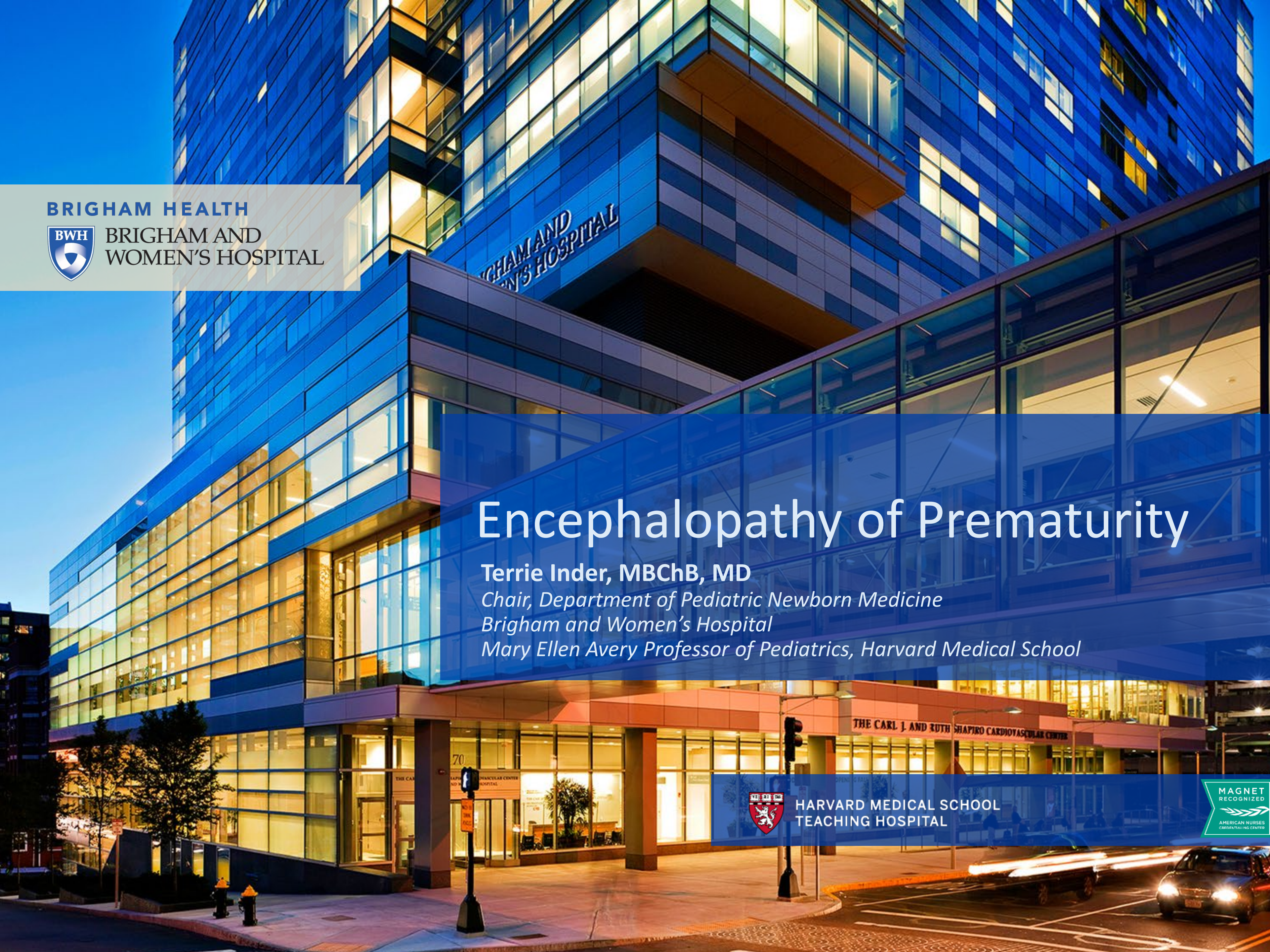


BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

Encephalopathy of Prematurity

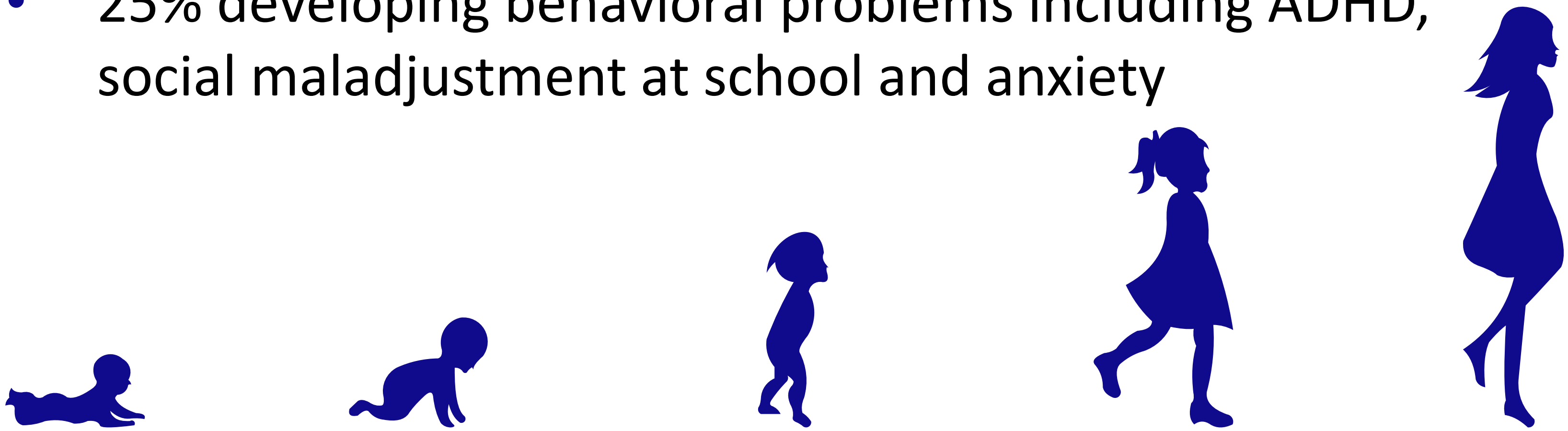
Terrie Inder, MBChB, MD
Chair, Department of Pediatric Newborn Medicine
Brigham and Women's Hospital
Mary Ellen Avery Professor of Pediatrics, Harvard Medical School

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Image courtesy of Terrie E. Inder, MBChB, MD.

Long Term Outcome for Very Preterm Infants

- 4%-5% risk of cerebral palsy, with 50% having an increased clumsiness and reduced physical ability
- 25%-50% of children requiring educational assistance in school
- 25% developing behavioral problems including ADHD, social maladjustment at school and anxiety



How can we define brain injury in the premature infant?

VLBW

Perinatal Practices
Steroids, BP, Nutrition

ALTERED BRAIN DEVELOPMENT

BRAIN INJURY

Social and environmental factors

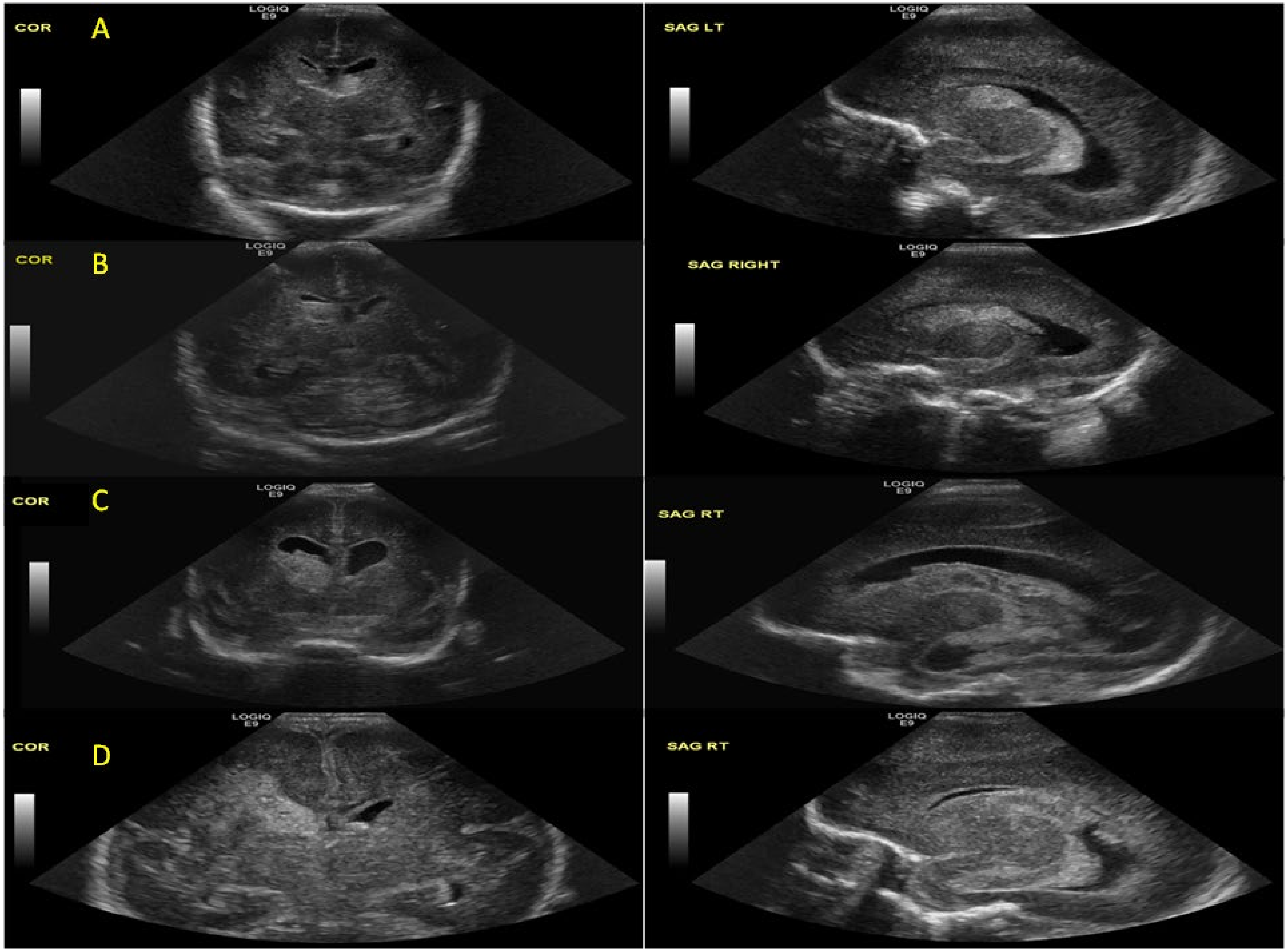
OUTCOME

What are the causes for adverse neurodevelopmental outcomes?

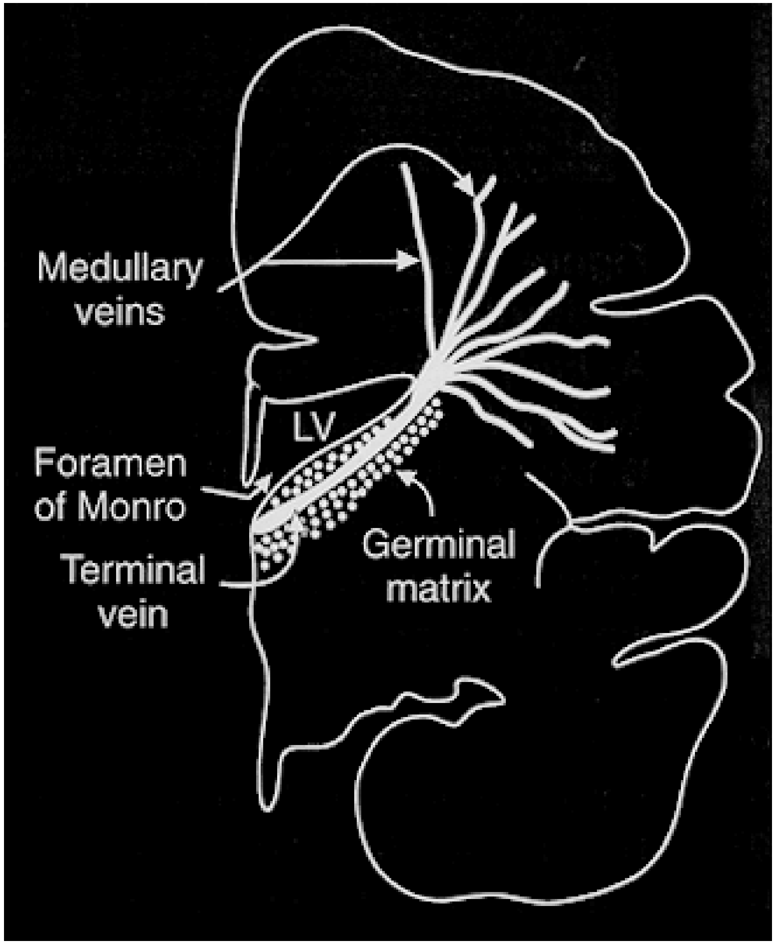
- Brain Injury
  - Intraventricular hemorrhage
  - White matter injury
  - Cerebellar hemorrhage
- Brain Development
  - Defining the nature of altered brain development
  - Factors driving alterations in brain development
    - The environment and exposures

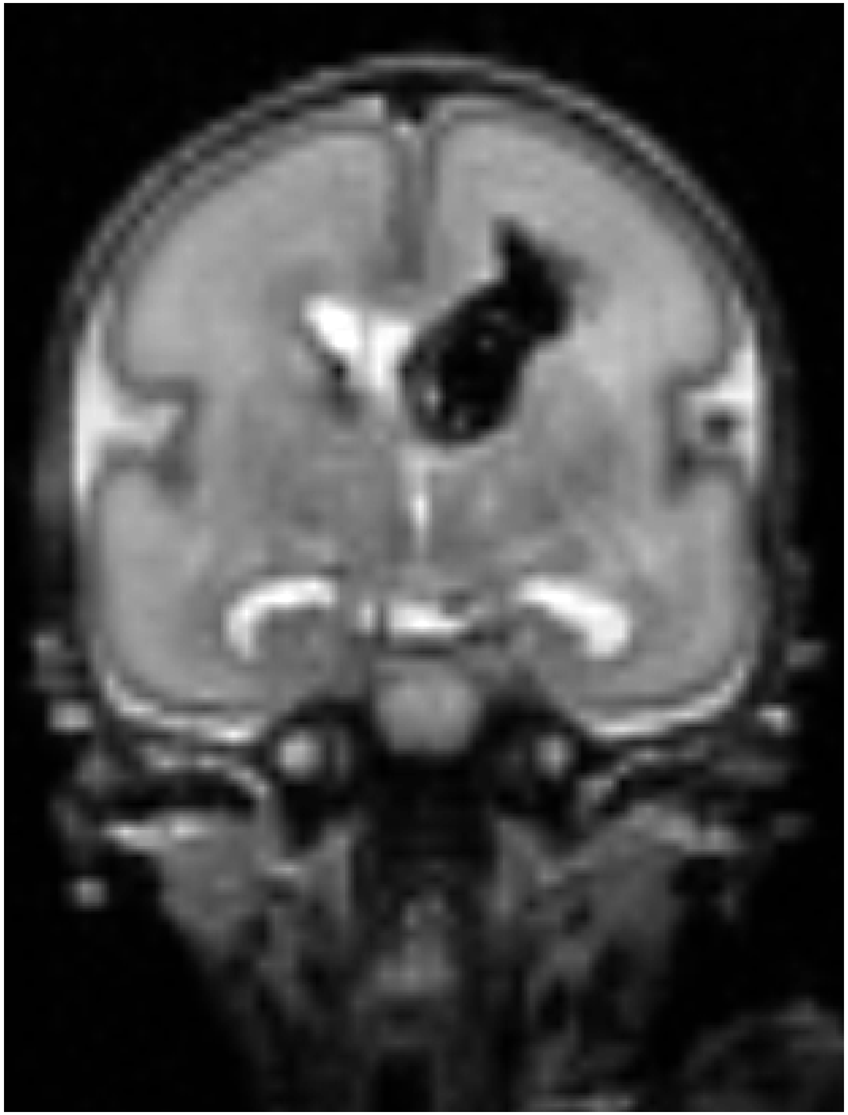
Intraventricular Hemorrhage (IVH)

Grades of IVH



Intraventricular Hemorrhage – Grade IV



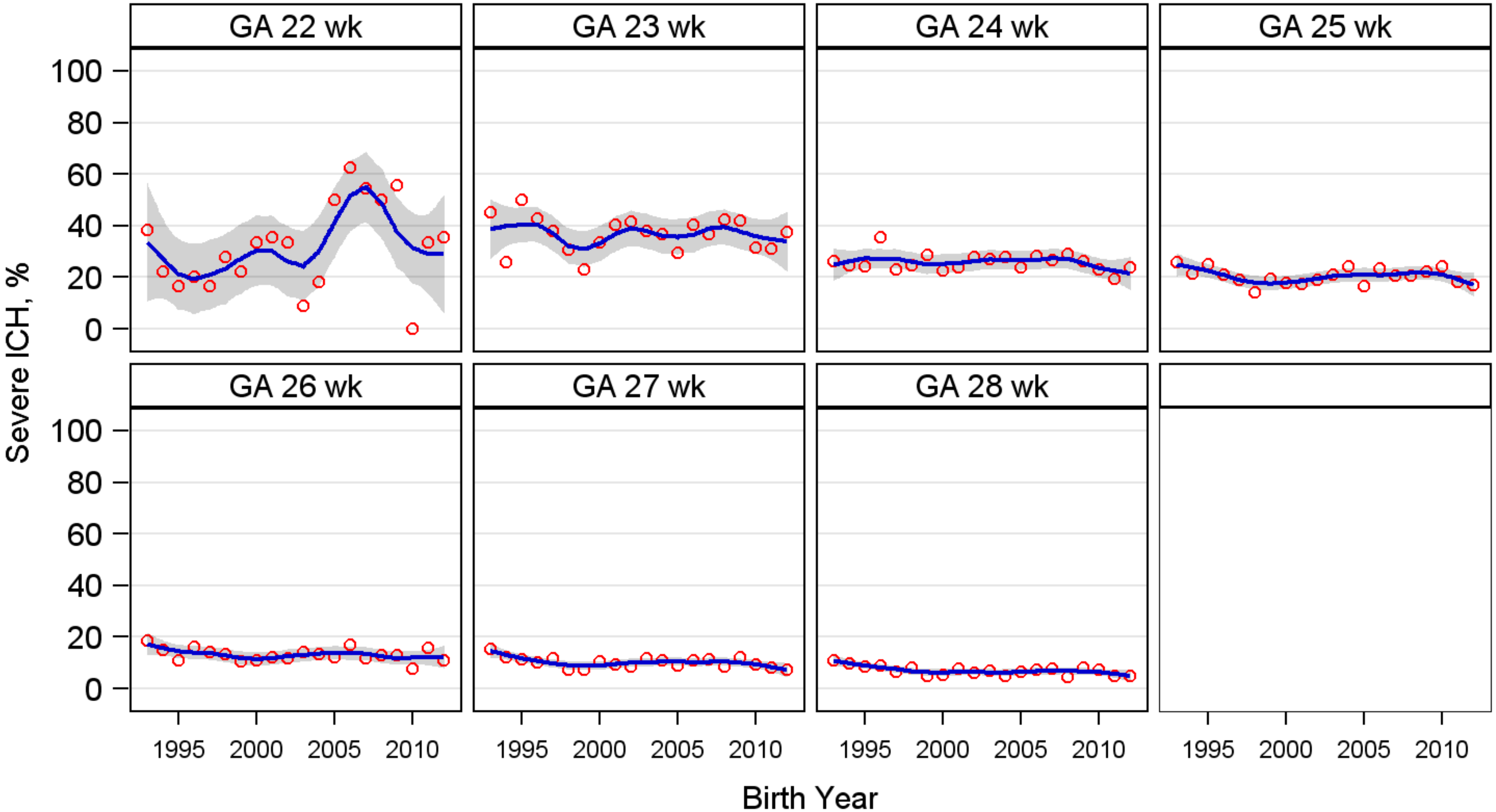


Grade IV intracranial hemorrhage is typically associated with spastic hemiparesis

Intraventricular Hemorrhage in the Preterm Infant

Prospective registry of 34,646 infants 22-28 weeks EGA at 26 Neonatal Research Network centers from 1993-2012

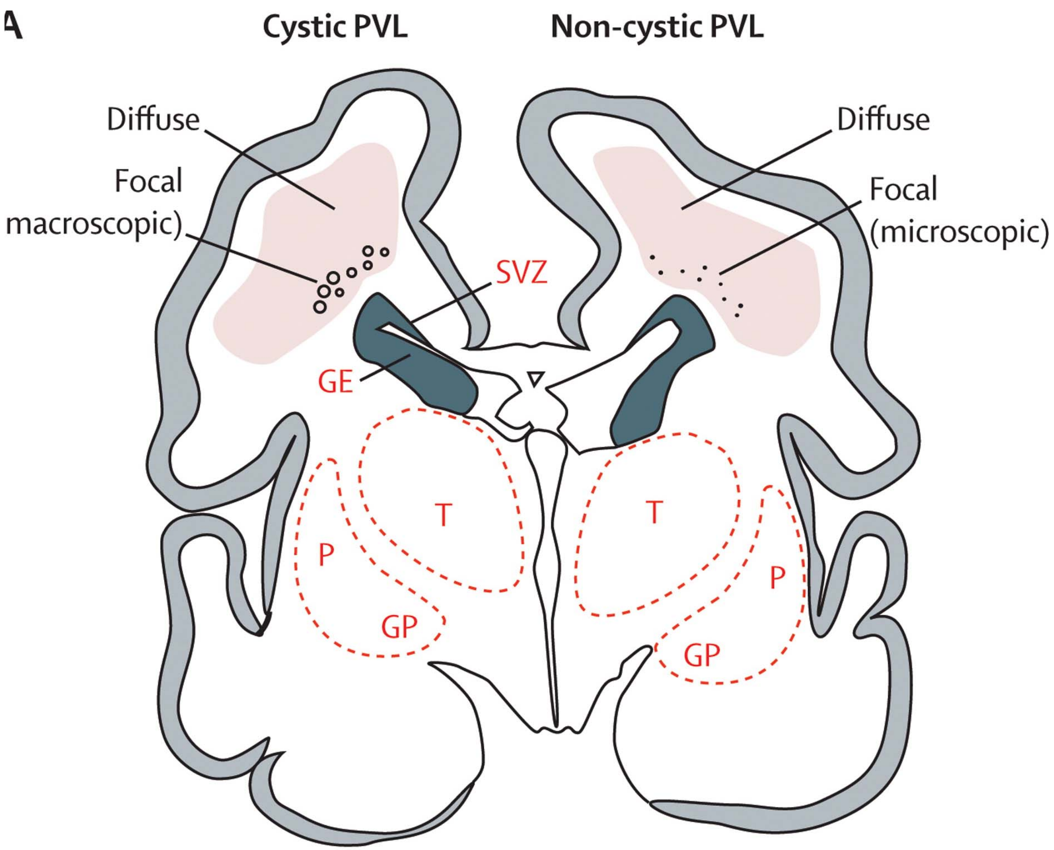
- Survival increased for infants ≥ 23 weeks (varied by age)
- Reduction in intracranial hemorrhage for infants 26-28 weeks EGA, but not 22-25 weeks
  - Antenatal steroids increased 24% → 87%
  - Intubation decreased 80% → 65%



Stoll BJ, et al. *JAMA.* 2015; 314(10):1039-51.

Periventricular Leukomalacia (PVL)

White Matter Abnormalities



Terminology

- White matter cysts
- White matter punctate lesions
- Loss of white matter volume
- Diffuse high signal changes throughout white matter

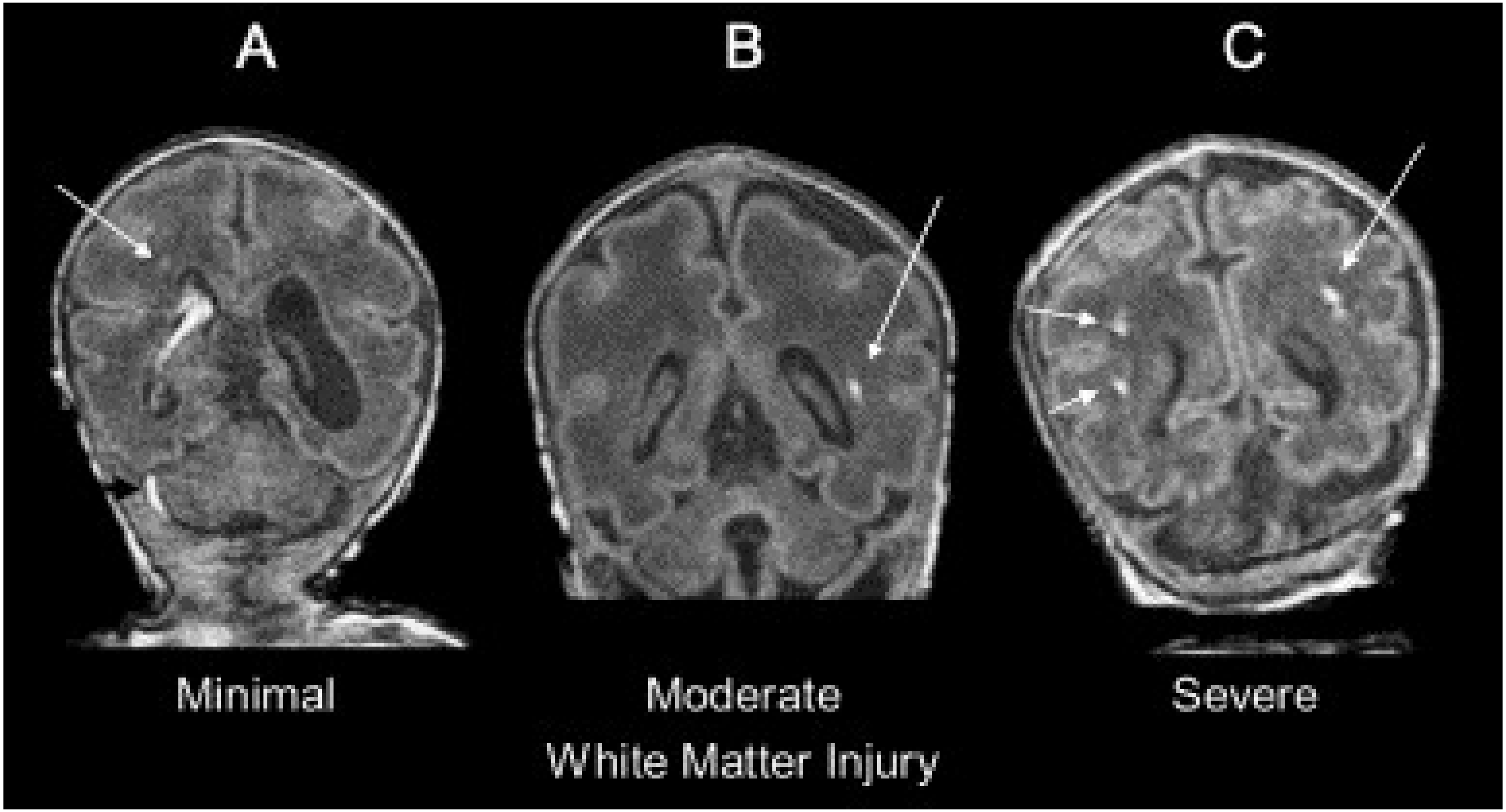
Volpe JJ. *Lancet Neurology.* 2009;8:110-24.

Predictors for MRI White Matter Injury

- SEPSIS
- Maternal factors
  - Fever (*p*=0.01)
  - Sepsis at delivery (*p*=0.03)
  - Chorioamnionitis
- Infant factors
  - Ischemia
    - IVH (*p*=0.015)
    - PDA (*p*=0.001)
    - Inotropes (p=0.002)
  - Sepsis/NEC during hospital course (*p*=0.03)

Inder et al. *Pediatrics.* 2005 Feb;115(2):286-94.

White Matter Abnormalities



Miller SP, et al. *J Pediatrics.* 2005;147:467-74.

BRIGHAM AND WOMEN'S HOSPITAL

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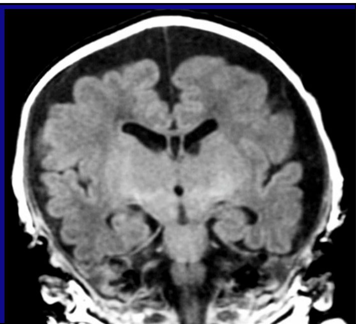
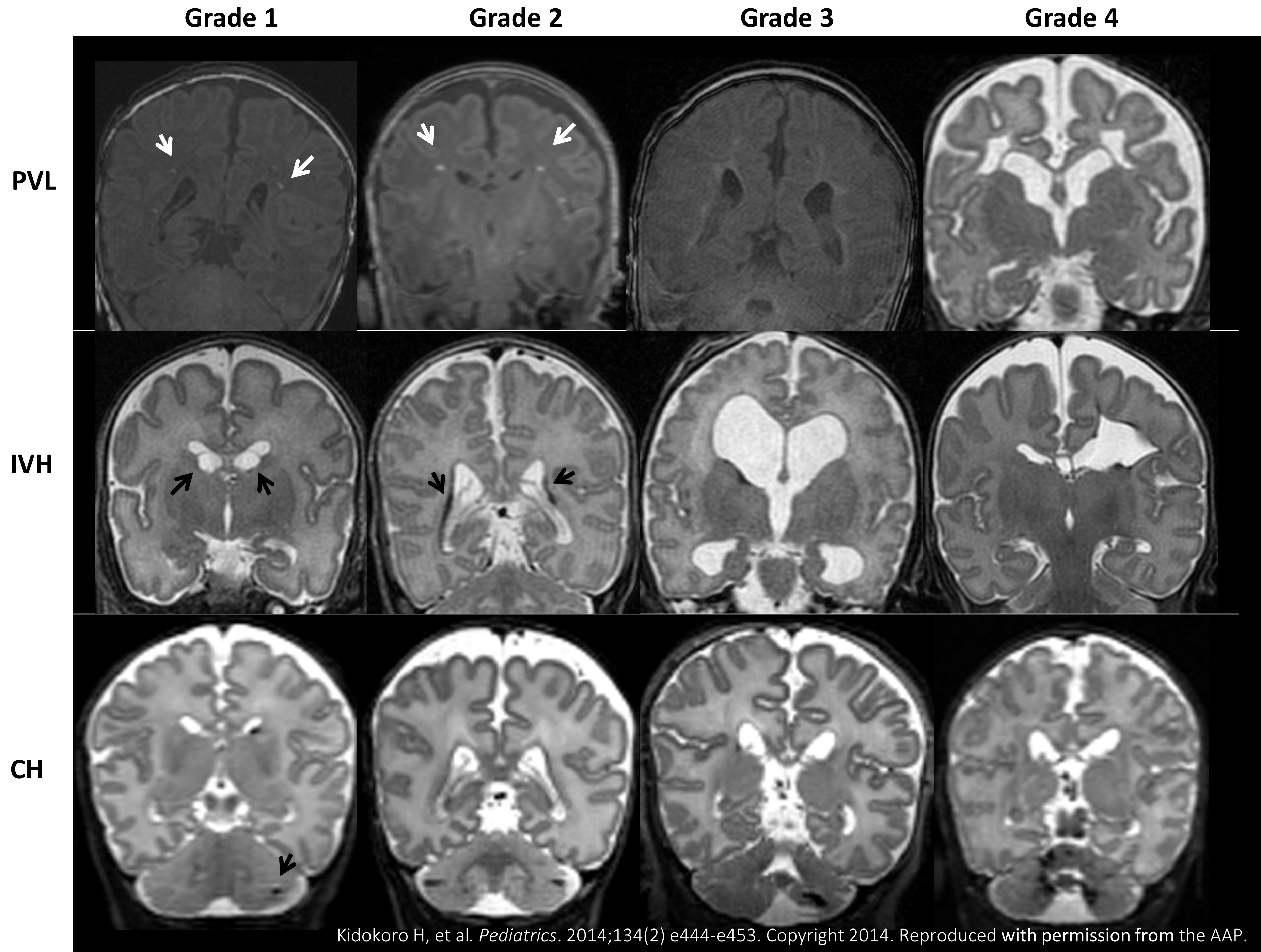
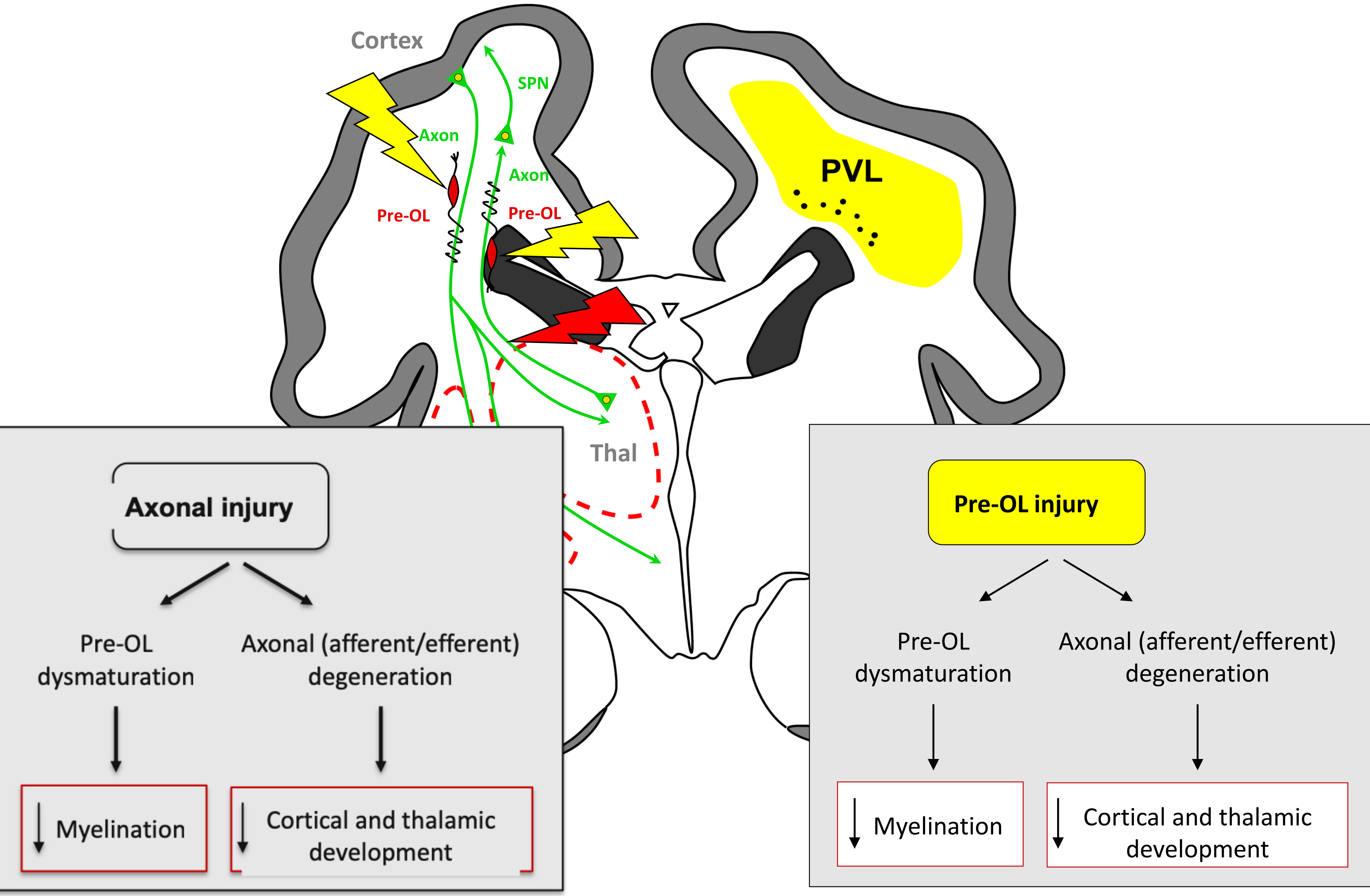
Is brain injury the major factor driving adverse neurodevelopmental outcome?

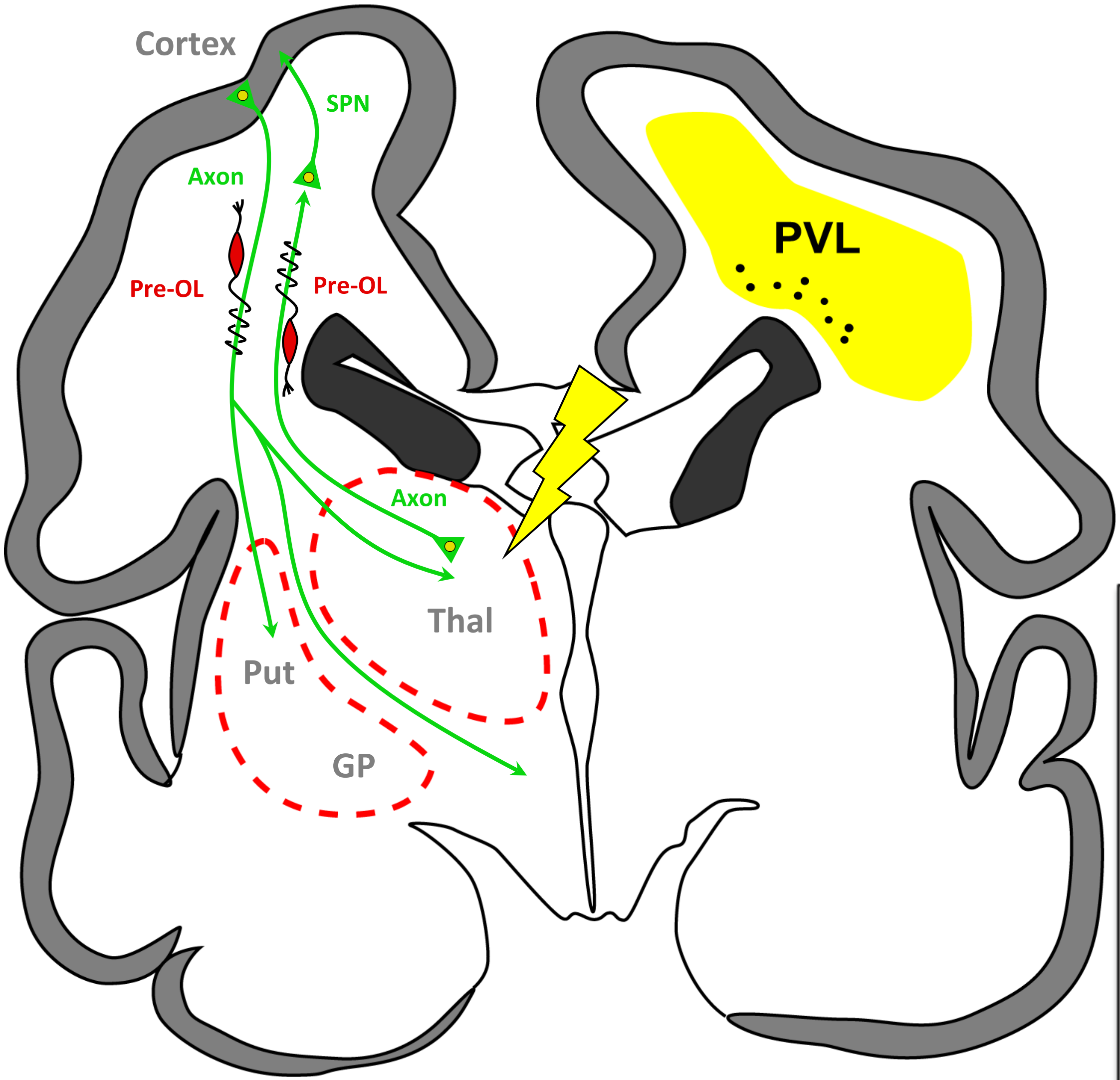


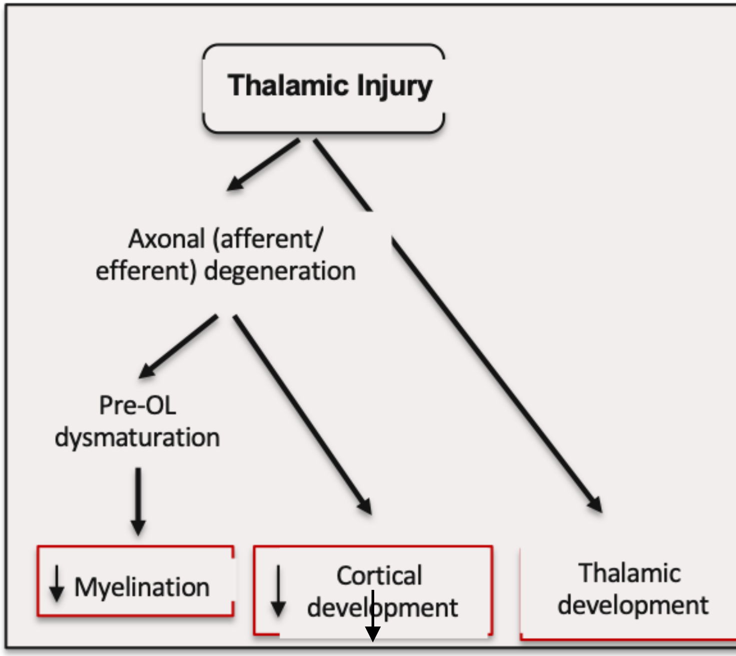

Grade 1
Grade 2
Grade 3
Grade 4
PVL
IVH
CH

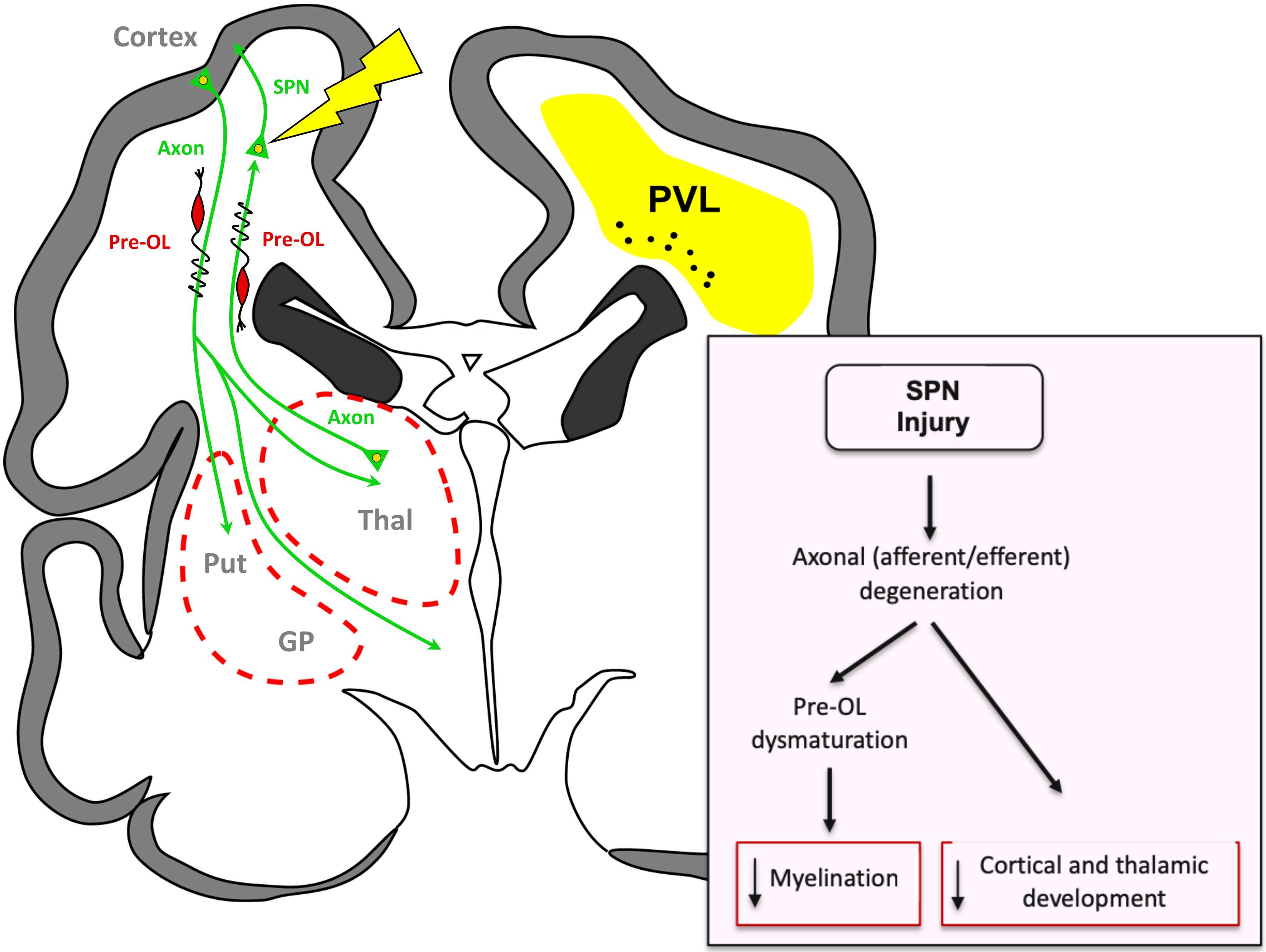
		No.	MDI Score (SD)	MDI<70 No. (%)	PDI Score (SD)	PDI<70 No. (%)	Cerebral palsy No. (%)
PVL							
	Grade 4						
	Grade 3						
	Grade 2						
	Grade 1						
IVH							
	Grade 4						
	Grade 3						
	Grade 2						
	Grade 1						
CH							
	Grade 4						
	Grade 3						
	Grade 2						
	Grade 1						
No injury		220	86.4(17.9)	28(13.5)	89.4(15.3)	21(10.1)	10(4.5)

		No.	MDI Score (SD)	MDI<70 No. (%)	PDI Score (SD)	PDI<70 No. (%)	Cerebral palsy No. (%)
PVL		34					
	Grade 4	4	49.3(18.5)	3(75.0)	49.3(18.5)	3(75.0)	4(100)
	Grade 3	5	61.2(20.4)	3(60.0)	55.6(29.4)	4(80.0)	4(80.0)
	Grade 2	14[c]	82.6(13.5)	3(21.4)	85.1(11.5)	1(7.1)	3(21.4)
	Grade 1	11[d]	85.7(20.5)	2(18.2)	86.2(18.3)	1(9.1)	1(9.1)
IVH		53					
	Grade 4	13	76.1(22.6)	4(30.8)	72.3(16.2)	4(30.8)	6(46.2)
	Grade 3	2	72.5(5.0)	2(100)	75.5(12.0)	1(50.0)	1(50.0)
	Grade 2	16	85.6(15.4)	1(6.3)	89.7(11.8)	0	1(6.3)
	Grade 1	20	88.1(14.1)	3(15.0)	90.9(12.4)	2(10.0)	1(5.0)
CH		22					
	Grade 4	1[e]	84	0	84	0	0
	Grade 3	2[f]	75.5(10.6)	1(50)	77.0(1.4)	0	1(50.0)
	Grade 2	4[a]	88.8(6.7)	0	95.3(12.2)	0	1(25.0)
	Grade 1	15[b]	84.3(15.6)	4(26.7)	87.4(17.6)	3(20.0)	2(13.3)
No injury		220	86.4(17.9)	28(13.5)	89.4(15.3)	21(10.1)	10(4.5)


Cortex
SPN
Axon
Axon
Pre-OL
Pre-OL
PVL
Thal
Axonal injury
Pre-OL dysmaturation
Axonal (afferent/efferent) degeneration
↓ Myelination
↓ Cortical and thalamic development
Pre-OL injury
Pre-OL dysmaturation
Axonal (afferent/efferent) degeneration
↓ Myelination
↓ Cortical and thalamic development


Cortex
SPN
Axon
Pre-OL
Pre-OL
Axon
Thal
Put
GP
PVL


Thalamic Injury
Axonal (afferent/ efferent) degeneration
Pre-OL dysmaturation
↓ Myelination
↓ Cortical development
Thalamic development

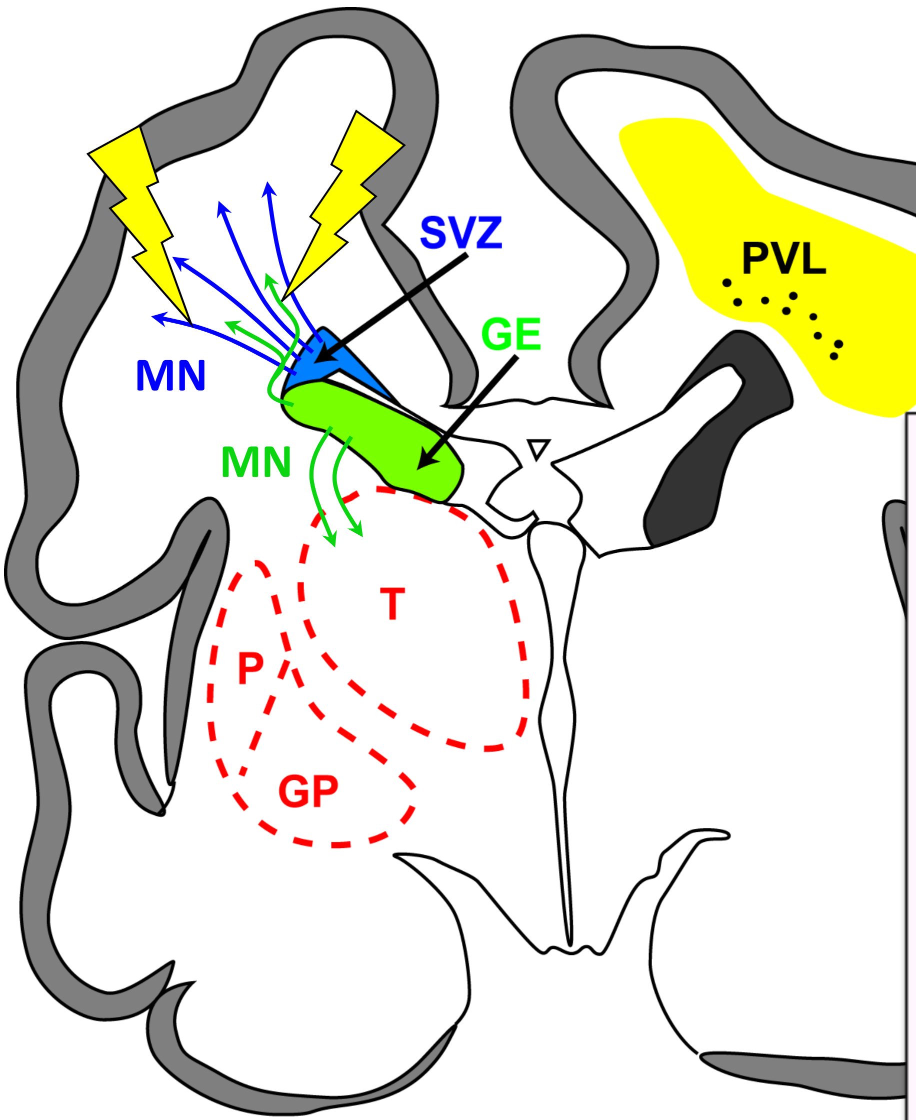

Cortex
SPN
Axon
Pre-OL
Pre-OL
PVL
Axon
Thal
Put
GP
SPN Injury
Axonal (afferent/efferent) degeneration
Pre-OL dysmaturation
↓ Myelination
↓ Cortical and thalamic development

Neuron Deficit in the White Matter and Subplate in Periventricular Leukomalacia

Hannah C. Kinney, MD,[1] Robin L. Haynes, PhD,[1] Gang Xu, MD, PhD,[1] Sarah E. Andiman, AB,[1] Rebecca D. Folkerth, MD,[2] Lynn A. Sleeper, ScD,[3] and Joseph J. Volpe, MD[4]

40% reduction in neuronal density in subplate with PVL

Kinney HC, et al. *Ann Neurol.* 2012;71:397-406.



Migrating GABAergic neuron injury

↓ GABAergic neurons

↓ Cortical development (upper cortical layers)

J Neuropathol Exp Neurol

Vol. 70, No. 10
October 2011
pp. 841–858

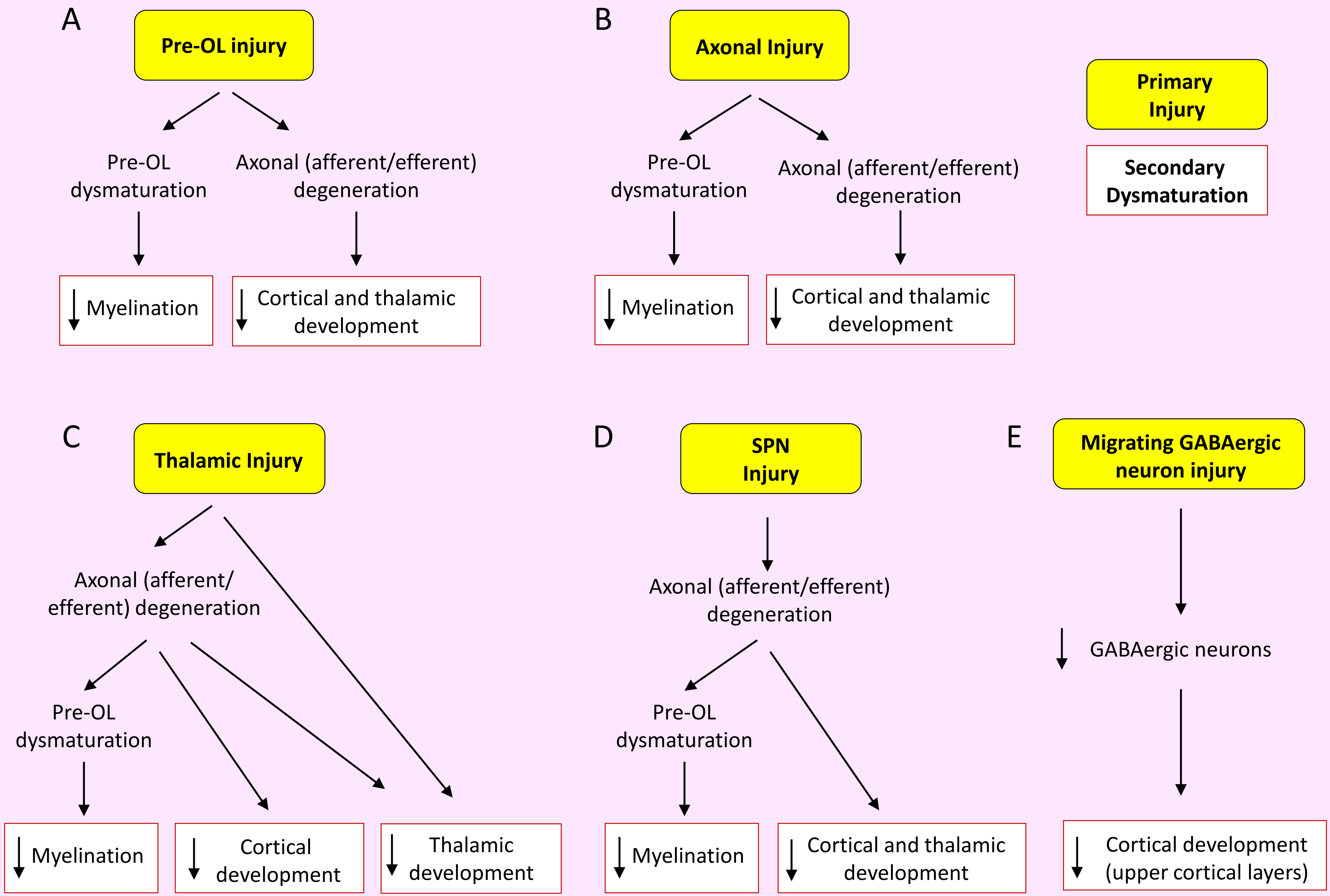
ORIGINAL ARTICLE

Late Development of the GABAergic System in the Human Cerebral Cortex and White Matter

Gang Xu, MD, PhD, Kevin G. Broadbelt, PhD, Robin L. Haynes, PhD, Rebecca D. Folkerth, MD, Natalia S. Borenstein, MS, Richard A. Belliveau, BA, Felicia L. Trachtenberg, PhD, Joseph J. Volpe, MD, and Hannah C. Kinney, MD

Migrating GABAergic neurons increase in cerebral white matter from 20 to 40 wks and peak at term

70 – 80% reduction with PVL

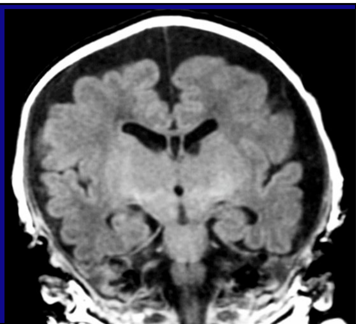


A
Pre-OL injury
Pre-OL dysmaturation
Axonal (afferent/efferent) degeneration
Myelination
Cortical and thalamic development
B
Axonal Injury
Pre-OL dysmaturation
Axonal (afferent/efferent) degeneration
Myelination
Cortical and thalamic development
Primary Injury
Secondary Dysmaturation
C
Thalamic Injury
Axonal (afferent/ efferent) degeneration
Pre-OL dysmaturation
Myelination
Cortical development
Thalamic development
D
SPN Injury
Axonal (afferent/efferent) degeneration
Pre-OL dysmaturation
Myelination
Cortical and thalamic development
E
Migrating GABAergic neuron injury
GABAergic neurons
Cortical development (upper cortical layers)

Summary of Brain Injury

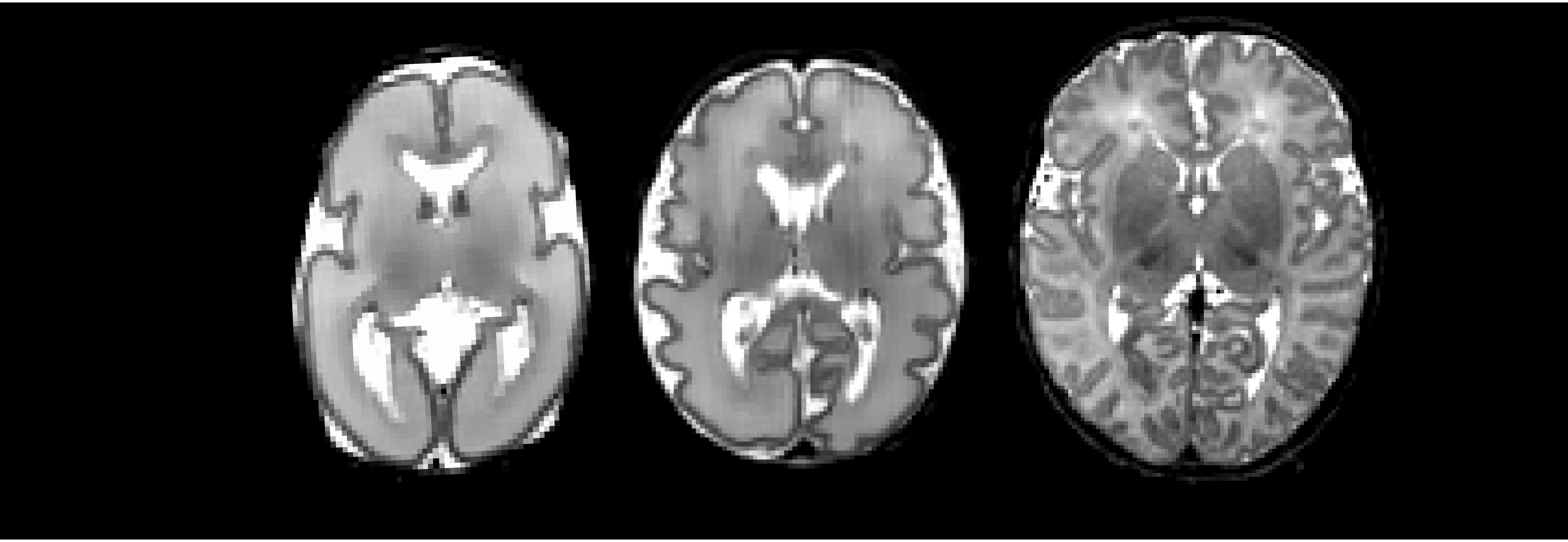
- Traditional Forms of Brain Injury
  - IVH, PVL, CBH
- Widespread (invisible) Brain Injury
  - Axons, thalamus, subplate, migrating GABAergic
- Down- and Up-Stream effects of Brain Injury
  - Deafferentation resulting in neuronal death
  - Alterations in cell fates/development
  - Impaired signaling at critical stages in development

Can we define the nature of alterations in brain development – the role of advanced imaging?

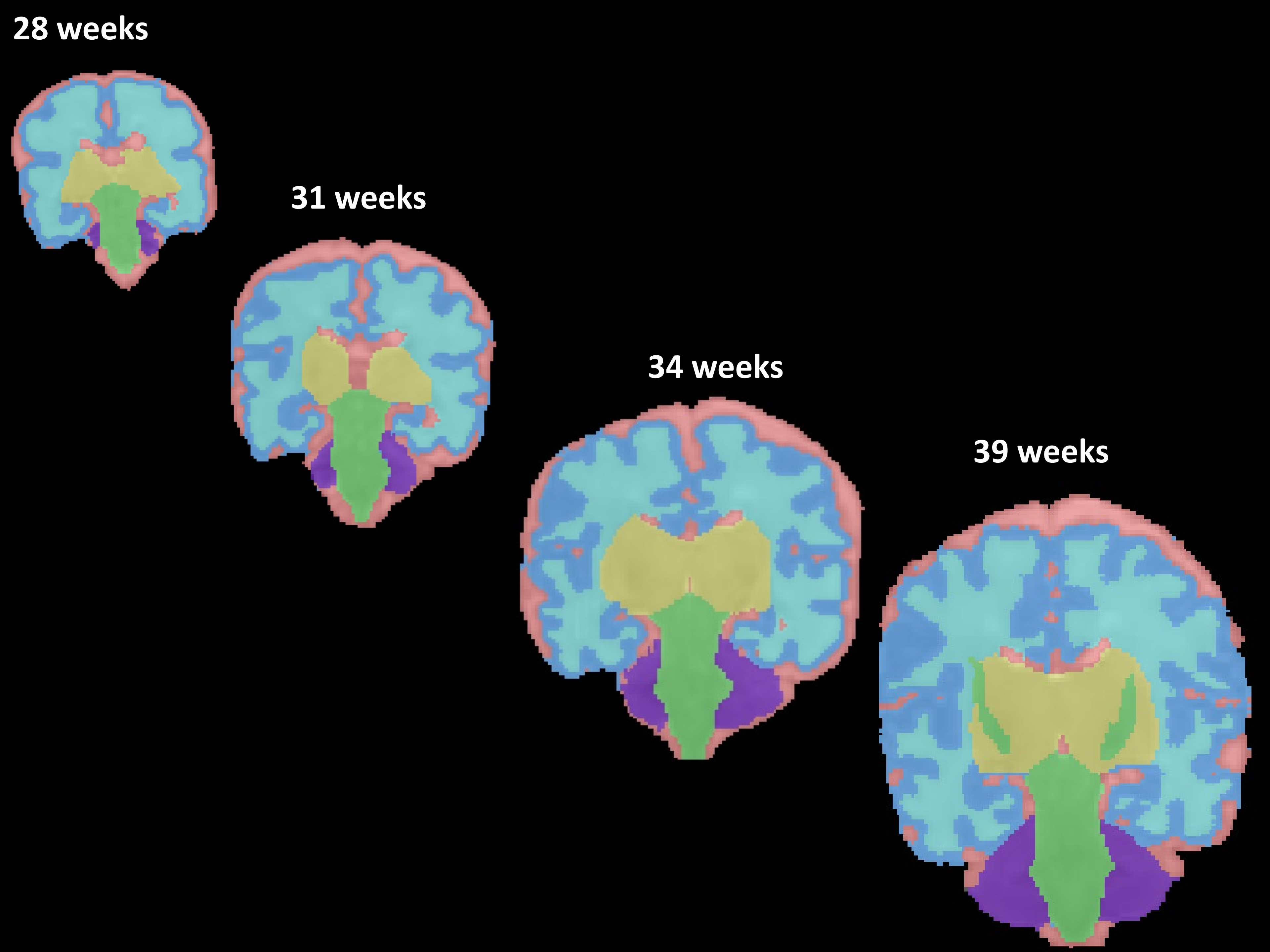


Cortical Folding in the NICU

25 weeks | 30 weeks | Term (38 weeks)



Rapid and extensive folding during 3rd trimester



28 weeks
31 weeks
34 weeks
39 weeks

Cortical folding

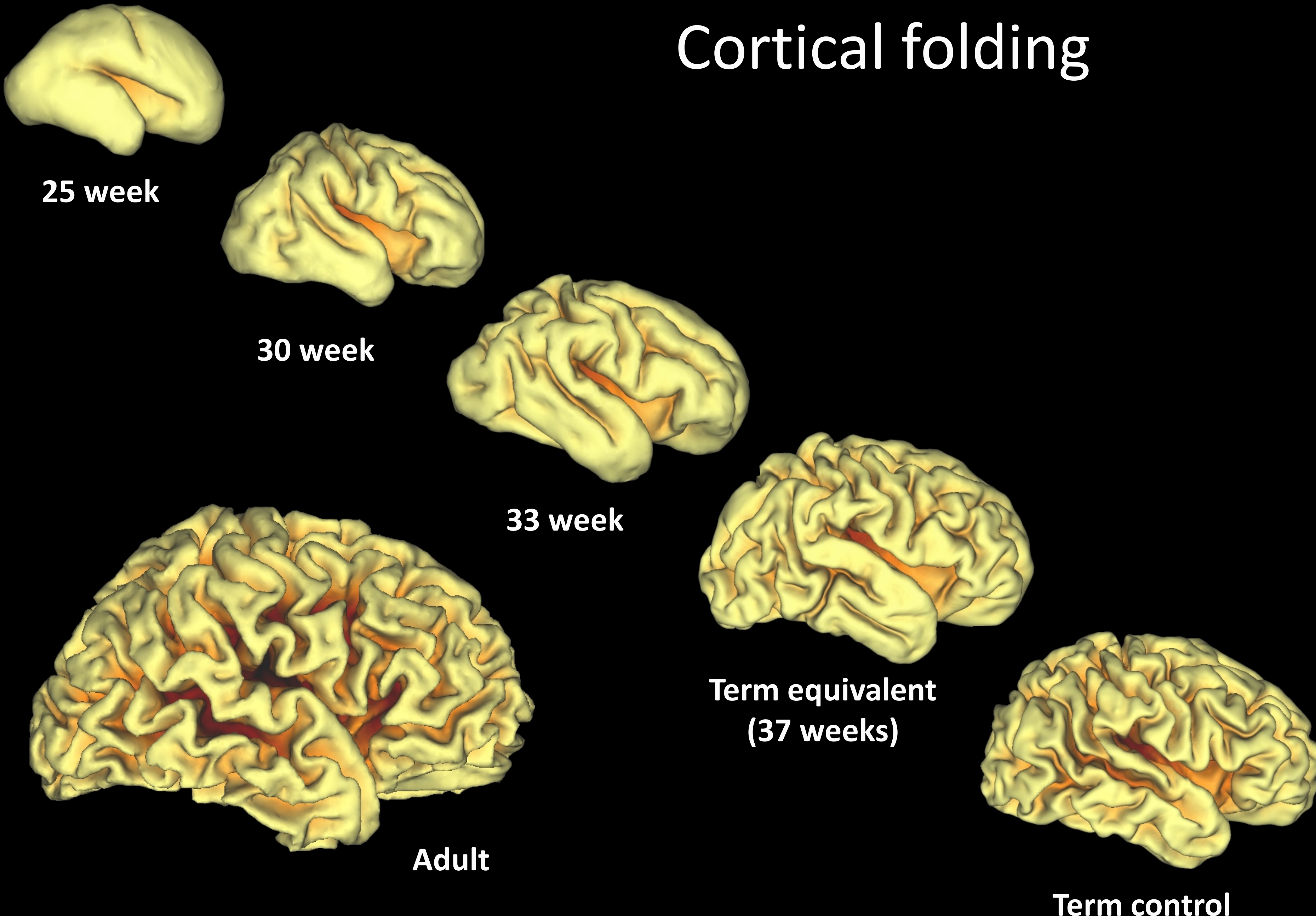
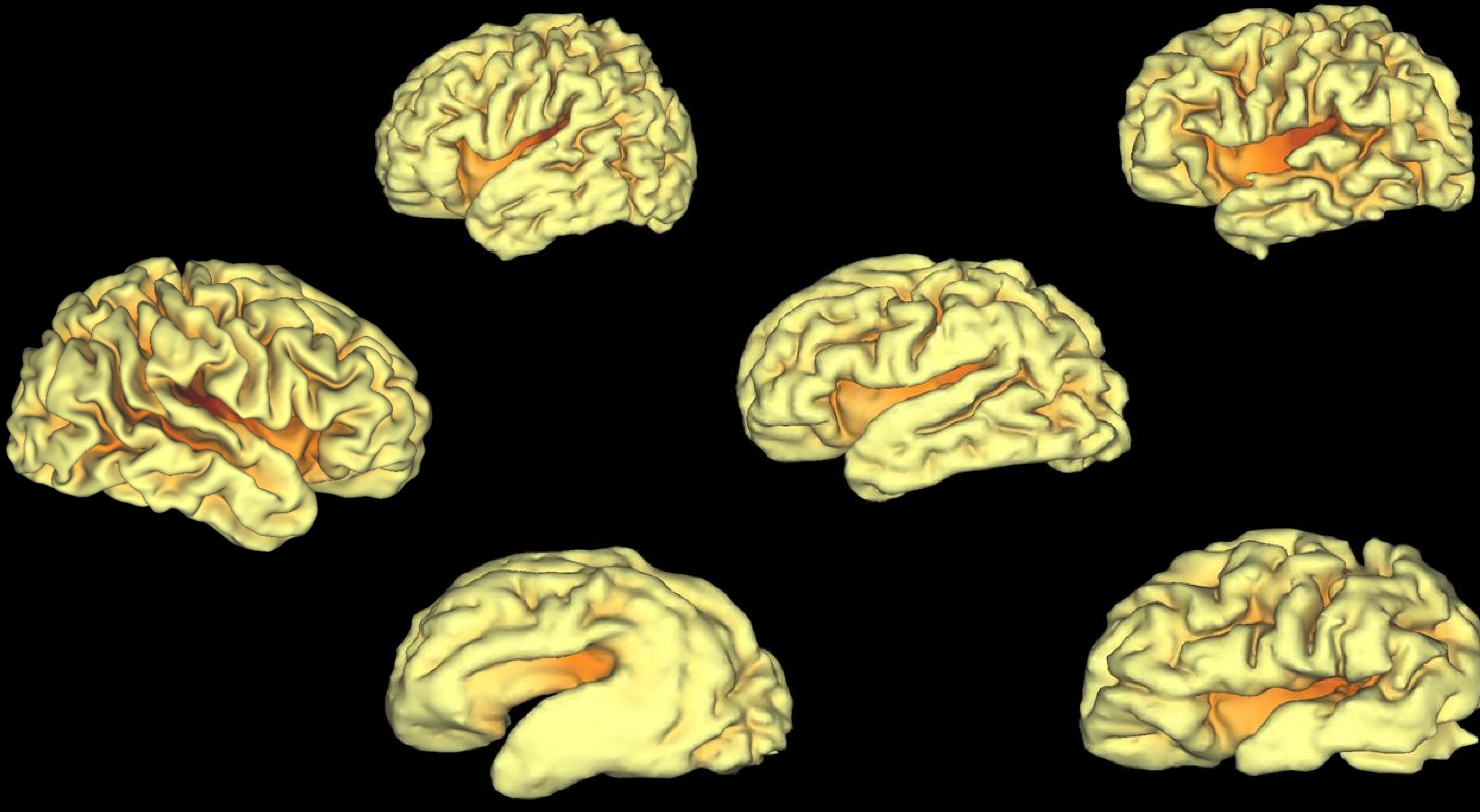


Image courtesy of Terrie E. Inder, MBChB, MD.

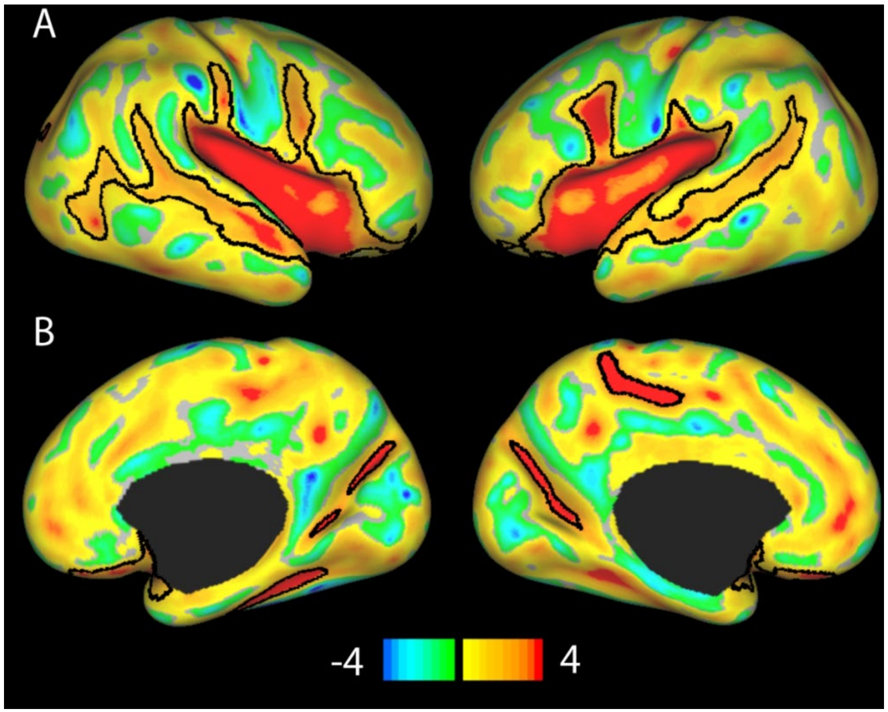
Surface reconstructions from Images obtained at term equivalent



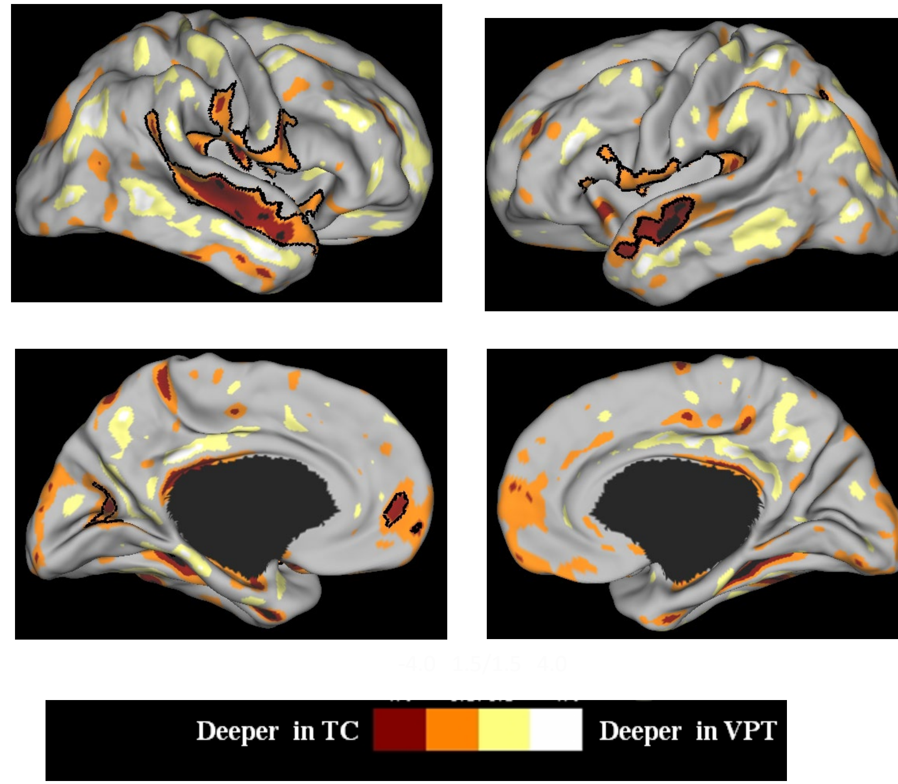
Comparison of Sulcal Depth Maps

39 weeks

7 years

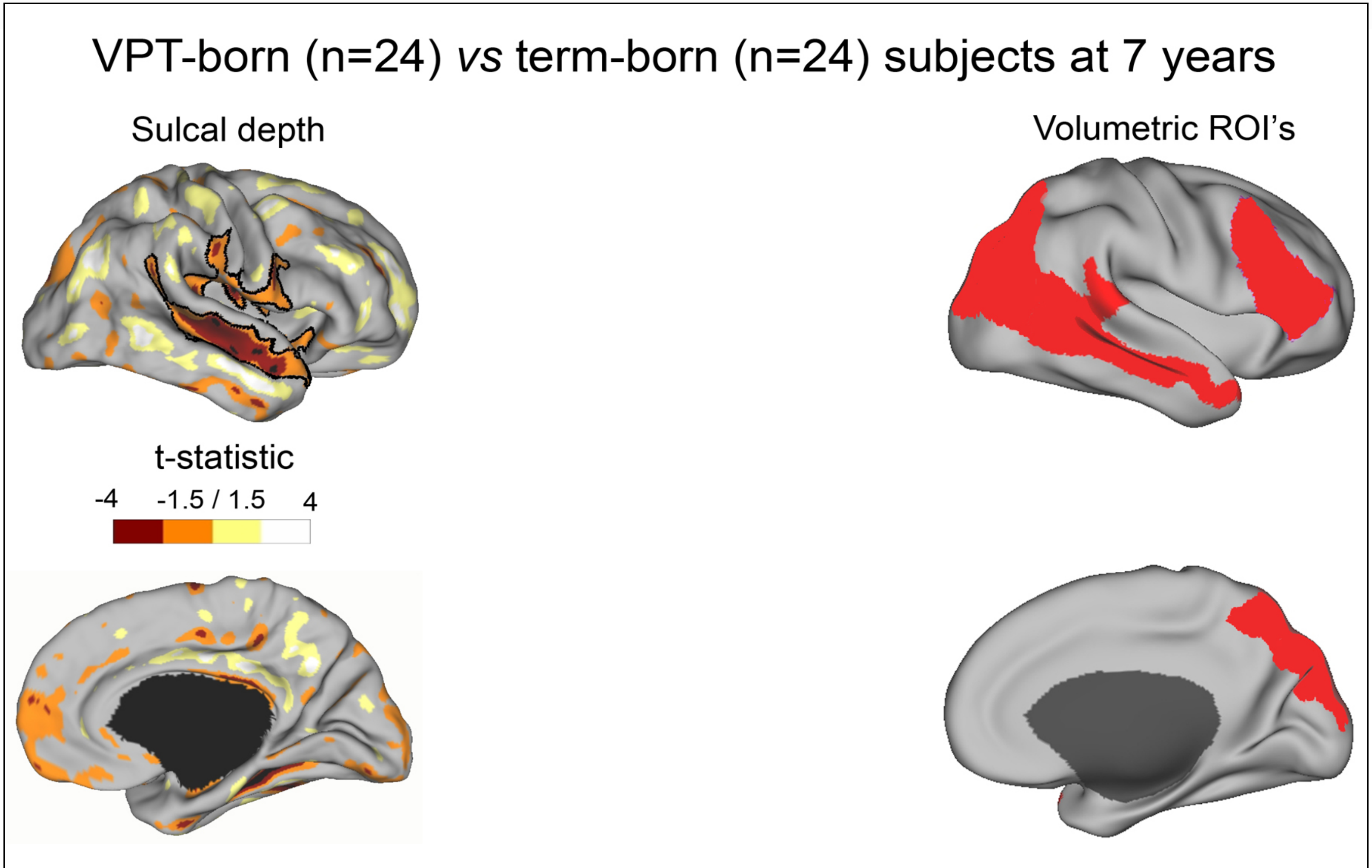


Deeper Sulci in VPT   Deeper Sulci in TC



Zhang Y, Inder TE, Neil JJ, et al. Cortical structural abnormalities in very preterm children at 7 years of age. *NeuroImage*. 2015;109:469-479.

Alterations in Brain Development in VPT infants



ARE traditional medical factors mediating the alterations in brain development?

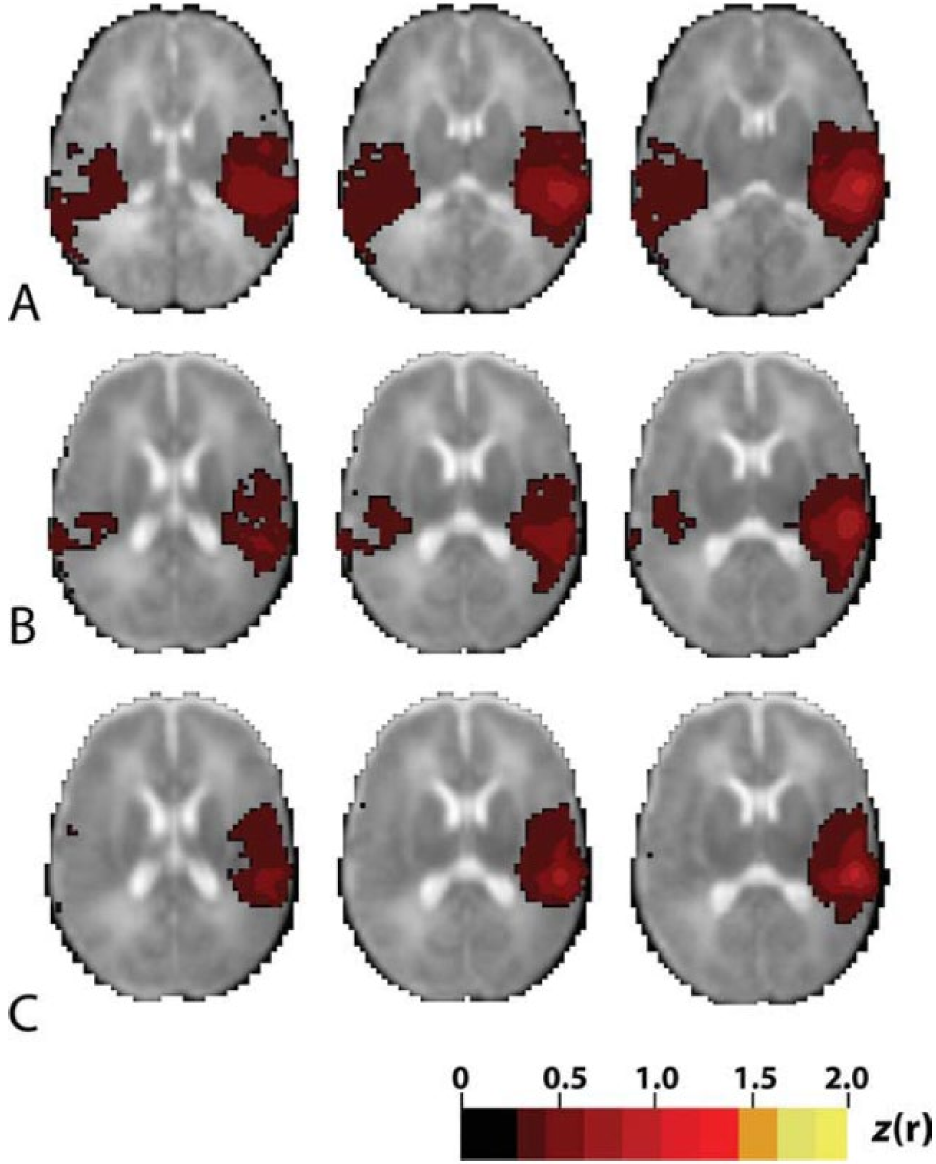
Photo by Cherie Diaz | Tampa Bay Times

Pain and Neonatal Stress

Average daily Neonatal Infant Stressor Scale score	
First 14 days (mean ± SD)	**106 ± 13**
First 28 days (mean ± SD)	**102 ± 18**
Admission until term equivalent/discharge (mean ± SD)	**80 ± 12**
Average daily number of procedures	
First 14 days (mean ± SD)	**11 ± 4**
First 28 days (mean ± SD)	**10 ± 5**
Admission until term equivalent/discharge (mean ± SD)	**7 ± 3**

Increased stress associated with decreased frontal lobe width, abnormal temporal lobe diffusion and neural networks (after adjusting for confounders of immaturity, length of ventilation, CRIB score, sepsis +).

Smith GC, et al. *Annals of Neurology.* 2011Oct;70(4):541-9. 2011.



Mean functional connectivity correlation maps generated using the right temporal lobe seed in (A) term control infants (n=10) (B) low-stress infants (n=10), and (C) high-stress infants (n=10). Illustrated quantity is Fisher z-transformed correlation coefficient

Neonatal pain and developmental outcomes in children born preterm: a systematic review.

Valeri B, et al. *Clin J Pain.* 2015

In infants born extremely preterm (gestational age ≤29 wk) greater numbers of painful procedures were associated with

- delayed postnatal growth
- poor early neurodevelopment
- high cortical activation
- altered brain development
- poor quality of cognitive and motor development at 1 year of age
- changes in cortical rhythmicity and cortical thickness in children at 7 years of age.

BWH BRIGHAM AND WOMEN'S HOSPITAL

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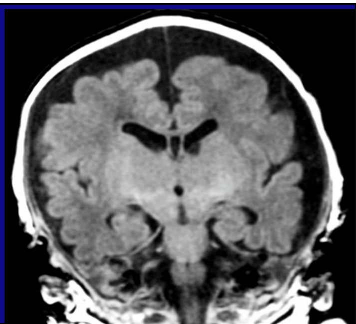
So if the infants are suffering from pain, then should we provide analgesia?



Neonatal morphine exposure in very preterm infants-cerebral development and outcomes.

Steinhorn R, et al. *J Pediatr.* 2015 Jul; 167(1):215.

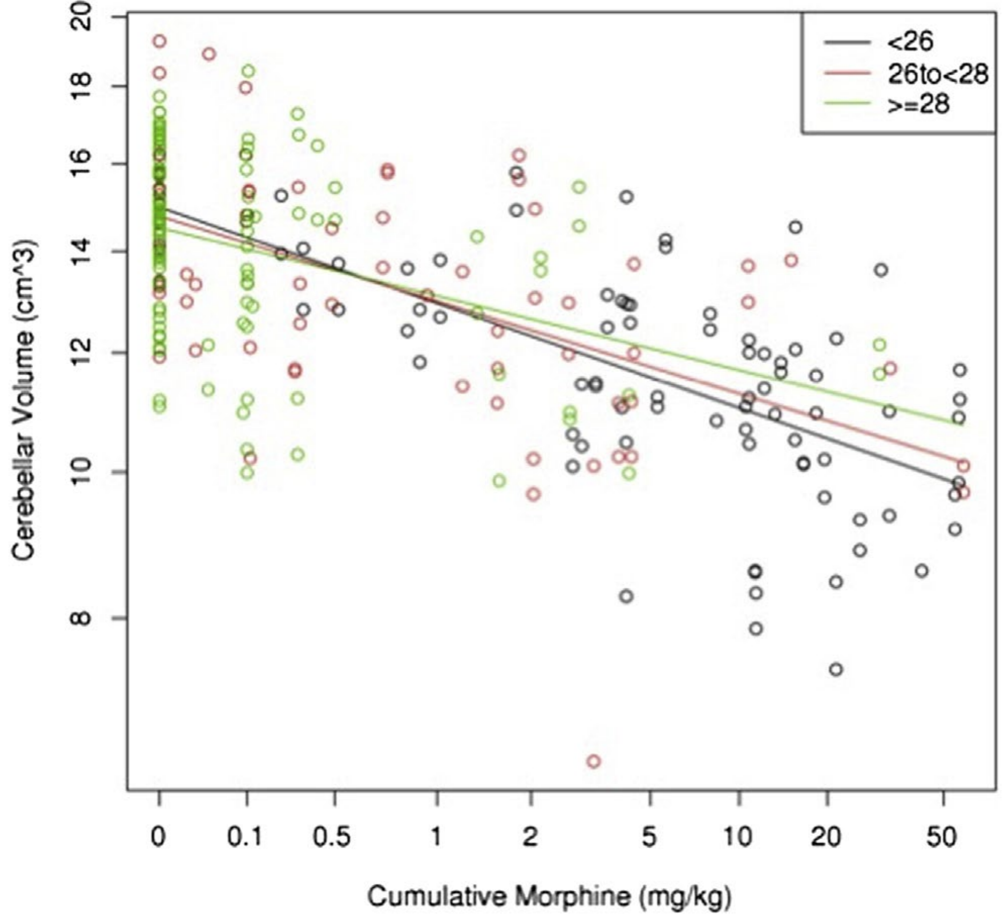
- Participants (n = 223) were assessed. Fifty-seven participants received morphine in the NICU (median cumulative dose 0.7 mg/kg, IQR 0.1-0.95 mg/kg, range 0.1-5.3 mg/kg). Thirty-two participants received only boluses; 21 received a mixture of boluses and infusion; 4 received an infusion only; no clinical factors differed between these 3 subgroups.

- At term, preterm infants who received morphine had a trend toward smaller cortical volumes in the orbitofrontal (*P*left = .002, *P*right = .01) and subgenual (*P*left = .01) regions. At 7 years, cortical volumes did not differ.

- At 7 years no impact of morphine on neurobehavioral outcome were observed.

Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine

Jill G. Zwicker, PhD, OT(C)[1,2,3], Steven P. Miller, MDCM[2,3,4], Ruth E. Grunau, PhD[2,3,5], Vann Chau, MD[4], Rollin Brant, PhD[3,6], Colin Studholme, PhD[7], Mengyuan Liu, BS[7], Anne Synnes, MDCM[2,3,5], Kenneth J. Poskitt, MDCM[3,8], Mikaela L. Stiver, BSc[4], and Emily W. Y. Tam, MDCM[4]



J Peds. 2016 May;172:81-87.e2.

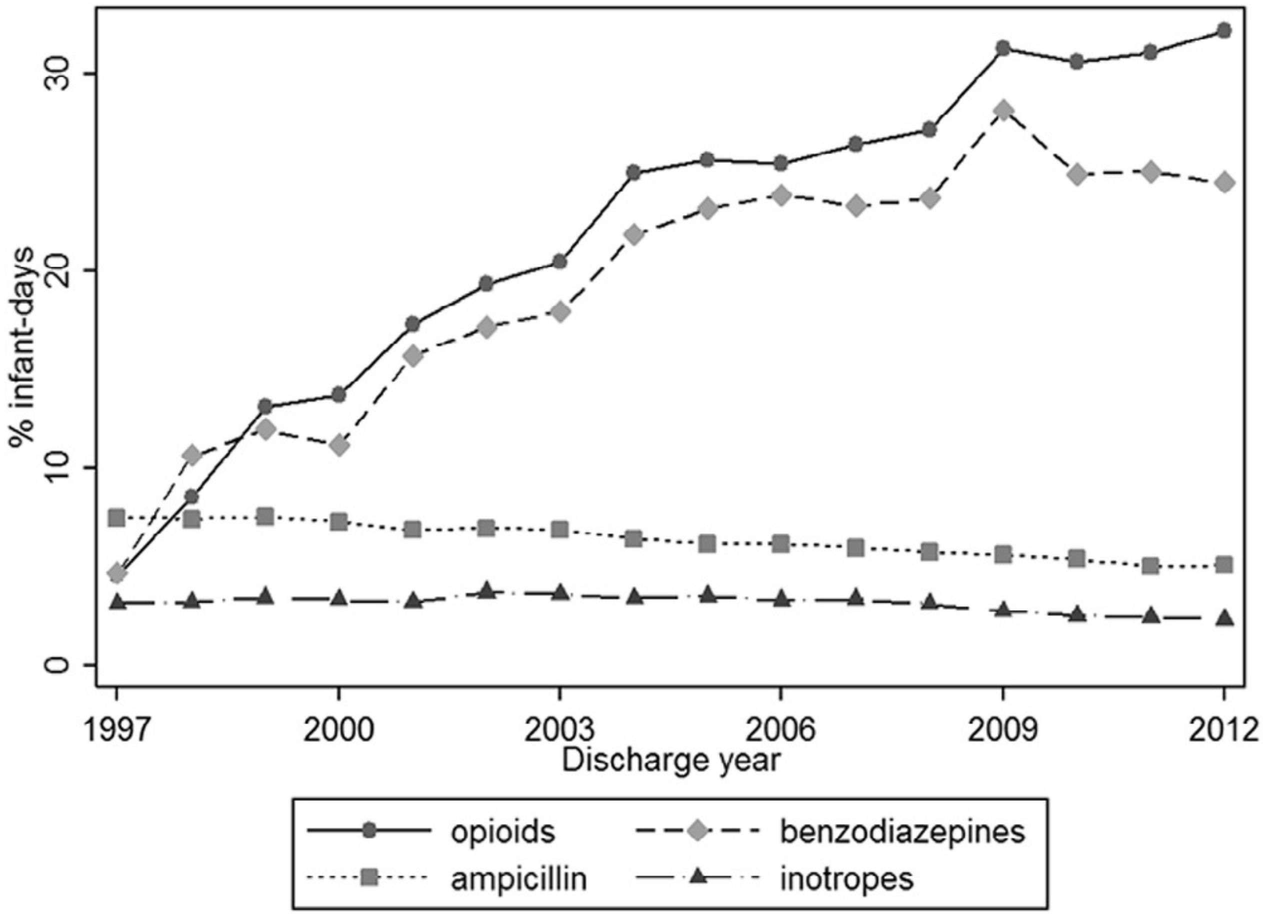
Brain injury and development in preterm infants exposed to fentanyl.

McPherson C, et al. *Ann Pharmacother*. 2015 Dec; 49(12):1291-7.

- Seventy-eight infants (76%) received fentanyl (median cumulative dose 3 µg/kg, interquartile range 1-441 µg/kg). Cumulative fentanyl dose in the first week of life correlated with the incidence of cerebellar hemorrhage after correction for covariates (odds ratio 2.1, 95% CI: 1.1-4.1).

- Cumulative fentanyl dose before term equivalent age correlated with reductions in transverse cerebellar diameter after correction for covariates, including the presence of cerebellar hemorrhage ($r = 0.461$, $P = 0.002$).

Use of Opiates and Benzodiazepines

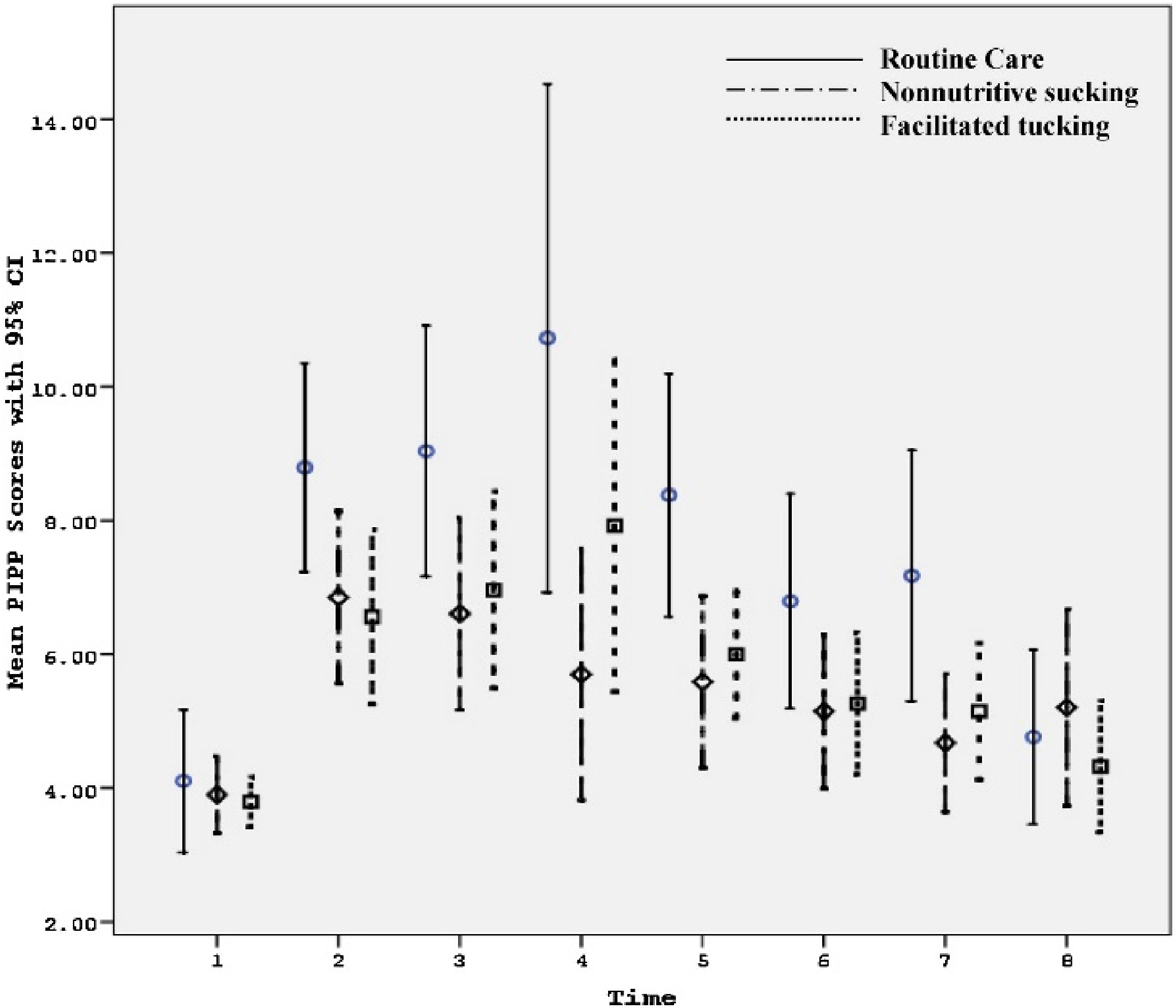


Zimmerman KO, et al. *J Pediatr.* 2017;180:99-104. Copyright 2017. Reproduced with permission from Elsevier.

NOT DRUGS

- Facilitated tuck (arms/legs in flexed position)
- Music Therapy
- Skin-to-skin contact ("kangaroo care")
- Infant massage
- Breastfeeding
- Nonnutritive sucking
- Developmentally appropriate care
  - Limited environmental stimuli
  - Lateral positioning
  - Supportive bedding
  - Attention to behavioral cues

Nonnutritive Sucking or Facilitated Tuck



Liaw JJ, et al. *Int J Nurs Stud.* 2012; 49: 300-9. Copyright 2012. Reproduced with permission from Elsevier.

Joan Smith – The M-Technique

Image courtesy of Terrie E. Inder, MD.

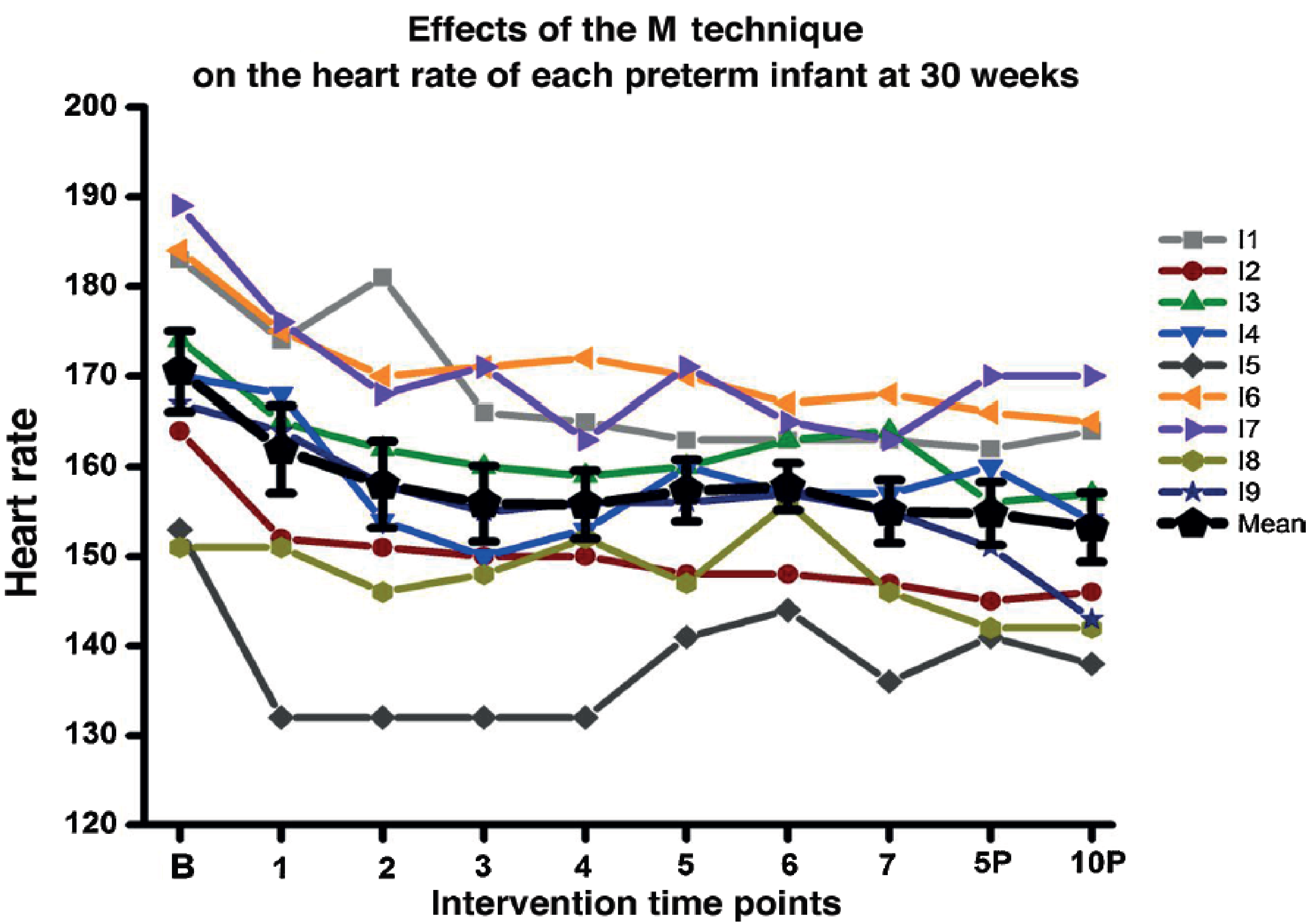
Pilot Study in Preterm Infants >30 Weeks

Each infant received standard neonatal intensive unit (NICU) care or standard NICU care plus a 7-minute M-Technique session, 6 times per week for 5 weeks.

An increased growth velocity ($P = 0.005$).

Smith JR, et al. *Adv Neonatal Care.* 2014; 14: 187-200.

Infant Massage



Smith JR, et al. *Adv Neonatal Care.* 2014; 14: 187-200. Reproduced with permission from Wolters Kluwer Health, Inc.

Infant Massage

Neurodevelopment at 2 years corrected age.

	Control group ($n = 38$)	Intervention group ($n = 35$)	p
MDI[a]	82.9 ± 5.61	85.1 ± 1.99	0.035
PDI[a]	84.2 ± 6.28	86.2 ± 2.14	0.072
MDI[b]			
<70	3 (7.9)	0 (0.0)	0.196
70–84	13 (36.1)	10 (28.6)	
PDI[b]			
<70	3 (7.9)	0 (0.0)	0.214
70–84	8 (21.1)	6 (17.2)	

Procianoy RS, et al. *Early Hum Dev.* 2010; 86: 7-11.

Sleep deprivation, pain and prematurity: a review study.

Bonan KC, et al. *Arq Neuropsiquiatr*. 2015 Feb;73(2):147-54.

- Importance of sleep in preterm infant with the need to spend 75% of time in sleep
- Development of circadian rhythm from 18 weeks
- Frequent disturbance of infant
- Lack of recognition of caregivers for sleep state
- Importance of kangaroo care or skin to skin for promoting sleep
- Inter-relationship of pain and poor sleep

The Neonatal Intensive Care Unit Environment

- Noisy, chaotic
- Exceeds sound and light recommendations from the AAP
  - Understood to adversely affect growth and development
- Sound abatement in the NICU is important
  - Developmental care
  - Family centered care
- Entered a period of rapid change in NICU design
  - Renovations to private rooms

The Developmental Effects of the NICU Single Patient Room

Image courtesy of Terrie E. Inder, MD.

Study NICU

- **½ single patient rooms**
  - 168 square feet
  - 3 walls; 4th wall is a sliding glass door
  - Individualized lighting
  - Parents can visit 24 hours a day
    - Lounger at the bedside for parents to sleep on

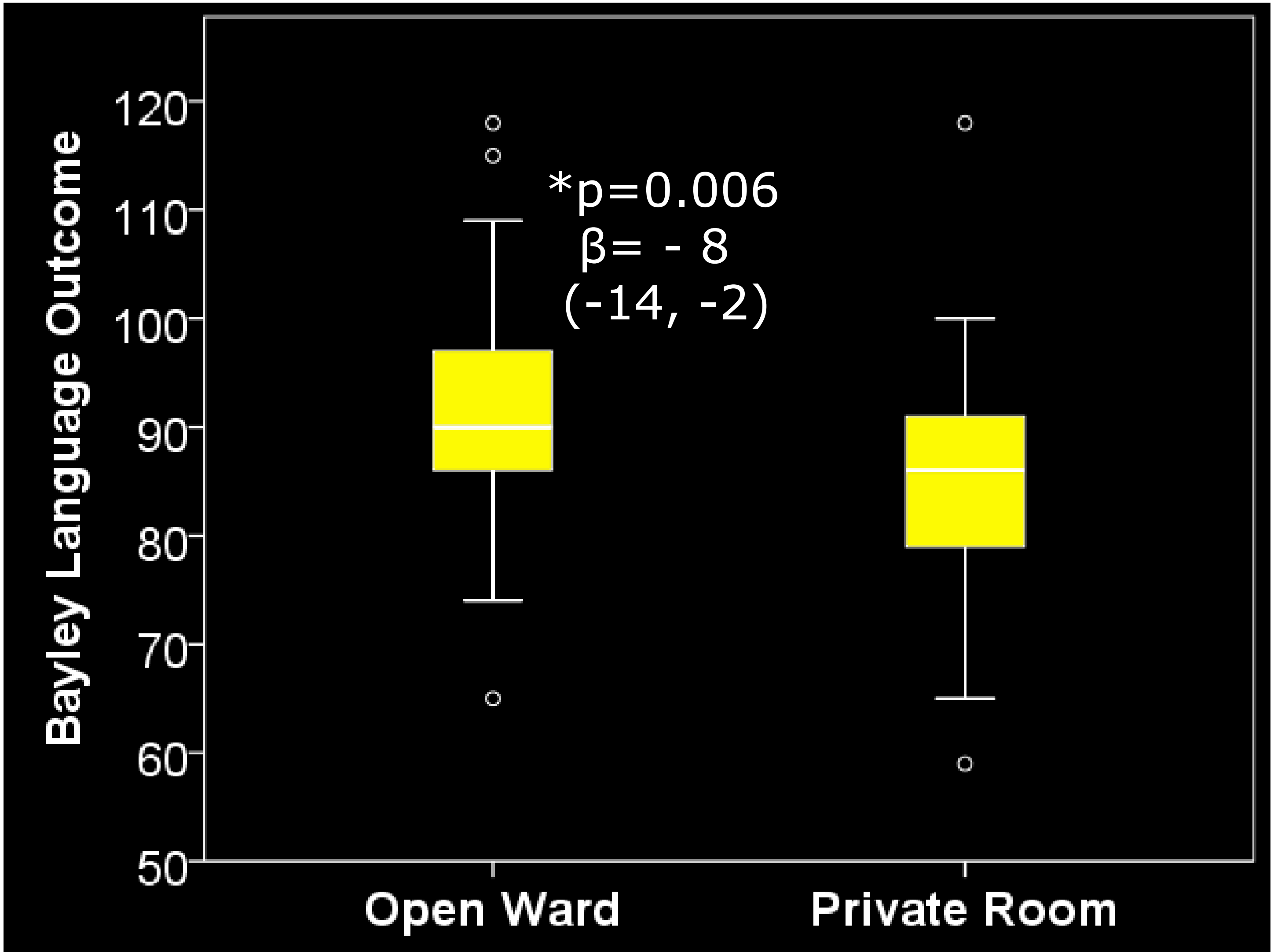
- **½ open bay beds**
  - Approx 10-12 beds in 1100 square feet of space
  - General lighting
  - Screens can be pulled to bedside for privacy
  - Parents can visit 24 hours a day
    - Sleep rooms available just outside the NICU

Images courtesy of Terrie E. Inder, MD.

Follow up at age 2 years

- 86 infants (83%) returned for developmental follow-up
  - Mean (SD): 27.4 (2.1) months
- Associations between room type and cognitive, language and motor outcome were explored, while controlling for:
  - CRIB score
  - Cerebral injury
  - Social risk score
  - Family functioning

Language Outcome



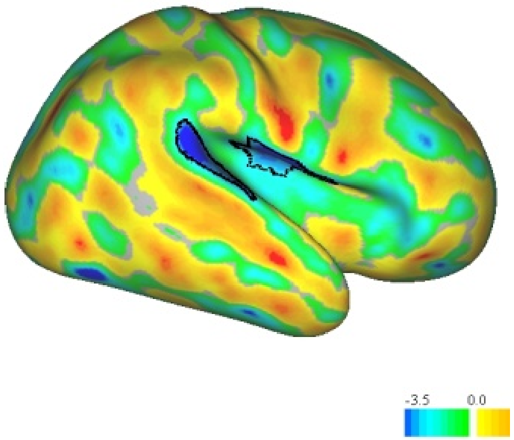
*Linear regression; controlling CRIB, cerebral injury, social risk and family functioning

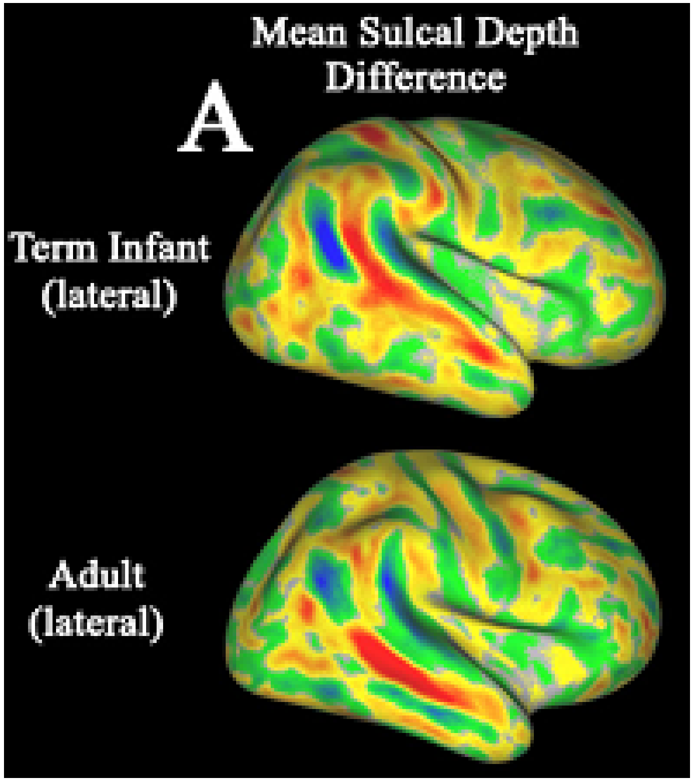
Pineda RG, Neil J, Dierker D, et al. Alterations in brain structure and neurodevelopmental outcome in preterm infants hospitalized in different neonatal intensive care unit environments. *J Pediatr*. 2014;164(1):52-60.e2. Copyright 2014. Reproduced with permission from Elsevier.

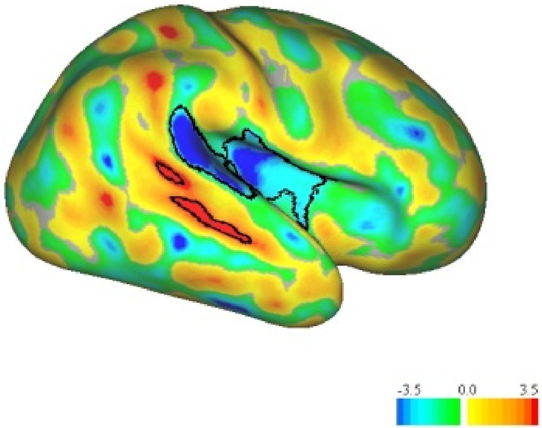
Hemispheric Asymmetries

Single Patient Room

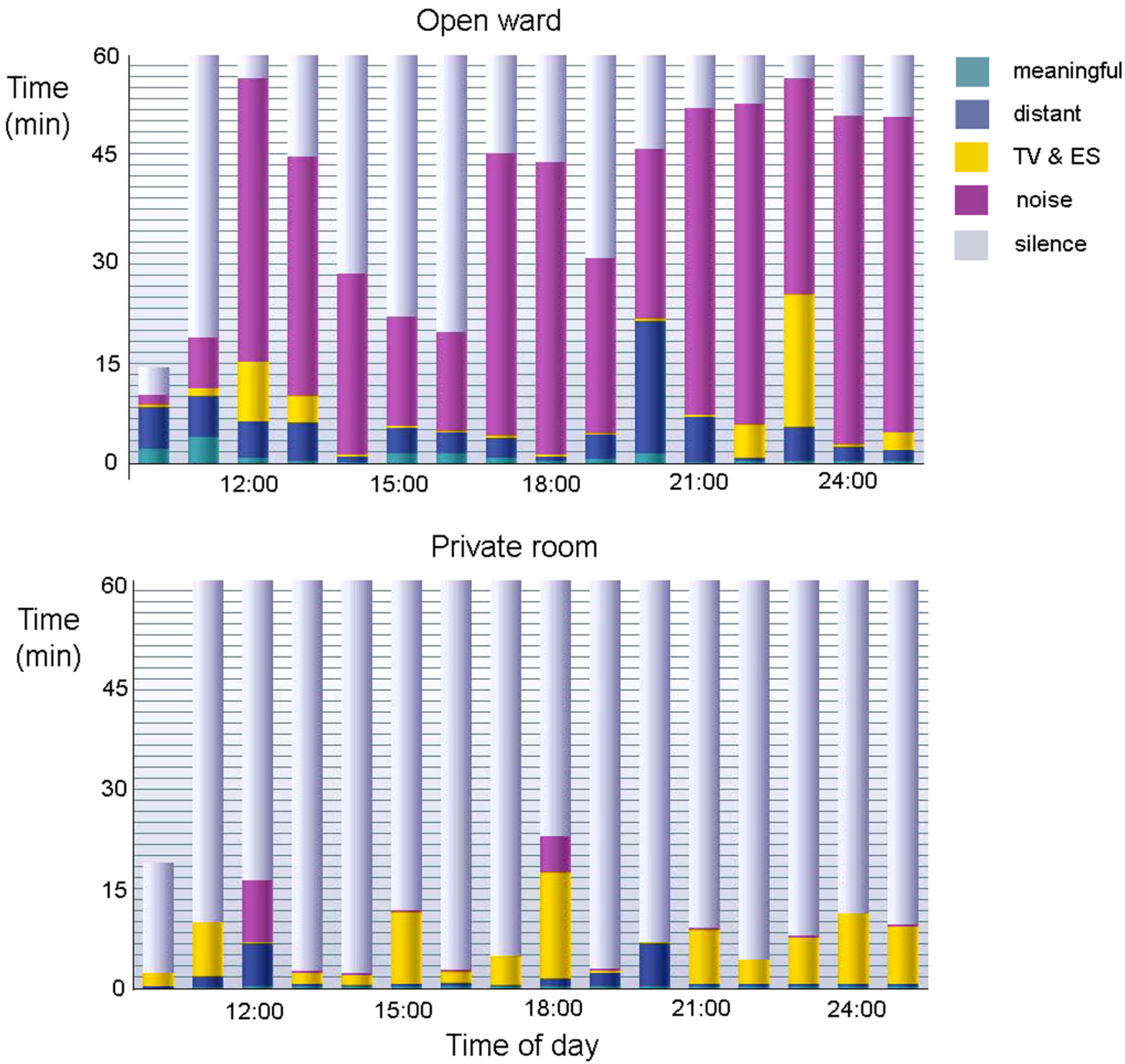
Open Bay







Hill J, et al. *J Neurosci*. 2010;30(6):2268-2276.


Open ward
Time (min)
60
45
30
15
0
12:00
15:00
18:00
21:00
24:00
meaningful
distant
TV & ES
noise
silence
Private room
Time (min)
60
45
30
15
0
12:00
15:00
18:00
21:00
24:00
Time of day

More than just auditory experience

The Journal of Pediatrics • www.jpeds.com COMMENTARY

A Risk of Sensory Deprivation in the Neonatal Intensive Care Unit

Alan H. Jobe, MD, PhD

Harry Harlow Rhesus Monkey Work

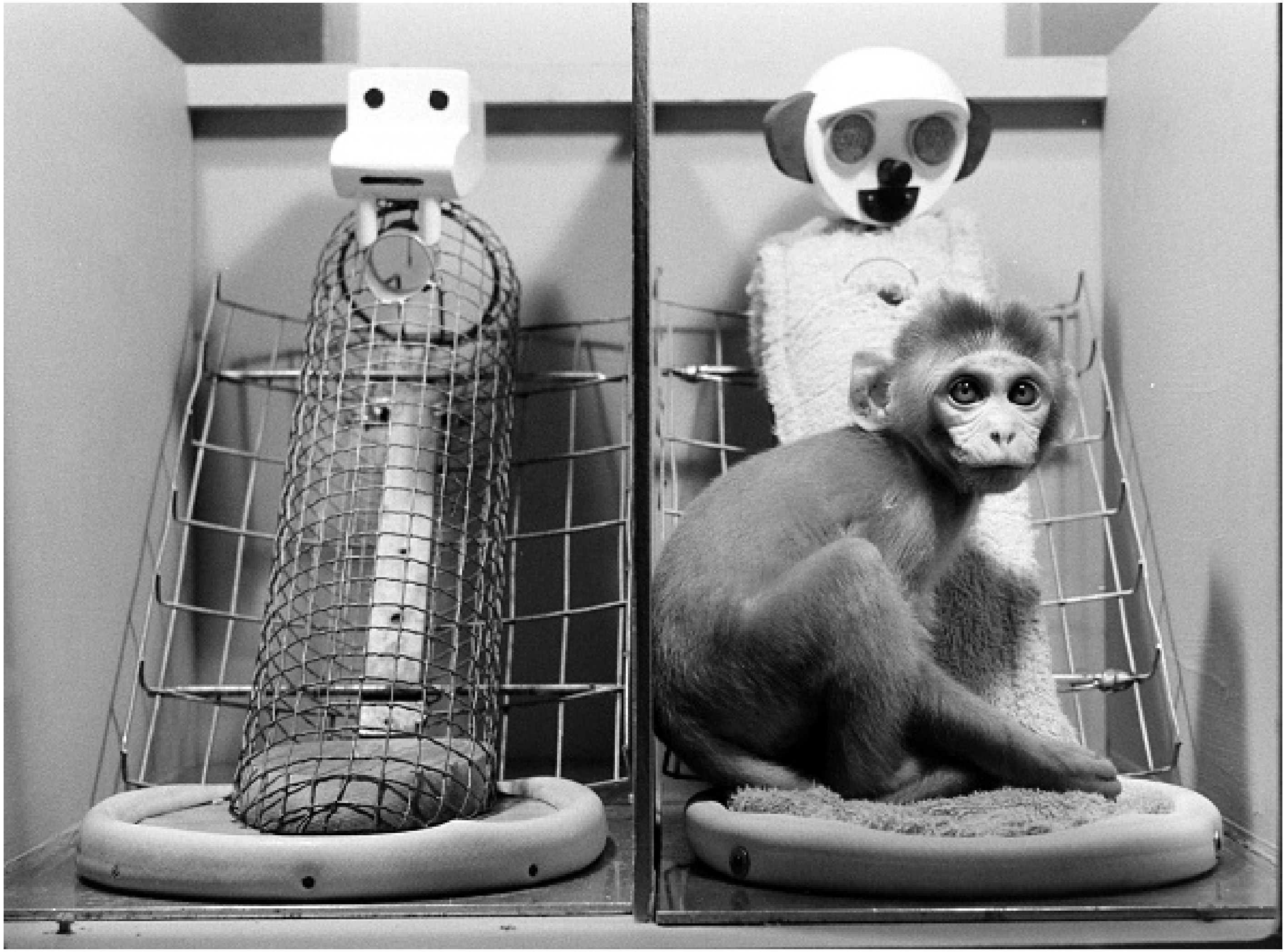


Photo by Al Fenn | The LIFE Picture Collection

Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life.

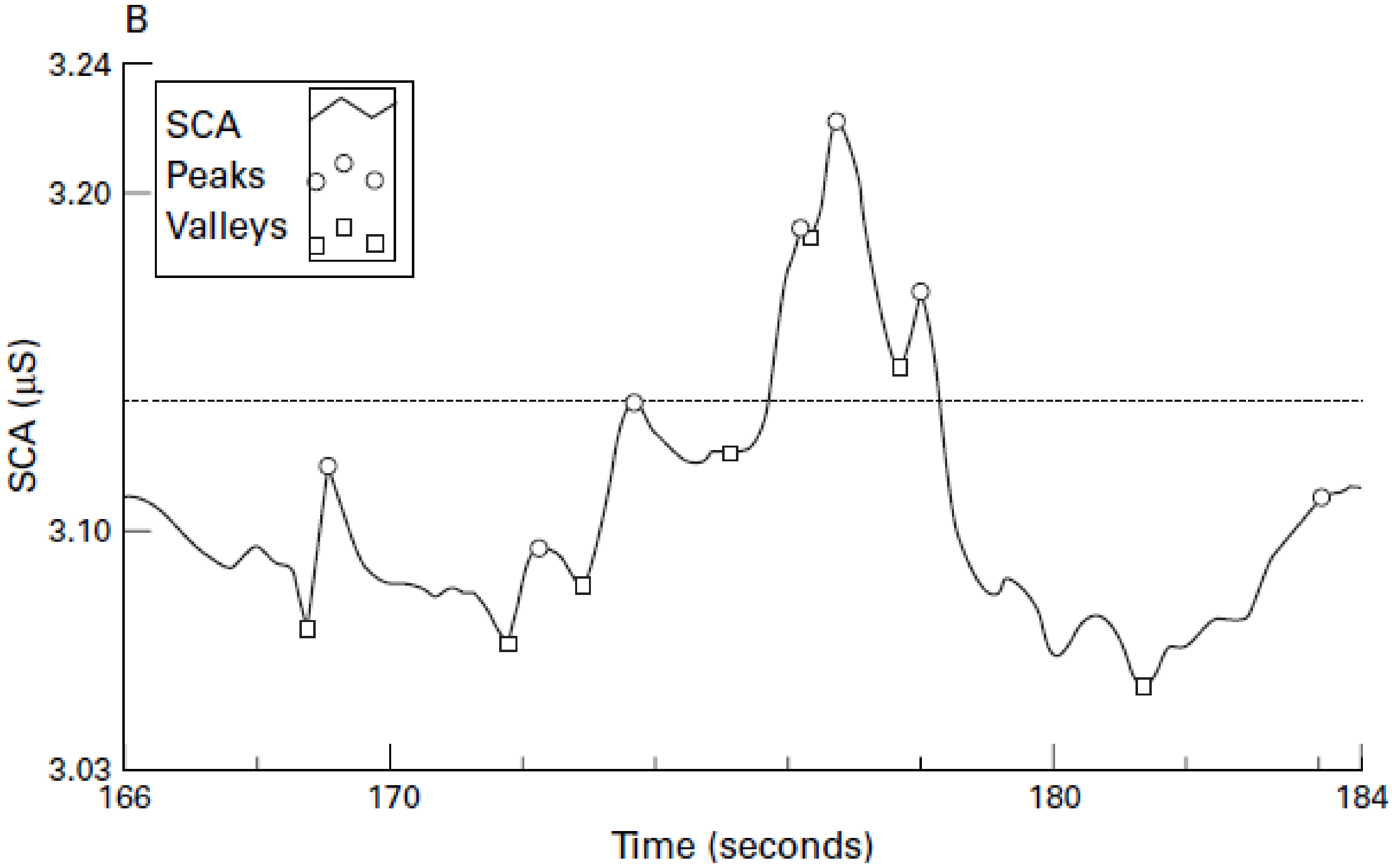
Feldman R, Rosenthal Z, Eidelman A. *Biological Psychiatry*. 2014.

- 73 premature infants and 73 matched controls
- 1 hour of Kangaroo Care each day for 14 days
- Improved autonomic control at term and improved
- Improved cognitive development throughout the first 10 years associated with better parent-infant interaction

Can we measure distress – skin conductance?

Photo by Dmitry Kalinovsky | shutterstock

Skin Conductance Amplitude During Pain



Storm H. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F143–F147. Reproduced with permission from BMJ Publishing Group Limited.

A

B

Lyngstad LT, et al. *J Early Hum Dev*. 2014;Vol 90(4)169-172.

Does skin-to-skin contact reduce stress during diaper change in preterm infants?

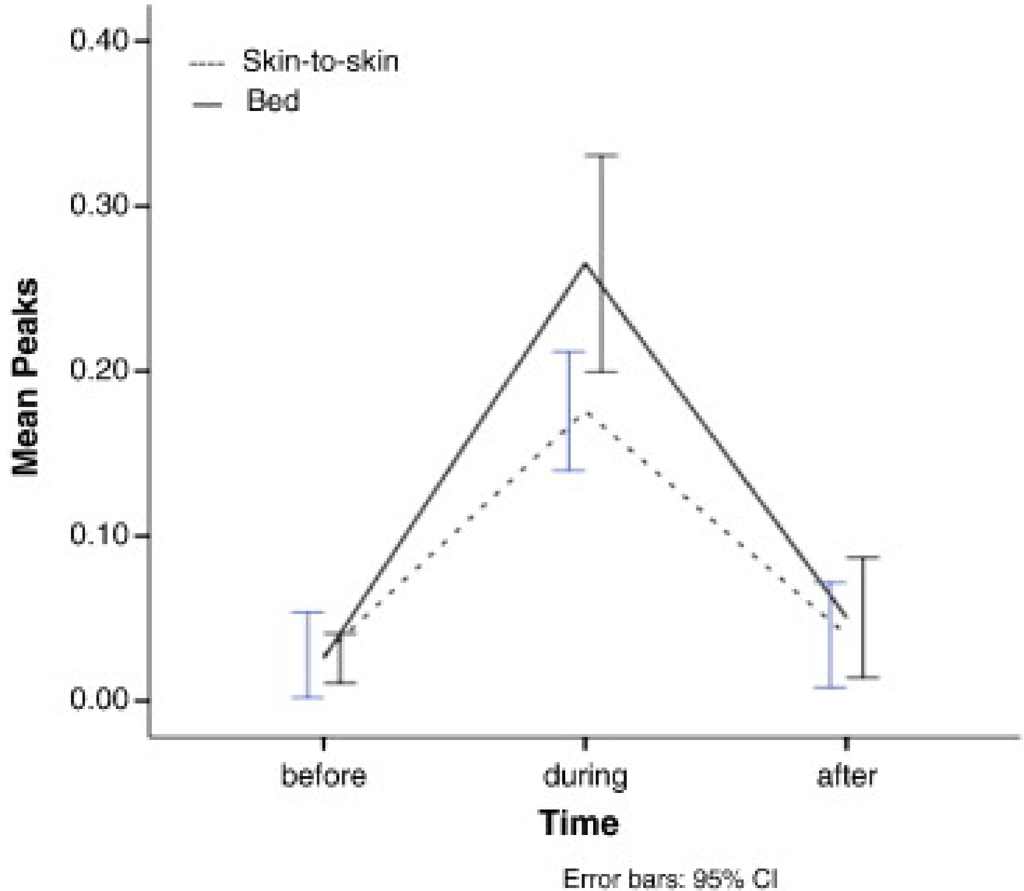
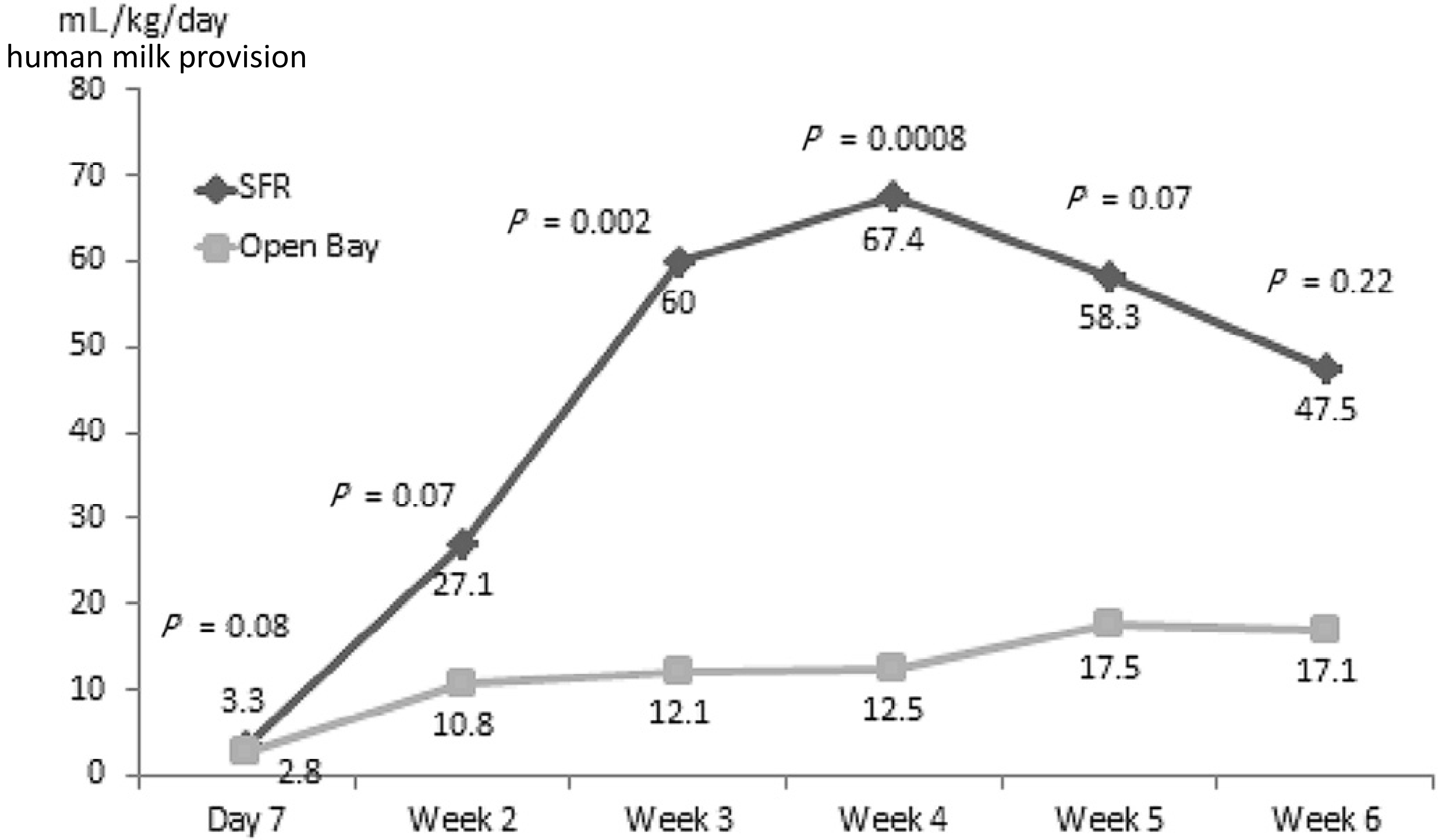


Fig. 1 Skin conductance peaks per sec before, during and after diaper change. In both groups there was a significant increase from before to during diaper change (p < 0.05). There was a significant difference between the groups only at time point durin...

Lyngstad LT, et al. *J Early Hum Dev*. 2014;Vol 90(4)169-172. Copyright 2014. Reproduced with permision from Elsevier.

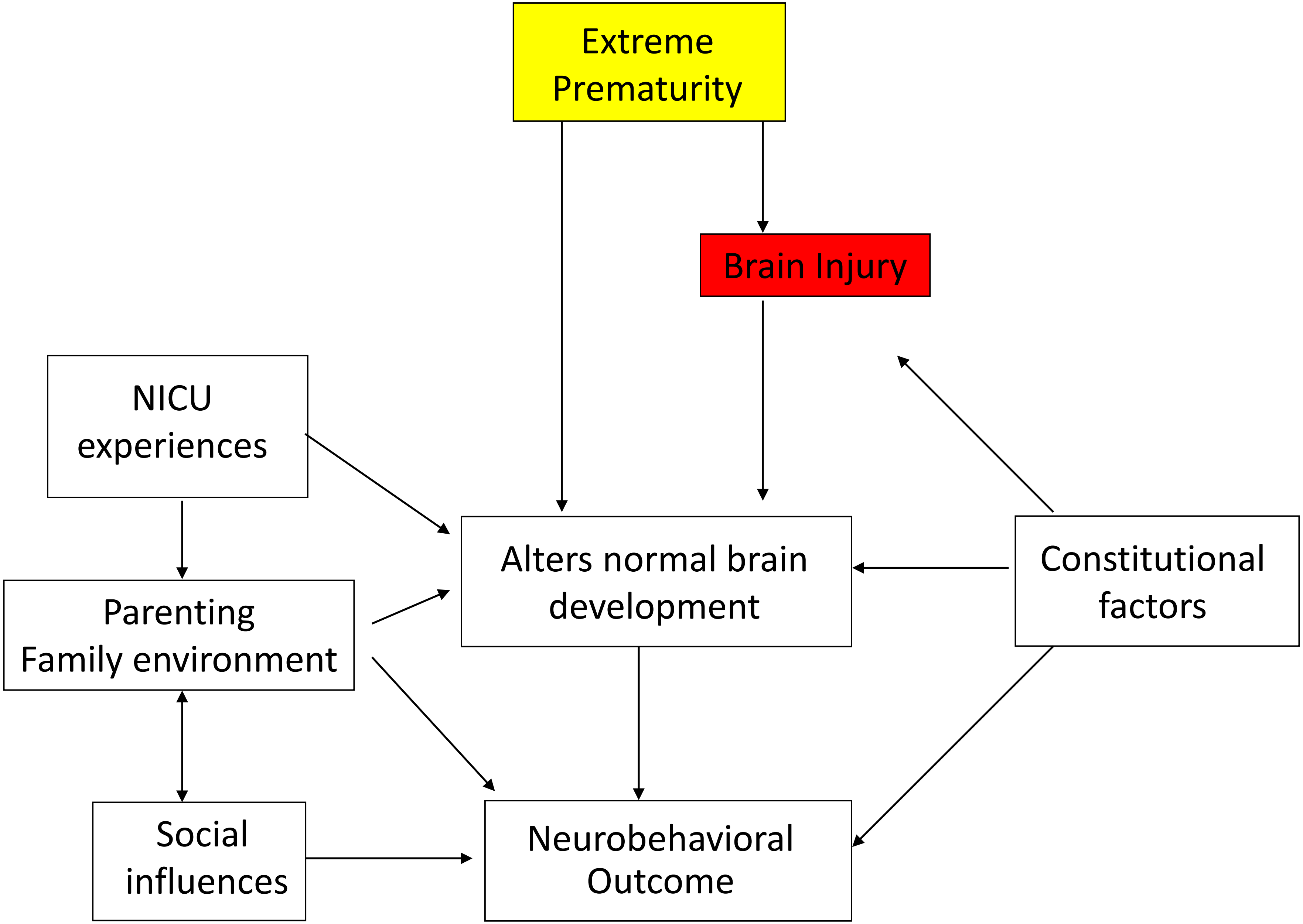
Advantages of Single Family Rooms

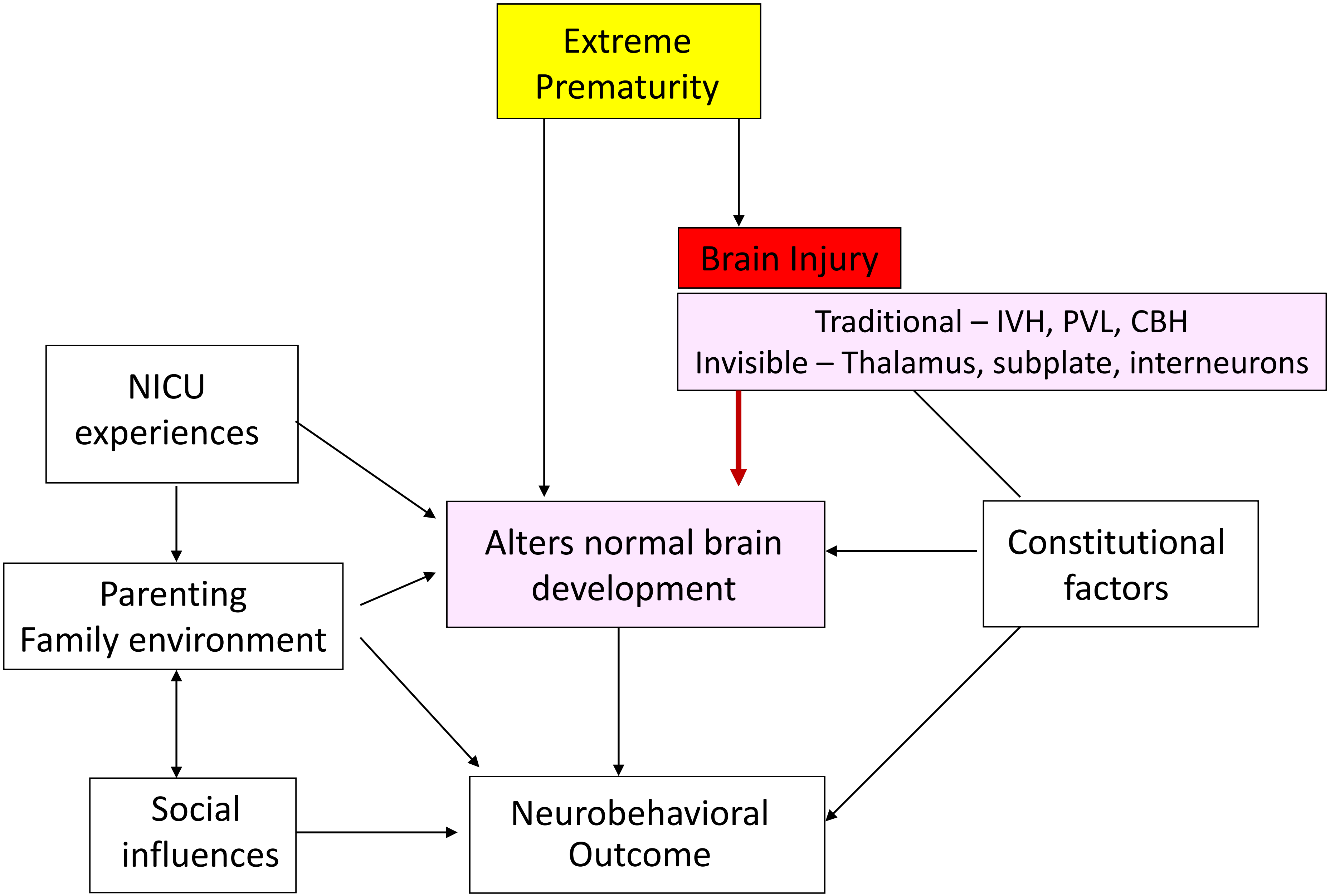


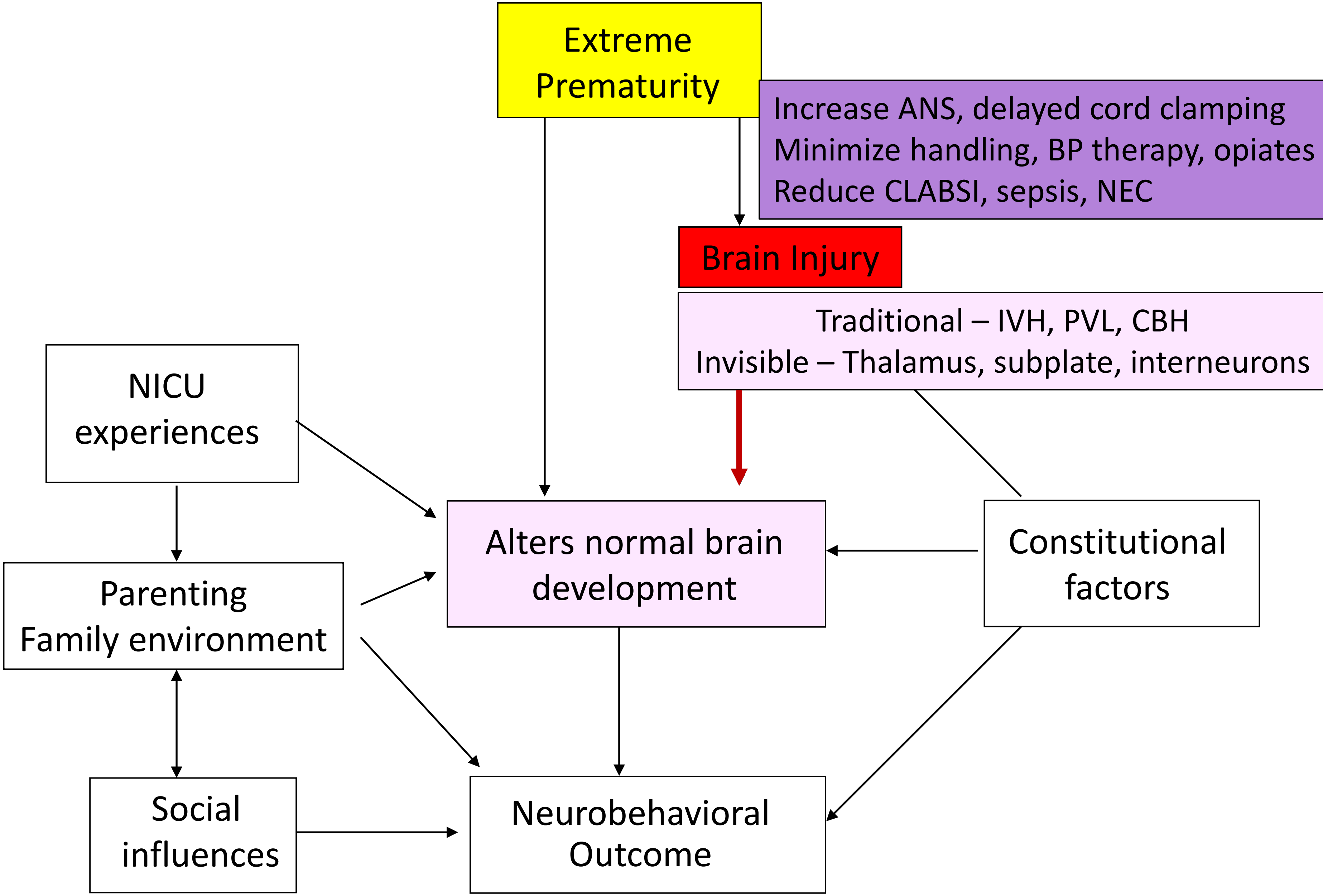
Vohr B, et al. *J Pediatr*. 2017 Feb 24. Copyright 2017. Reproduced with permision from Elsevier.

Improved Outcomes

- SFR NICU was associated with a 2.55-point increase in Bayley cognitive scores and 3.70-point increase in language scores.
  - Prior work appears to be strongly mediated by the presence of parents
- Every 10 mL/kg/day increase of human milk at 4 weeks was independently associated with increases in Bayley cognitive, language, and motor scores (0.29, 0.34, and 0.24, respectively).


Extreme Prematurity
Brain Injury
NICU experiences
Alters normal brain development
Constitutional factors
Parenting Family environment
Social influences
Neurobehavioral Outcome


Extreme Prematurity
Brain Injury
Traditional – IVH, PVL, CBH
Invisible – Thalamus, subplate, interneurons
NICU experiences
Alters normal brain development
Constitutional factors
Parenting
Family environment
Social influences
Neurobehavioral Outcome


Extreme Prematurity
Increase ANS, delayed cord clamping
Minimize handling, BP therapy, opiates
Reduce CLABSI, sepsis, NEC
Brain Injury
Traditional – IVH, PVL, CBH
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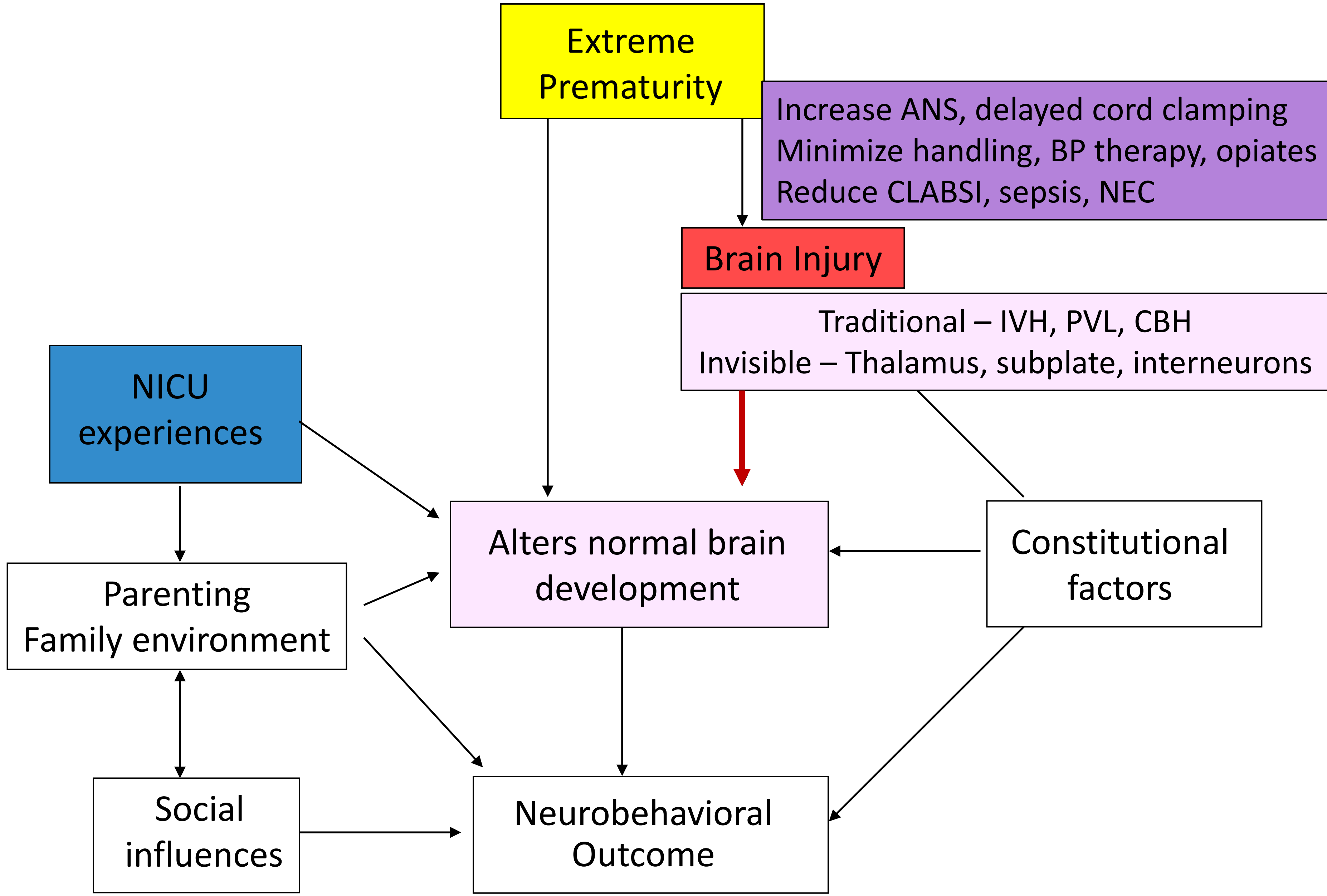
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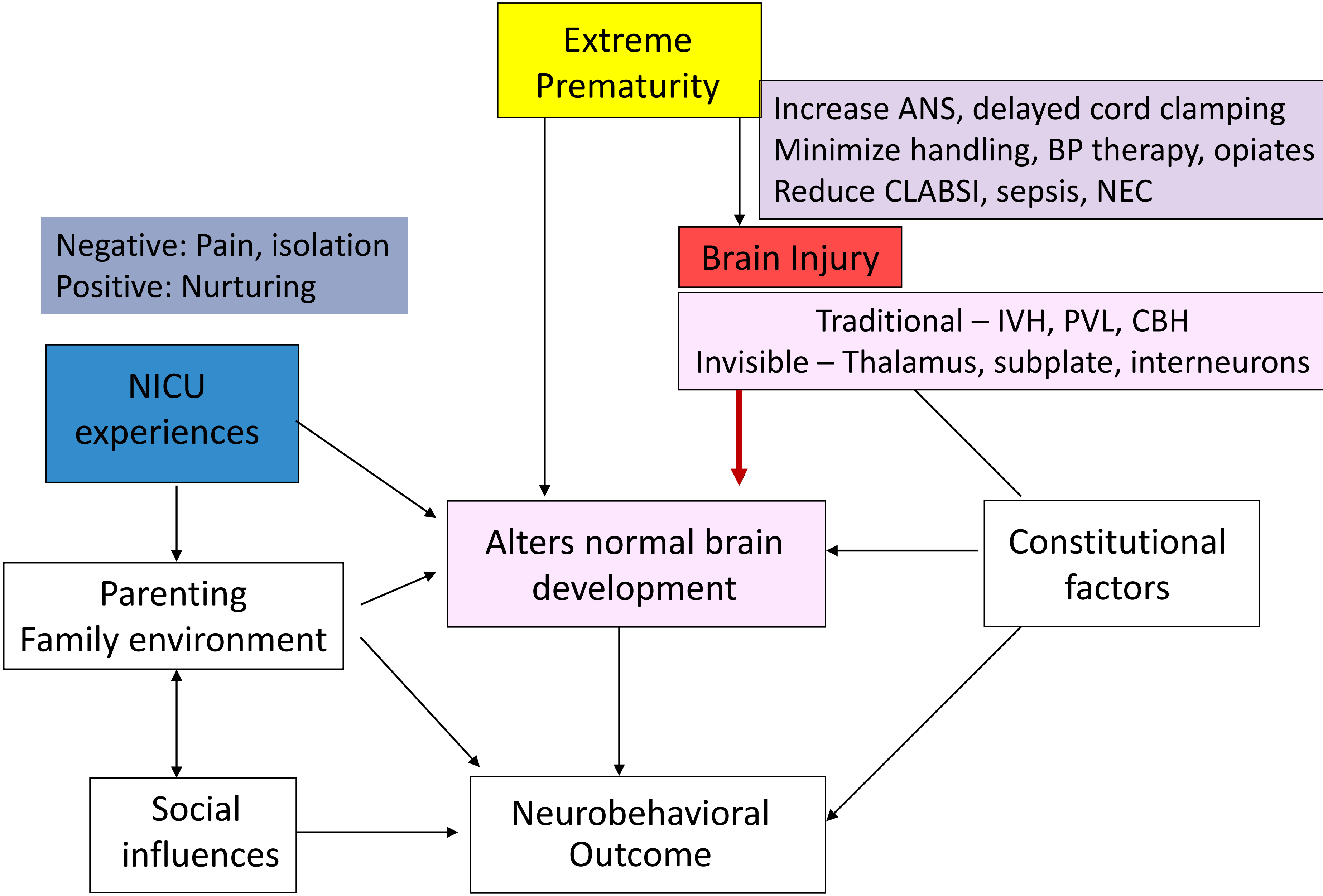
Extreme Prematurity
Increase ANS, delayed cord clamping
Minimize handling, BP therapy, opiates
Reduce CLABSI, sepsis, NEC
Negative: Pain, isolation
Positive: Nurturing
Brain Injury
Traditional – IVH, PVL, CBH
Invisible – Thalamus, subplate, interneurons
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Parenting
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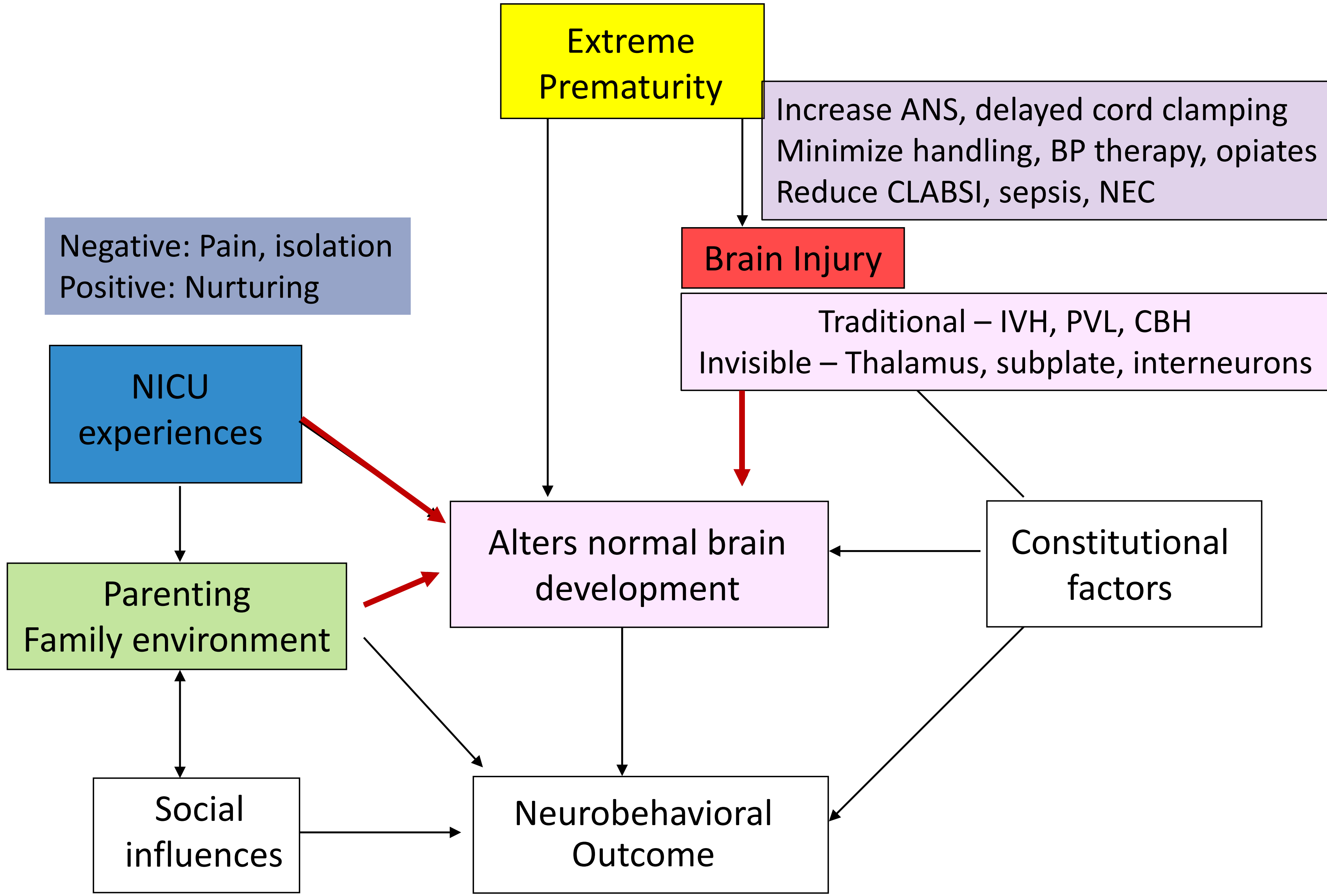
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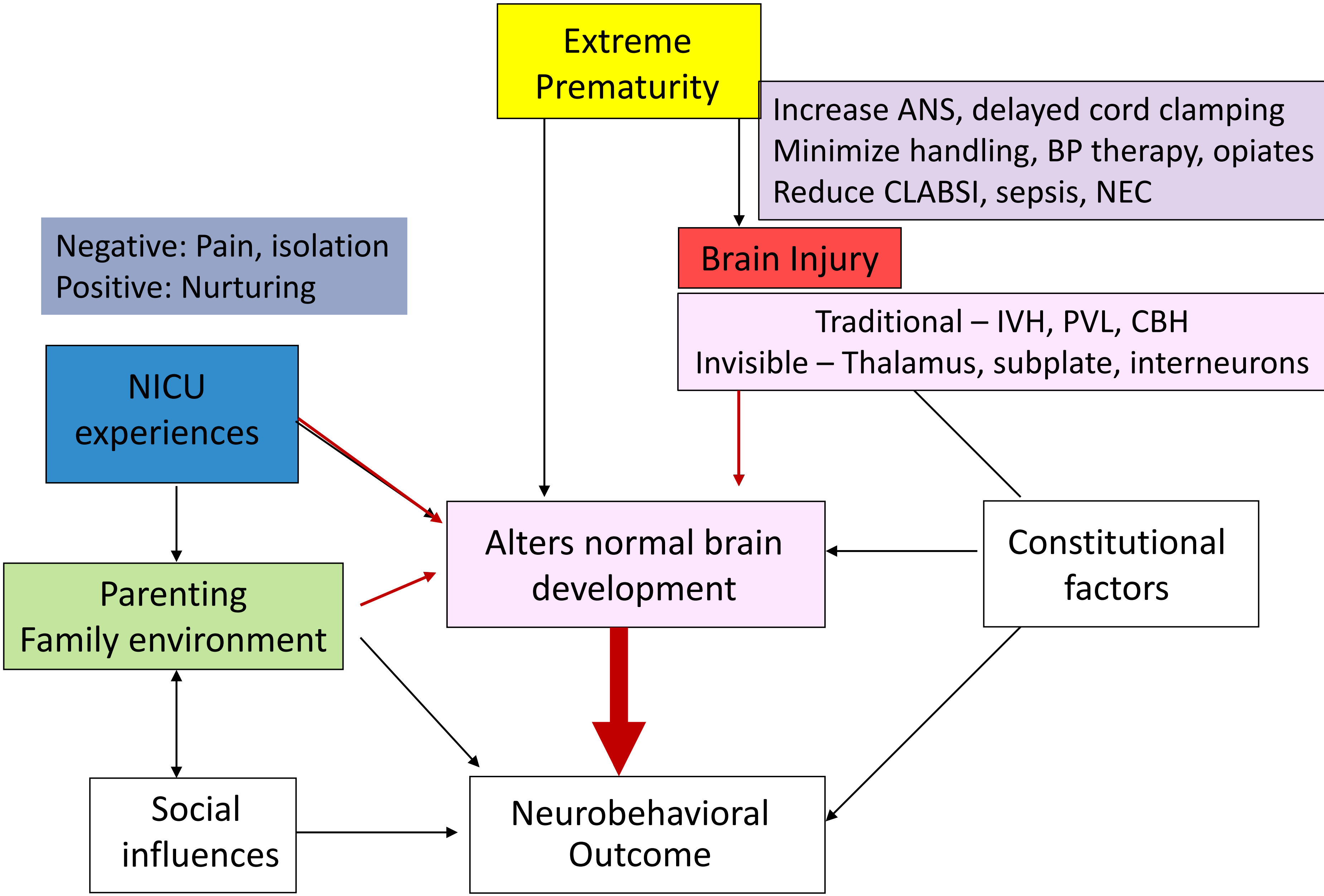
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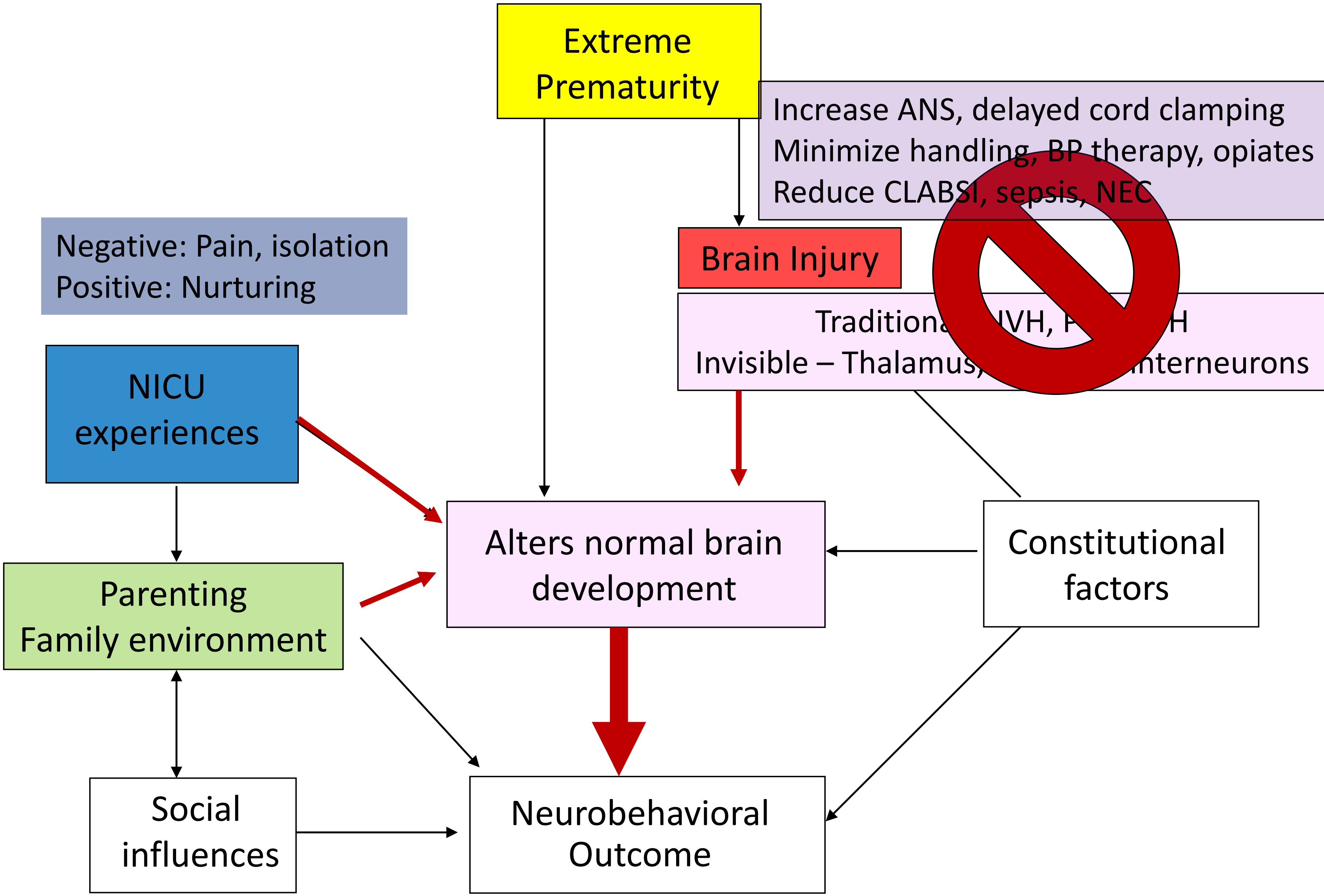
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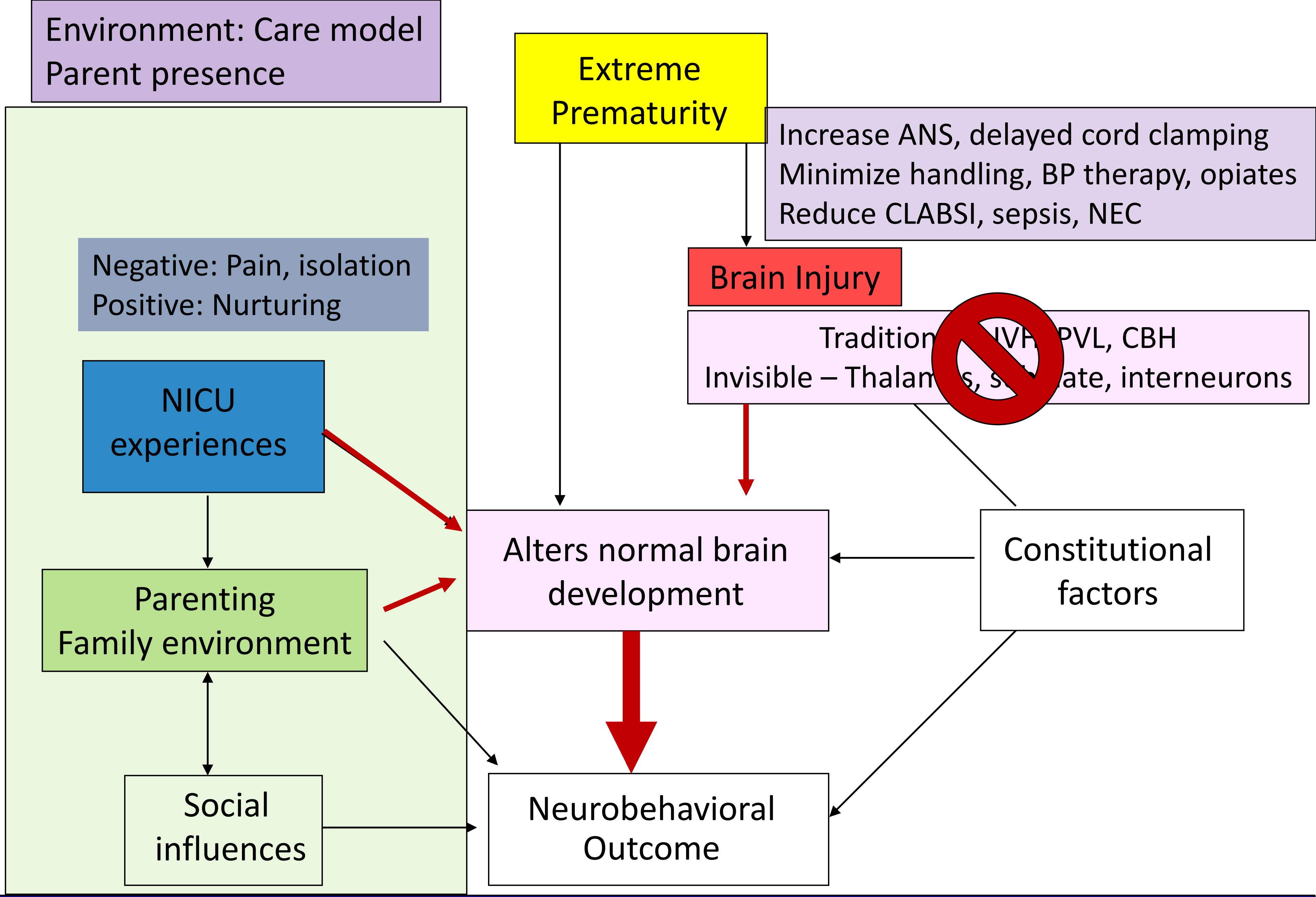
Environment: Care model
Parent presence
Extreme Prematurity
Increase ANS, delayed cord clamping
Minimize handling, BP therapy, opiates
Reduce CLABSI, sepsis, NEC
Brain Injury
Tradition IVH PVL, CBH
Invisible – Thalam s, s ate, interneurons
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Caring in the NICU

Our past
The Boston Lying In Hospital

Our present
Brigham NICU care

Our future
As bright as the stars

THE WALL STREET JOURNAL.

HEALTH | JOURNAL REPORTS: HEALTH CARE

The New, Improved World of Infant Care

A host of high-tech advances are giving newborns a better shot at avoiding a range of ailments. The long-term impact could be profound.

Six research centers are trying to identify the causes of premature birth, which can cause serious and costly disabilities. PHOTO: JUSTIN METZ FOR THE WALL STREET JOURNAL

The Wall Street Journal, Sept. 16 2018

Summary

- Brain Injury is important to reduce
- Many forms of brain injury in the preterm infant remain invisible
- Injury has a prolonged secondary dysmaturation effect – protracted vulnerability
- Experience and exposures alter brain development during this CRITICAL period of brain development to term equivalency
- Reduce adverse experience – pain, negative handling, alarm noise; as pain, stress and sensory isolation appear to adversely influence brain structure and outcome
- Increase positive experience – mother's voice; music; skin-to-skin and touch therapy.
- Parental mental health, empowerment and attachment are also powerful for outcomes
- Take care of the caregivers – wellbeing of the providers

Image courtesy of Terrie E. Inder, MBChB, MD.