

# Neonatal Stress, Pain and Cognitive Deficits

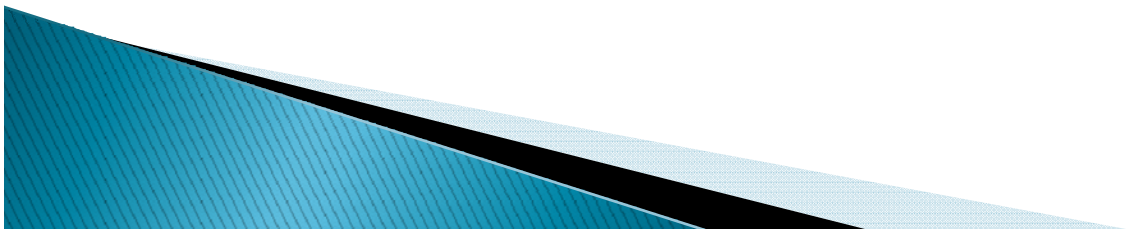
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# Learning objectives

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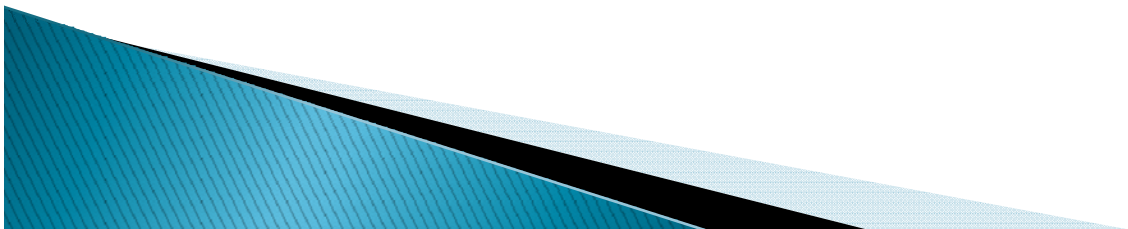
- ▶ Scope of pain and stress in the preterm baby in the NICU
- ▶ Effect of neonatal pain and stress on the brain
- ▶ Long term effects on neurocognitive outcomes
- ▶ What are the potential mechanisms of pain associated effects on long term cognitive deficits



# Background

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- ▶ Preterm infants undergo repeated pain from therapeutic procedures as a necessary part of neonatal intensive care at a time of very rapid brain development
  - 10-14 painful procedures a day
  - 20% of preterms have surgery while admitted in the NICU



# Background

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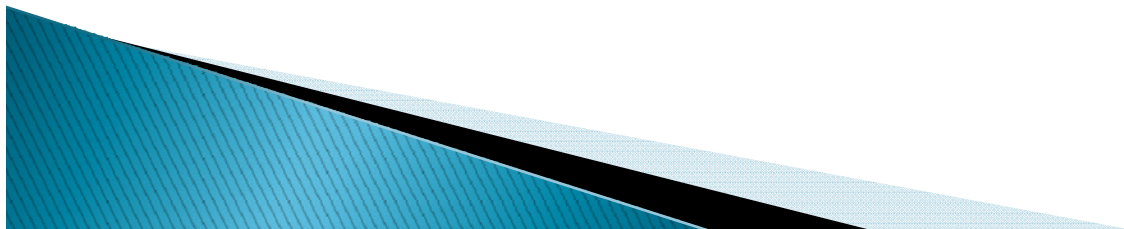
- ▶ **Unmanaged pain affects**
  - Hemodynamic stability:
    - hypertension
    - tachycardia
  - Physiologic stability:
    - apneas
    - desaturations
  - Stress expression:
    - elevated cortisol
- ▶ **Measure pain scores:**
  - Behavioural
  - Physiologic



# Interventions to Treat Pain


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- ▶ Non- pharmacologic:
  - facilitated tucking,
  - non-nutritive sucking
  - skin to skin care
- ▶ Oral glucose or sucrose
- ▶ Pharmacologic:
  - CNN < 33 wks GA 2010-2014 n= 20,744
  - Narcotics 23%
  - Sedatives 17%
  - Narcotics or sedatives 29%



# RCT of Routine Morphine

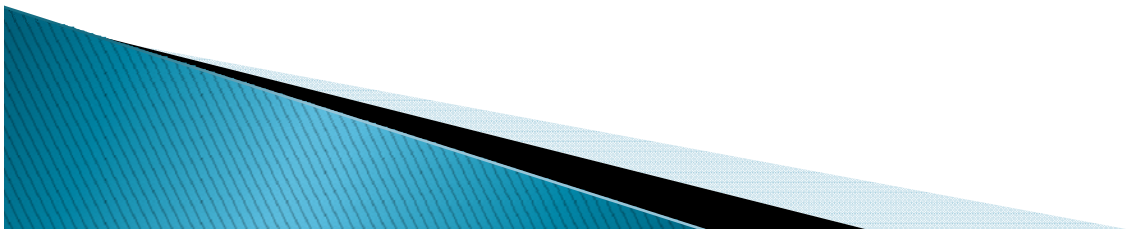
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- ▶ **NOPAIN trial** (Simons SH, Anand KJ JAMA 2003)
    - RCT of 150 ventilated newborns
    - Morphine (100 µg/kg loading and 10 µg/kg per hour) or placebo infusion was given for 7 days
    - No difference in pain scores (10.1 vs 10.0)
    - Decreased IVH (23% vs 40%, P = .04) but
    - Poor neurologic outcome (10% vs 16%, P = .66).
    - At 5 yrs, morphine associated with worse visual analysis domain of intelligence
  - ▶ **Conclusion:**
    - Lack of a measurable analgesic effect and absence of a beneficial effect on neurologic outcome do not support the routine use of morphine.
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# RCT of Routine Morphine

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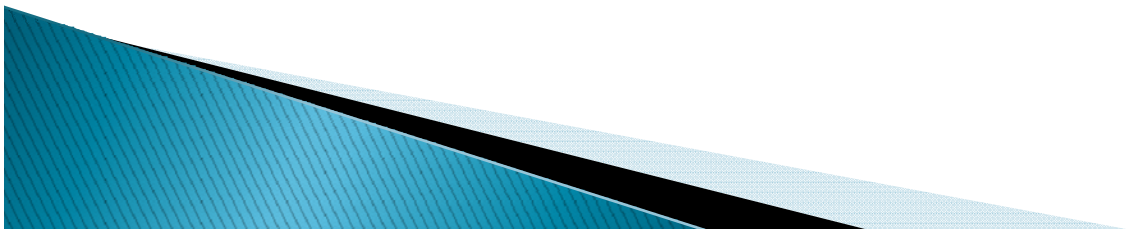
- ▶ **NEOPAIN trial** (Anand KJ Lancet 2004)
  - Increased IVH, PVL or death with randomized or open label morphine
  - At 36 wks CGA increased popliteal angle tone
  - At 8 mos CGA, worse motor scores
  - A subset at 5-7 yrs,
    - smaller head circumference
    - Impaired short term memory
    - More social problems
- ▶ **Conclusion:**
  - No benefit of routine morphine



# Pain in the Neonate

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- ▶ Preterm babies feel pain, even at lowest GA
- ▶ Ascending neural pathways for nociception mature before the descending inhibitory pathways which localize and mitigate pain (Fitzgerald 1986)
- ▶ Pain is also increased because of the excitability of nociceptive neurons in the dorsal horn (Taddio, 2009)

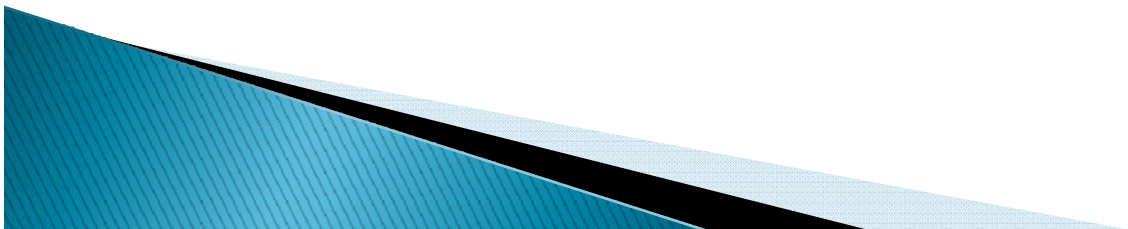




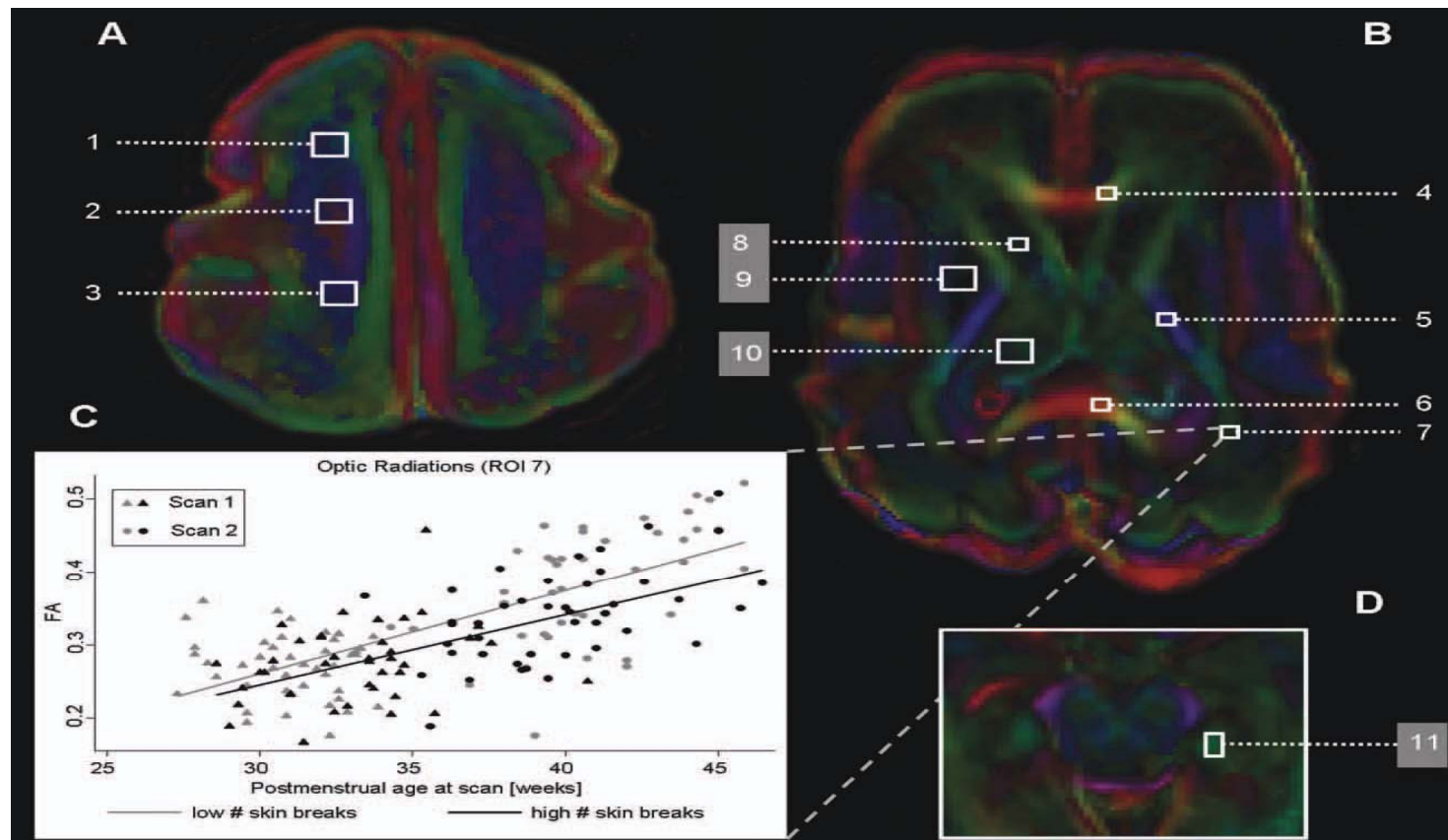
# Neonatal Pain and the Brain

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- ▶ Procedural pain /stress are associated with
  - Decreased frontal and parietal brain growth (Smith 2011)
  - Altered organization and neuronal connections in the temporal lobes (Brummelte 2012)
  - Worse cognitive and motor function at 8 and 18 months (Grunau 2009)
  - Altered spontaneous cortical oscillations (MEG) in the resting brain at school age (Doesburg 2013)



# Procedural Pain and Brain Development in Premature Newborns



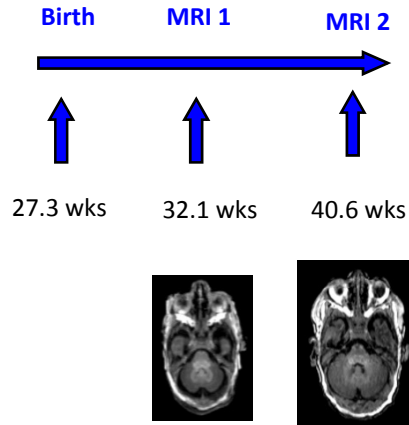
- ▶ Early procedural pain in very preterm infants may contribute to impaired brain development.

Brummelte et al. Ann Neurol 2012

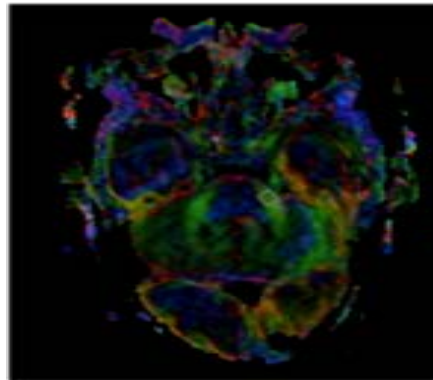
# Morphine Exposure is Associated with Altered Cerebellar Growth in Premature Newborns

Jill G Zwicker et al

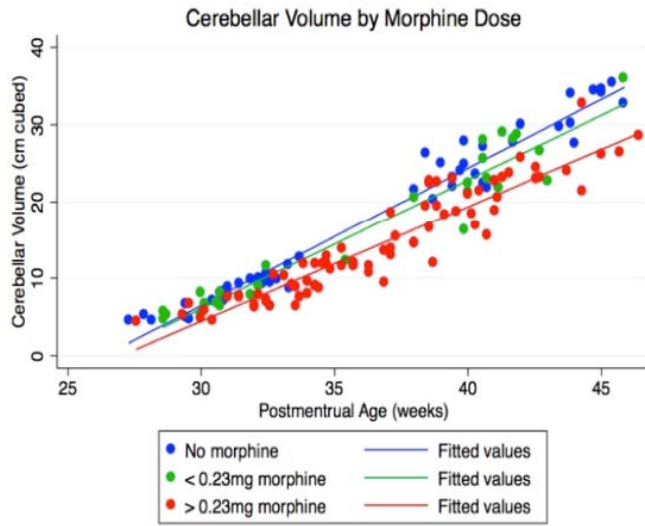
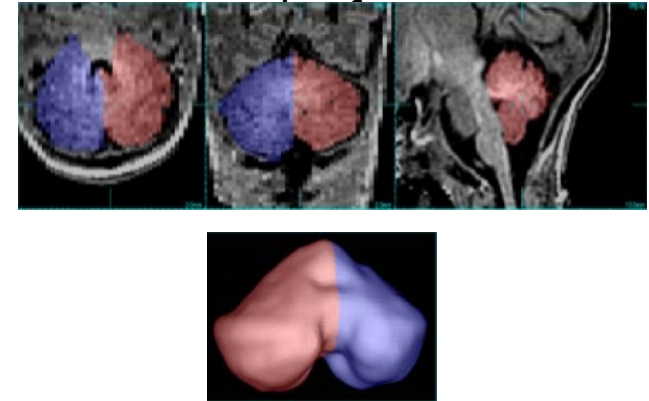
Using advanced MRI, we studied 76 premature newborns born at 24-32 wks GA



CEREBELLAR DEVELOPMENT



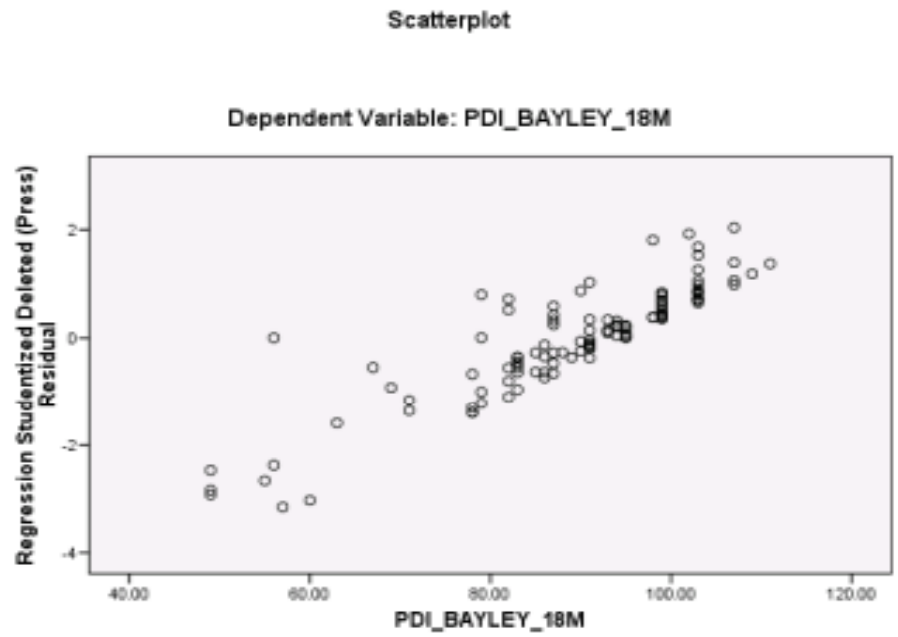
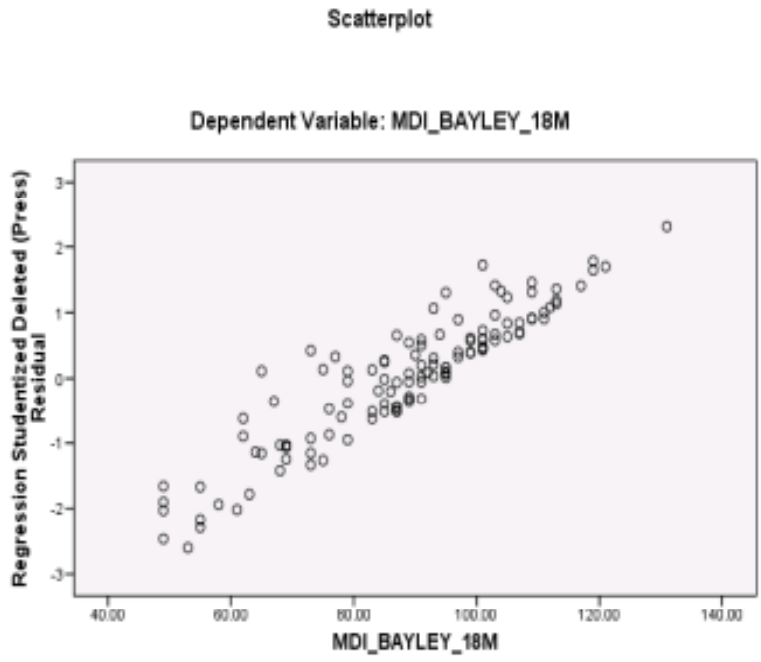
MACROSTRUCTURAL: Bi-hemispheric cerebellar



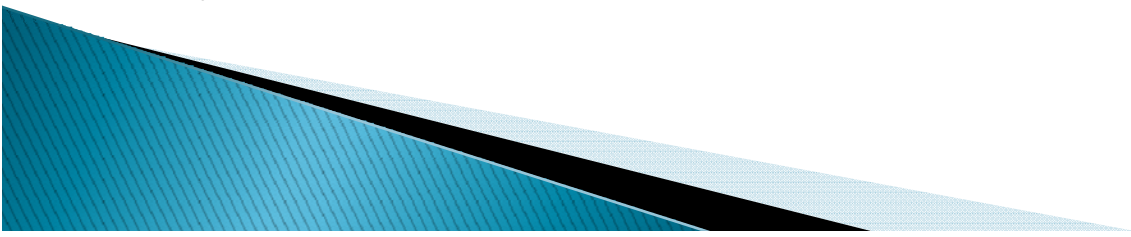
- Animal models suggest reduction in cerebellar volume with morphine exposure may be related to Purkinje cell loss.
- Morphine is associated with impaired macrostructural development of the cerebellum in premature newborns

# Cumulative Neonatal Pain-Related Stress in Very Preterm Infants Predicts Poorer Cognitive and Motor Outcomes at 8 and 18 Months Corrected Age

RE Grunau et al



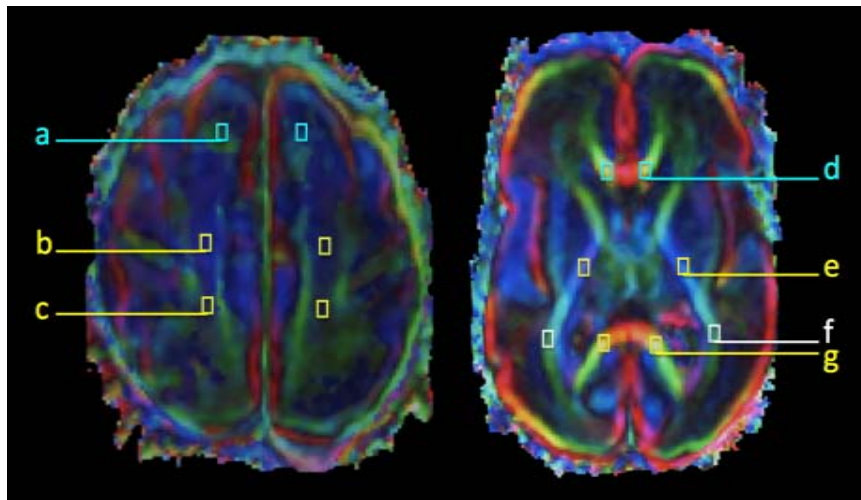
- (21.4).
- Higher number of skin-breaking procedures from birth to term, and longer time on mechanical ventilation in the NICU, predicted poorer cognitive and motor development
  - Family factors moderated cognitive, but not motor, development at 18 months CGA
  - Greater exposure to IV morphine was not protective for neurodevelopment, and may contribute to poorer early motor function



# Early neonatal pain exposure and brain microstructure predict cognitive ability : 18 months corrected age in children born very preterm

Jillian Vinall et al

To examine whether early neonatal pain exposure interacts with quantitative measures of brain microstructure (fractional anisotropy) to predict cognitive outcome (Bayley-III at 18 months corrected age (CA) in children born very preterm (n=114)



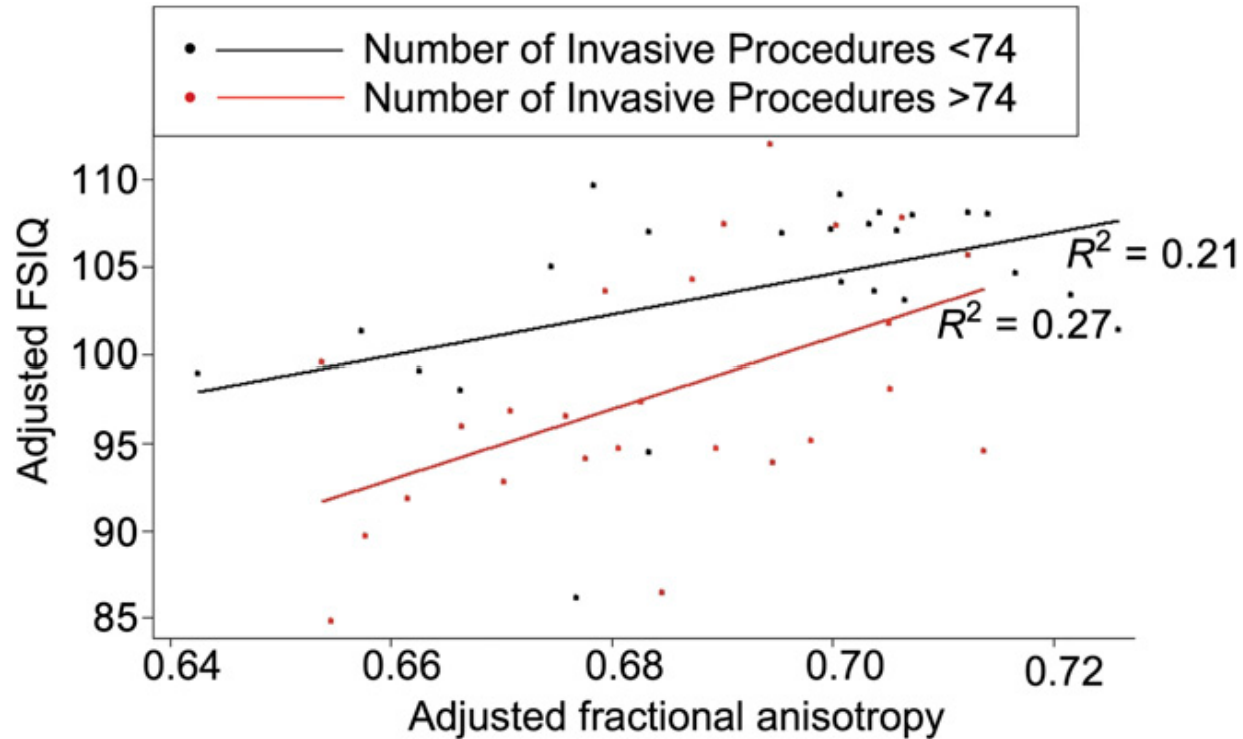
Repeated pain exposure during NICU care impacts white matter microstructure and child cognition in children born very preterm at 18 months CA, after adjusting for clinical confounders.

Predictors	Child Cognition	
	$\beta$	P Value
Neonatal pain x fractional anisotropy	-2.36	0.007
Fractional anisotropy	1.81	0.005
Number of skin breaks	1.37	0.007
Gestational age	0.14	0.45
Small for gestational age	0.23	0.03
Illness severity on day 1	0.001	0.99
Mechanical ventilation	0.01	0.95
Morphine exposure	-0.15	0.34
Postnatal infection	-0.005	0.97
Necrotizing Enterocolitis	-0.10	0.36
Age at Scan	0.14	0.37
WMI	0.02	0.87
IVH	0.04	0.67
Cerebellar Hemorrhage	-0.03	0.80



# Invasive Procedures in Preterm Children: Brain and Cognitive Development at *School Age*

Jillian Vinall et al.



Altered myelination at school age is associated with greater numbers of invasive procedures during hospitalization in very preterm children without severe brain injury or neurosensory impairment. Greater numbers of invasive procedures and altered brain microstructure interact to predict lower IQ.

# Neonatal pain-related stress and morphine predicts internalizing in very preterm school-age children

Manon Ranger PhD<sup>1,2</sup>, Anne R Synnes MDCM<sup>1,2,3</sup>, Jillian Vinal BA<sup>2</sup>, & Ruth E Grunau PhD<sup>1,2,3</sup>

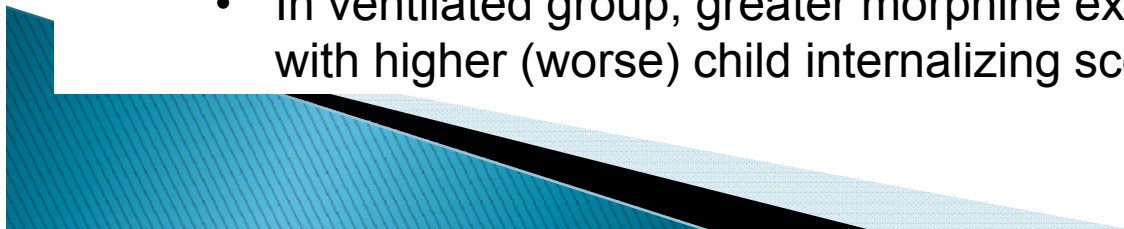
**Non-ventilated** very preterm (n = 44)

Predictors	B (unstandardized)	p-value
GA	-1.025	0.387
SNAP-II day 1	0.024	0.931
Infections	0.885	0.927
<b>Skin-breaks</b>	<b>17.127</b>	<b>0.03</b>
<b>PSI Parenting stress</b>	<b>0.166</b>	<b>0.002</b>

**Ventilated** very preterm (n = 57)

Predictors	B (unstandardized)	p-value
GA	0.947	0.329
SNAP-II day 1	0.114	0.386
Infections	0.942	0.779
Surgeries	-3.14	0.166
Ventilation days	-7.344	0.311
Skin-breaks	-0.012	0.999
<b>Morphine exposure</b>	<b>20.909</b>	<b>0.002</b>
PSI Parenting stress	0.099	0.06

- After adjusting for neonatal clinical factors
  - In non-ventilated group, higher skin-breaking procedures ( $p = 0.03$ ) and parenting stress ( $p = 0.002$ ) were related to greater internalizing behaviors (anxiety / depressive) at 7 years
  - In ventilated group, greater morphine exposure ( $p = 0.002$ ) was associated with higher (worse) child internalizing scores



# Potential Mechanisms of Procedural Pain

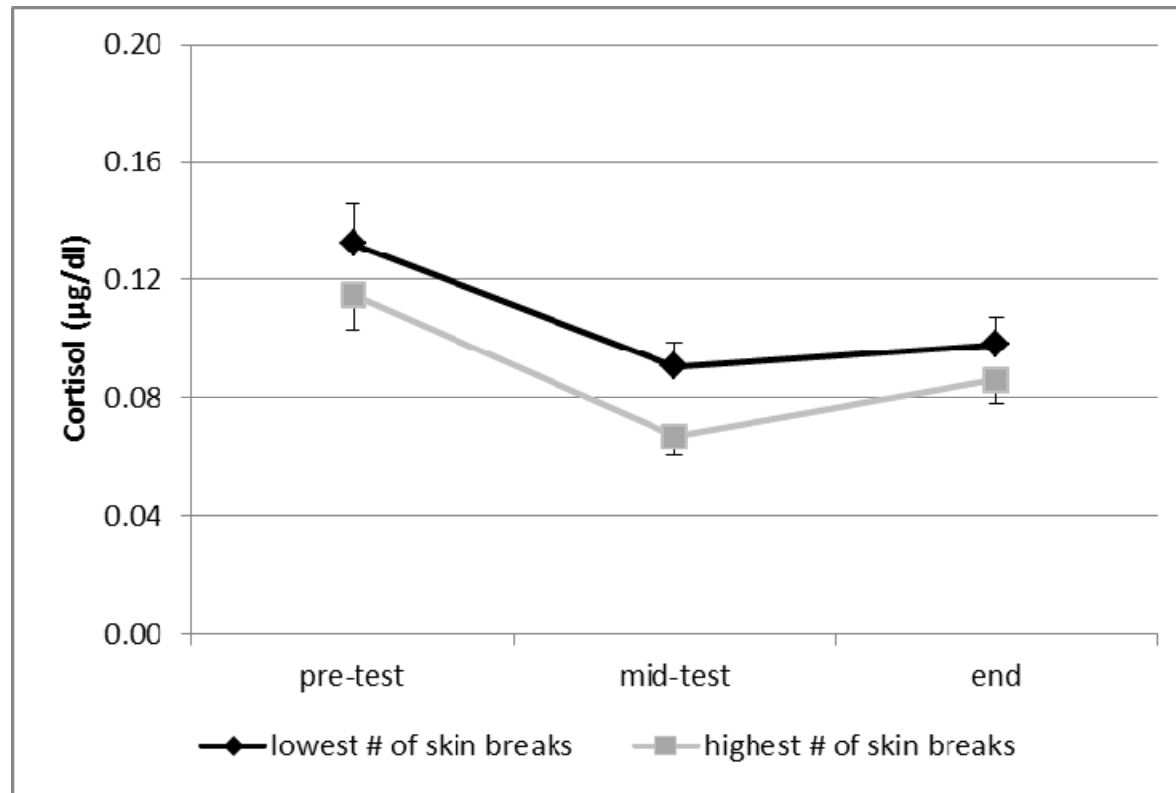
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- ▶ Pain itself
  - In rats, early inflammatory pain or repeated injections induce cell death in the brain
  - Cortisol
- ▶ Treatment of pain
  - Hypotension associated with analgesics
  - Opioid receptor associated effects on neurons
  - Morphine exposure in animal models is associated with Purkinje cell death and impaired cerebellar development (Hauser 2000, Bekheet 2010)
  - Individual differences in susceptibility
- ▶ Confounding factors





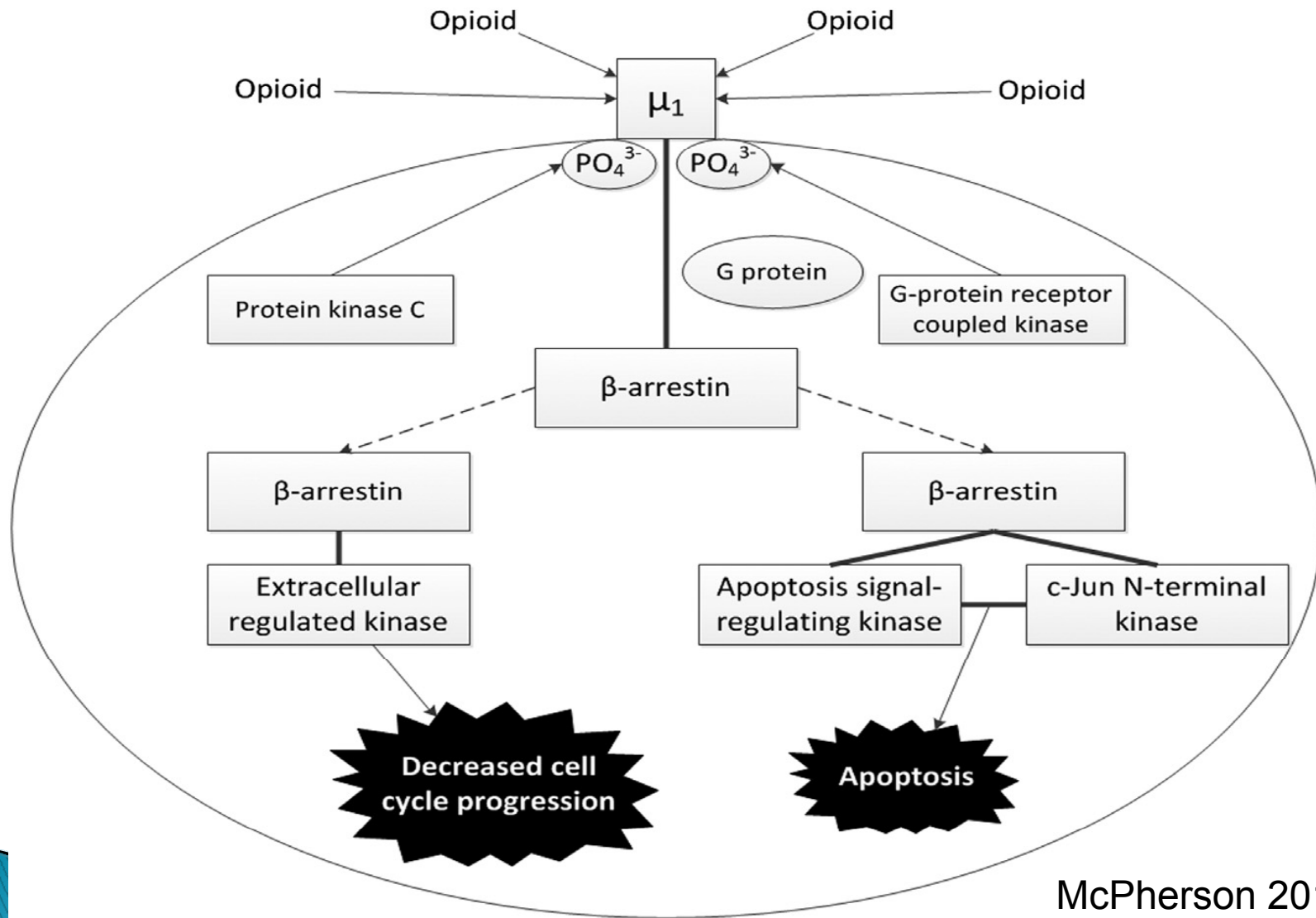
## Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress



Salivary cortisol levels before and after cognitive assessment for preterms with low or high number of skin breaking procedures. There was a negative association between neonatal pain (corrected for morphine) and diurnal cortisol ( $p = 0.044$ ).

Brummelte et al Psychoneuroendocrinology 2015

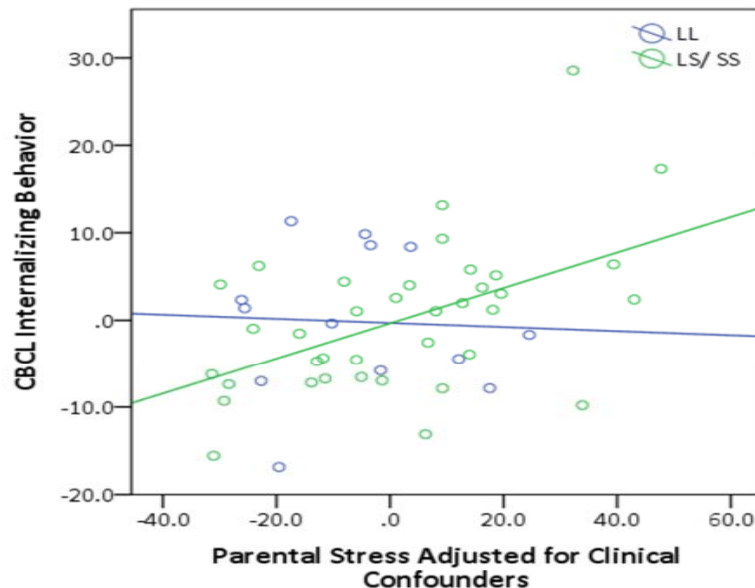
# Opioid Effects in Rodent Model



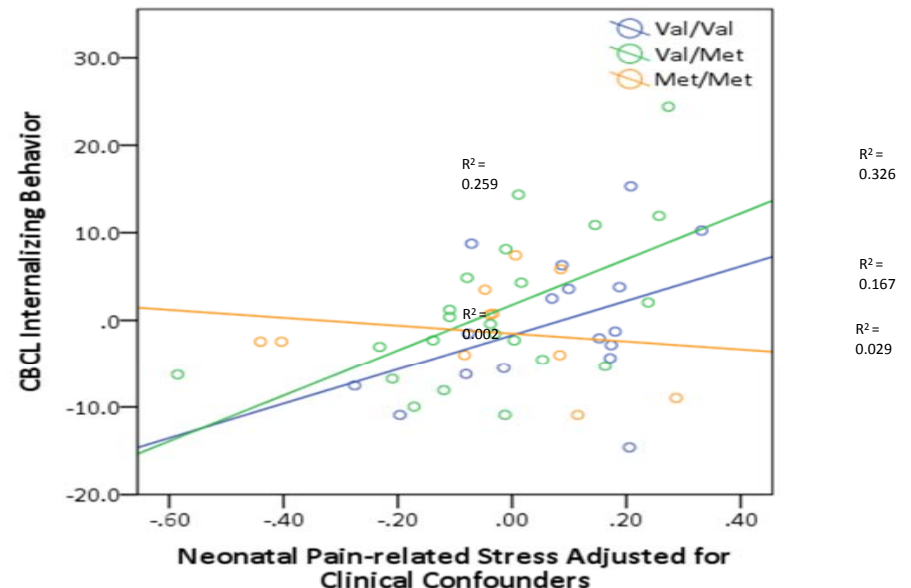
# Neonatal Pain-Related Stress Interacts With *SERT 5HTTLPR* and *COMT* rs4680 Genotype to Predict Internalizing Behavior in Girls Born Very Preterm

Cecil MY Chau et al

Risk for developing internalizing behavior is related to serotonin transporter (*5HTTLPR*) and to Catechol-*O*-methyltransferase (*COMT*) genotypes in humans exposed to early adversity



***SERT 5HTTLPR***



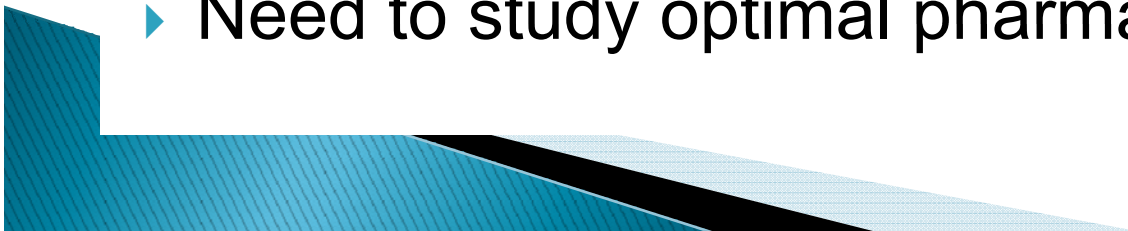
***COMT* rs4680**

SERT and COMT genotype by stress interactions differentially predict internalizing behaviors in very preterm *girls* at age 7 years but not boys

# Conclusions

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- ▶ Invasive procedures are common in preterm newborns in NICUs
- ▶ Unmanaged pain is associated with short term adverse outcomes
- ▶ Procedural pain is associated with adverse MRI, cortisol, 8, 18 month and school age outcomes
- ▶ Narcotics and sedatives are used frequently with potential adverse affects on the preterm brain.
- ▶ Avoid unnecessary painful procedures
- ▶ Nonpharmacologic management recommended
- ▶ Need to study optimal pharmacologic treatments





# Acknowledgments

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- ▶ Steven Miller
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- ▶ Cecil Chau
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- ▶ Jill Zwicker
- ▶ Emily Tam



National Institute of Child  
Health & Human Development





# Narcotics and Sedatives in the NICU

L Borenstein-Levin, MD<sup>1</sup>, SP Miller, MDCM<sup>2</sup>, RE Grunau, PhD<sup>1</sup>, A Synnes, MDCM<sup>1</sup>, P Shah, MD<sup>2</sup> and the Canadian Neonatal Network<sup>TM</sup>  
Department of Pediatrics, BC Women's Hospital, Vancouver, BC, Canada and <sup>2</sup>Department of Pediatrics, University of Toronto, Toronto, ON, Canada.



## Background

- Pain and stress in preterm newborns are associated with adverse Outcomes
- Narcotics and sedatives are associated with abnormalities of brain metabolism and microstructure and other important side effects
- Long term follow up as well as data from animal models suggest a potential harm of midazolam and opioids on the developing brain
- The optimal management is unknown
- The current use of narcotics and sedatives in Canadian NICUs is unknown

## Objectives

To evaluate the use of narcotics and sedatives in Canadian NICUs and characteristics of patients who receive these medications

## Methods

All neonates < 33 weeks' GA that were born 2010-2013 in 1 of 30 participating CNN sites were included in the study

Infants who received one or more doses of sedative or narcotic drug during their NICU stay were identified from the CNN database

Other demographic and morbidity data were collected from the CNN data

The incidence of babies ever exposed to narcotics, sedatives or narcotics or sedatives during NICU stay, trend in annual incidence, variation by site adjusted for gestation, surgery and ventilation were calculated using multiple logistic regression

## Results

Figure 1. Site comparisons for narcotics usage adjusted for gestational age, surgery and mechanical ventilation

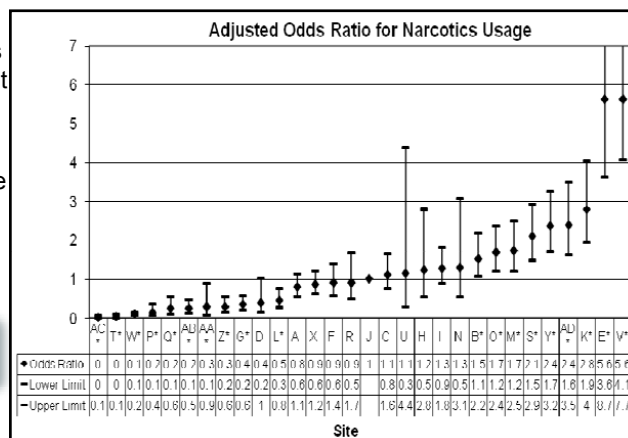


Figure 2. Site comparisons for sedatives usage adjusted for gestational age, surgery and mechanical ventilation

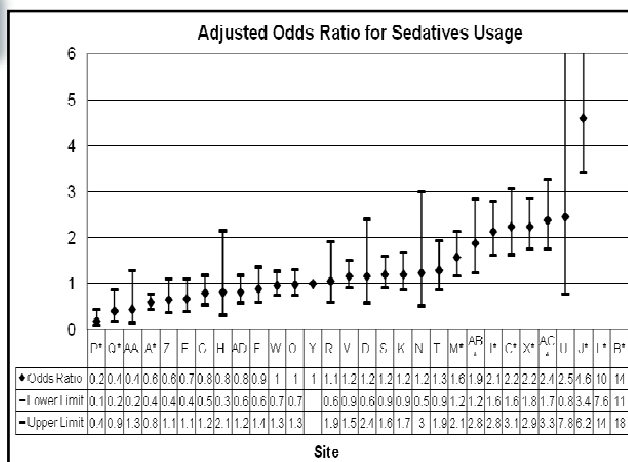


Table 1. The incidence of narcotics or sedatives usage among premature babies < 33 wk

	% preterm babies < 33wk who received narcotics / all preterm < 33wk	% preterm babies < 33wk who received sedatives / all preterm < 33wk	% preterm babies < 33wk who received narcotics or sedatives / all preterm < 33wk
2010	18% (736/4039)	17% (678/4039)	27% (1097/4039)
2011	20% (775/3880)	16% (640/3880)	28% (1080/3880)
2012	19% (807/4196)	16% (656/4196)	25% (1066/4196)
2013	18% (737/4134)	18% (735/4134)	27% (1101/4134)
Total 2010-2013	19% (3055/16249)	17% (4344/16249)	27% (8344/16249)
p-value from Cochran-Armitage trend test over 4 years (2010 – 2013)	0.4847	0.4150	0.1982

## Conclusions

- Exposure to narcotics or sedatives is common in preterm NICU babies despite concerns about adverse outcomes related to these drugs
- The tremendous variation in practice provides suggests that further research on current practices and identifying optimal practice is warranted

## Limitations

The specific drug or the reasons for administration of the drug were not documented as well as the length of treatment

References:  
 Neonatal Pain-Related Stress Predicts Cortical Thickness at Age 7 Years in Children Born Very Preterm Manon Ranger, Cecil M. Y. Chau, Amanmeet Garg, Todd S. Woodward, Mirza Faisal Beg, Bruce Bjornson, Kenneth Poskitt Kevin Fitzpatrick, Anne R. Synnes, Steven P. Miller, Ruth E. Grunau. PLOS ONE, 2013 Volume 8 Issue 10 e76702  
 Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants. *Clin Perinatol*. 2014 Mar;41(1):209-27. [McPherson C, Grunau RE](#)  
 Sedation and analgesia in mechanically ventilated preterm neonates: continue standard of care or experiment? *J Pediatr Pharmacol Ther*. 2012 Oct;17(4):351

We would like to thank the Canadian Neonatal Network<sup>TM</sup> (CNN) Coordinating Centre at the Maternal-Infant Care Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada, for providing organizational support to the CNN and the CNN Coordinating Centre is supported by funding from the Health Research and Mount Sinai Hospital



# Frontal brain activation, systemic cardiovascular and behavioral responses to heel lance in very preterm infants

Manon Ranger<sup>1,2</sup>, Ruth E Grunau<sup>1,2</sup>, Oana Craciunoiu<sup>2,3</sup>, Anne R Synnes<sup>1,2</sup>, Willy NJM Colier<sup>4</sup>, & Liisa Holsti<sup>2,3</sup>

<sup>1</sup>Department of Pediatrics, University of British Columbia, Vancouver, BC Canada; <sup>2</sup>Developmental Neurosciences & Child Health, Child & Family Research Institute, Vancouver, Canada; <sup>3</sup>Department of Occupational Science & Occupational Therapy, UBC, Vancouver, Canada; <sup>4</sup>Artinis Medical Systems B.V., Elst, The Netherlands.

## INTRODUCTION

- Preterm infants undergo repeated pain from therapeutic procedures as a necessary part of neonatal intensive care
- Pain causes immediate physiological and behavioral reactions and repeated exposure is associated with altered brain development<sup>1,2</sup>
- Effective management of acute procedural pain begins with accurate pain assessment, but this remains challenging in very preterm infants<sup>3</sup>
- Near-infrared spectroscopy (NIRS) in infants reveals that painful stimuli induce hemodynamic changes in specific cortical regions

## OBJECTIVE

To examine the relationship between cerebral hemodynamic, cardiac, and behavioral changes displayed during a clinically required heel lance procedure in infants born very preterm

## METHODS & MEASURES

- N=10 very preterm infants  $\leq 32$  weeks gestational age (GA)
- Exclusion: congenital anomaly, PDA, on pressor support, abrupt changes in oxygen needs, received analgesics/sedatives (<72h prior), hematocrit <0.45 (24h prior)
- New NIRS device, PortaLite mini, measures local cerebral oxygenation: oxygenated [O<sub>2</sub>Hb], deoxygenated [HHb], and total hemoglobin [tHb] concentrations
- Heart rate (HR) and video recordings for behavioral pain responses (Behavioral Indicators of Infant Pain- BIIP scores)
- Changes in oxygen concentration of frontal cerebral hemoglobin, HR and BIIP during four 60-second epochs: Baseline, Heel Lance/Squeeze, Last Touch, and Recovery

## RESULTS

### Neonatal Characteristics n = 10 (5 boys)

#### Birth

GA (weeks)	28.4 (27-32)
Birth weight (grams)	1246 (960-1940)
Severity of illness day 1 (SNAP-II)	14.1 (0-44)

#### Study day

Postnatal age (days)	33.4 (10-63)
Respiratory support (number, %)	5 (50%)
Last handling (minutes)	134 (30-360)

(Means and range) Nature of last handling: Suction, heel lance/IV

## RESULTS

In response to Heel Lance/Squeeze:

- PortaLite mini device was able to detect changes in cerebral oxygenation
- Mean *absolute* changes in [tHb] in response to heel lance was (10.5  $\pm$  16.2)  $\mu$ mol/L
- Mean changes in HR from baseline were (21.1  $\pm$  11.6) beats/min and moderate pain- BIIP scores 5.3/9 ( $\pm$  3.0)
- High correlations** between changes in [tHb], and HR  $r = 0.73$ , and BIIP scores  $r = 0.76-0.84$ , ( $p < 0.05$ )

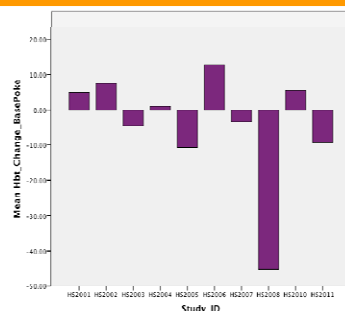


Figure 1. Mean change in total hemoglobin [Hb] between Baseline and Heel Lance/Squeeze

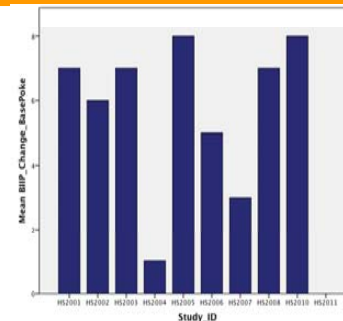
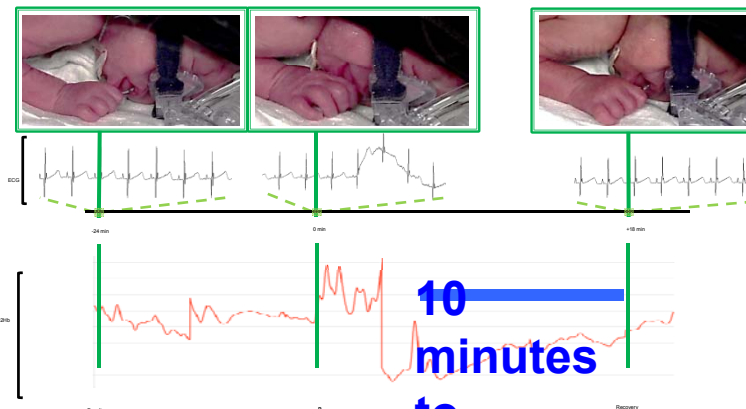


Figure 2. Change in BIIP scores in response to Heel Lance/Squeeze

## Multimodal pain assessment approach: Facial, Autonomic (HR) and Cerebral hemodynamic responses



## 10 minutes to Recover

## CONCLUSIONS

- A new NIRS technology designed for the head size of the very preterm neonate, PortaLite mini, can reliably record changes in cerebral oxygenation in response to a noxious stimulation
- Cerebral hemodynamic response correlates highly with other standard indicators of infant pain (facial expression, heart rate)

## REFERENCES

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- Holsti, Grunau. 2007. Initial validation of the Behavioral Indicators of Infant Pain (BIIP). Pain;132(3):264-272.
- Ranger et al. 2007. Current controversies regarding pain assessment in neonates. Semin Perinatol;31(5):283-288.
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## FUNDING

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