby V5A 1S6, Canada; Department of Audiology and Speech Sciences [A.T.H.], University of British Columbia, Vancouver V6T 1Z3, Canada; Down Syndrome Research Foundation [A.M., T.C.], Burnaby, V5B 4J8, Canada; Department of Pediatrics [S.P.M., M.F.W., A.S., R.E.G.], University of British Columbia, Vancouver V6H 3V4, Canada; Department of Radiology [K.J.P.], University of British Columbia, Vancouver V5Z 4E3, Canada
Decreased height for age in the Morphine gr (p=0.02); likely due to SGA (Morphine 26.5%, Placebo 12.2%)
Cognitive outcome: No differences when adjusted for open-label morphine, neonatal ventilation, and other clinical factors
“Visual analysis” in RAKIT → negative effects for Morphine (p=0.02)
Visual-Motor Integration: lower scores in the Morphine group; with significant effect for open-label morphine
No differences in child behavior (parent- or teacher-rated), prevalence of chronic pain, or health-related quality of life (HUI-15)
Follow-up of 89/132 (67%) children at 8-9 years of age corrected age

No differences in those attending mainstream classes (54% vs. 59%)

Morphine group children had less externalizing behaviors (parents), slightly more internalizing behaviors (teachers)

Morphine group children had better executive functions: BRIEF rated by parents (inhibition, organization) & teachers (planning, organizing)

Significant differences increased after adjustment for IQ scores

Additional morphine open-label doses did not affect any outcomes
School records of Arkansas NEOPAIN children

- Arkansas Public School Computer Network contains records for 150 ex-preterm NEOPAIN children
- Placement data from objective testing scores were available for 130 children in mathematics and 131 children in literacy
- Morphine-treated children placed higher in mathematics ($\chi^2=5.361; p=0.02$), but literacy was similar in the morphine and placebo groups ($\chi^2=0.0456; p=0.5$)
Cognitive scores lower in Morphine (94 ± 14.5) vs. Placebo (99.8 ± 12.9) (p=0.049); no differences when adjusted for clinical factors

“Visual analysis” showed significant negative effects for Morphine group (p=0.02) and use of 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 scores (parent- or teacher-rated), or chronic pain, or health-related quality of life (HUI-15)
Follow-up of 89/132 (67%) children at 8-9 years corrected age

- No differences in school classes (54% vs. 59%), visual-motor functions
- Morphine group children had less externalizing behaviors (parents), slightly more internalizing behaviors (teachers)
- Morphine exposure improved executive functions: higher BRIEF scores by parents (inhibition, organization) and teachers (planning, organization) →
- Fewer problems in Behavioral Regulation Index (P = 0.006), Metacognition Index (P = 0.03), Global Executive Composite (P = 0.009) in Morphine group
Animal studies show that:

- Morphine blocks the long-term effects of inflammatory pain in newborn rats
- Prolonged morphine exposure (prenatal/postnatal) in the absence of pain impairs brain development, cognitive outcomes
- No neurotoxic effects, may be neuroprotective effects

Clinical implications:

- May improve cognitive and neuromotor outcomes following birth asphyxia or repetitive neonatal pain
- Delays visual-motor function, socialization, task completion
- May improve executive functions and mathematical skills
Dexmedetomidine

- Analgesia, anxiolysis, & sedation, but tolerance does occur
- Stimulates $\alpha_{2A}$- and $\alpha_{2C}$-adrenergic receptors, indirect effects via opioid and $\gamma$-aminobutyric acid receptors
- 8-fold greater specificity than Clonidine
- Infusions 0.2 μg/kg/hr, maximum rates 0.7-1.5 μg/kg/hr
- Analgesic plasma levels are 0.6-1.25 μg/L (adult pts)
- Sedative plasma levels are 0.4–0.8 mcg/L (pediatric pts)
- No significant changes in BP, HR, SaO$_2$
- Dexmedetomidine during surgery reduces postop pain and analgesic usage (11 RCTs, n=434 vs. n=440; Dex vs. placebo or opioids) (Schnabel et al. Paediatr Anaesth. 2013;23(2):170-9)
Dexmedetomidine in infants: bottom line

- Animal studies show:
  - Neuroprotective effects in multiple animal models, following focal or global cerebral ischemia, or spinal cord ischemia, or traumatic brain injury
  - Blocks the neurotoxicity following high-dose Ketamine (75 mg/kg), or Isoflurane, as well as glutamate-induced excitotoxicity

- Clinical implications:
  - No clinical data related to neurotoxic or neuroprotective
  - Limited data on the safety, efficacy, and long-term effects of dexmedetomidine in neonates
Recruited infants 26-60 weeks PMA → inguinal herniorrhaphy
Randomized to regional (n=363) vs general anesthesia (n=359)
Blinded assessment using Bayley Scales III at 2 years age
Composite score was 98.6 (RA) vs. 98.2 (GA) groups
Average duration of general anesthesia = 54 minutes
No differences in complications or other outcomes
Outcomes from the PANDA Study

Age at Exposure to Surgery and Anesthesia in Children and Association With Mental Disorder Diagnosis
(Anesthes Analg 2017;XXX:00–00)

Caleb Ing, MD, MS,*† Ming Sun, MS,*‡ Mark Olfson, MD, MPH,§
Charles J. DiMaggio, PhD, MPH, PA-C,‖ Lena S. Sun, MD,*¶ Melanie M. Wall, PhD,‡§ and
Guohua Li, MD, DrPH*†

- Medicaid database 38,493 vs. 192,465 children <5yr.
- Compared diagnoses of mental disorder, or ADHD, or developmental delay
- Increase hazard risk ratios 1.26, 1.31, 1.26 (p<0.01)
- No increased risks at younger age groups
Current thinking regarding potential neurotoxicity of general anesthesia in infants

Mary Ellen McCann^a and Jurgen de Graaff^b
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:

Improved neurologic outcomes in ex-preterm babies
Reduced cell death in the developing brain
Improved cognition and less behavioral problems
Increased ability to cope with stress
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}
Brain-derived methods provide the best surrogate measures of infant pain and be more directly linked to pain experiences.

Used EEG to identify and validate a template of nociceptive brain activity that is sensitive to analgesic administration.

Studied 72 neonates across 5 studies: 1 derive a template for acute pain activity, 2 examine its specificity to noxious stimuli, 3 apply to preterm neonates 34-36 wks GA, 4 relationship to pain-related behaviors, 5 sensitivity to analgesic modulation.
Performance:
- 64% sensitivity, 65% specificity to heel lance
- 57% sensitivity, 68% specificity to noxious experimental stimuli
How are infants exposed to ketamine?

- Clinical uses:
  - Anesthetic induction and maintenance
  - Pain management for acute and chronic pain
  - Sedation for procedures in the PICU and Emergency Dept.
  - Antidepressant effects in Major Depressive Disorder

- Recreational use:
  - In bars, nightclubs, parties
  - Bump, K, Ket, Kit Kat, Kizzo, Special K, Vitamin K

Administration Routes:
- Intravenous (IV)
- Intramuscular (IM)
- Oral
- Rectal
- Nasal
- Epidural
Ketamine: an NMDA receptor antagonist

- NMDA: most expressed of the ionotropic glutamate receptors
- A ligand-gated ion receptor channel (Ca$^{2+}$)
- Ketamine: a noncompetitive NMDA receptor antagonist
- Binds to synaptic, extra-synaptic NMDA receptors
- Effects on opioid, serotonin, acetylcholine, $\alpha_2$-AR receptors
- Neuroprotective effects in ischemic, traumatic brain injury
Use of Opioids in Asphyxiated Term Neonates: Effects on Neuroimaging and Clinical Outcome

DANILYN M. ANGELES, NATHANIEL WYCLIFFE, DAVID MICHELSON, BARBARA A. HOLSHouser, DOUGLAS D. DEMING, WILLIAM J. PEARCE, LAWRENCE C. Sowers, AND STEPHEN ASHWAL

- Retrospective review of 52 neonates admitted with birth asphyxia
- 17 neonates received opioids (morphine or fentanyl) at < 7 days
- Greater HIE (lower 5-min Apgar, lower pH, higher pCO₂ [p<0.05], higher lactate p<0.001) in the opioid vs. non-opioid group (n=35)
- MRI scans showed less severe damage in the opioid group
- Opioid therapy was associated with improved long-term outcomes (higher PCPC & higher neuromotor scores) at 18 months age