

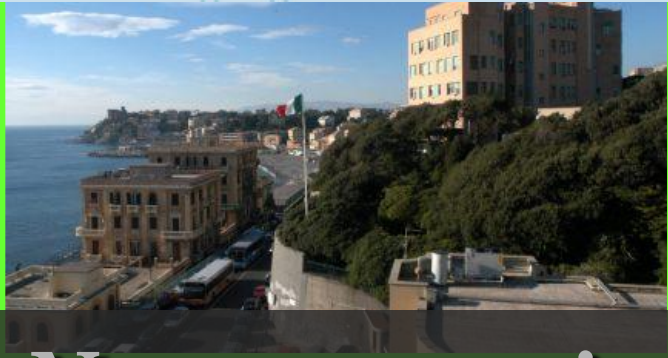


**gora**



**SIMP**  
Società Italiana di Medicina Perinatale

**Congresso Nazionale  
della Società Italiana  
di Medicina Perinatale**

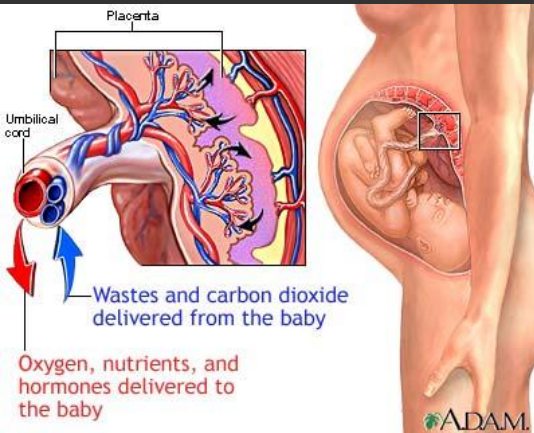


# *Neuroprotezione*

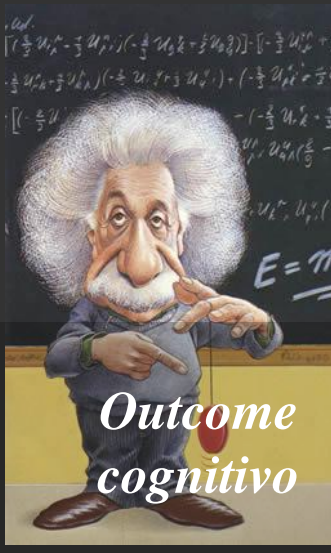
**Luca A. Ramenghi MD PhD**

**Patologia Neonatale e Terapia Intensiva  
Neonatale "G. Gaslini" IRCCS Genoa**





*Outcome motorio*



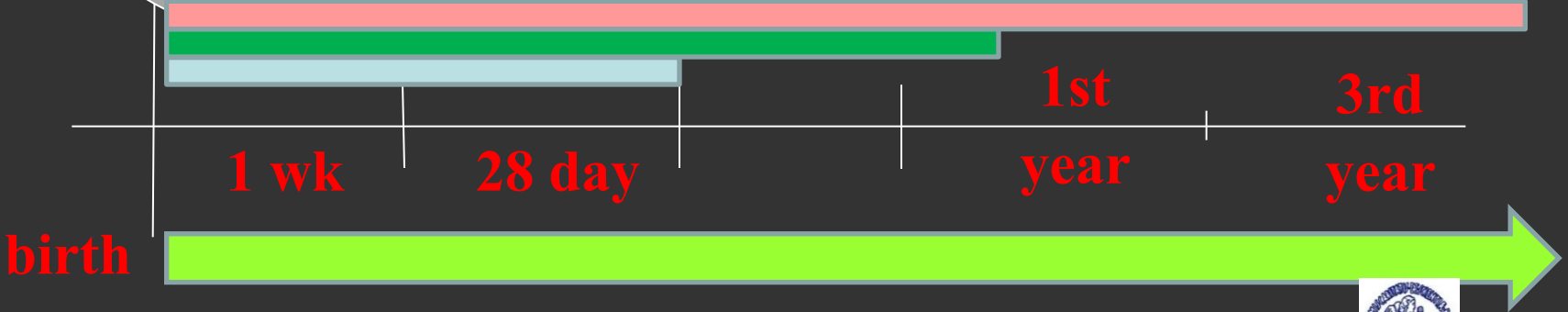
*Outcome cognitivo*

«Developmental Care NIDCAP»

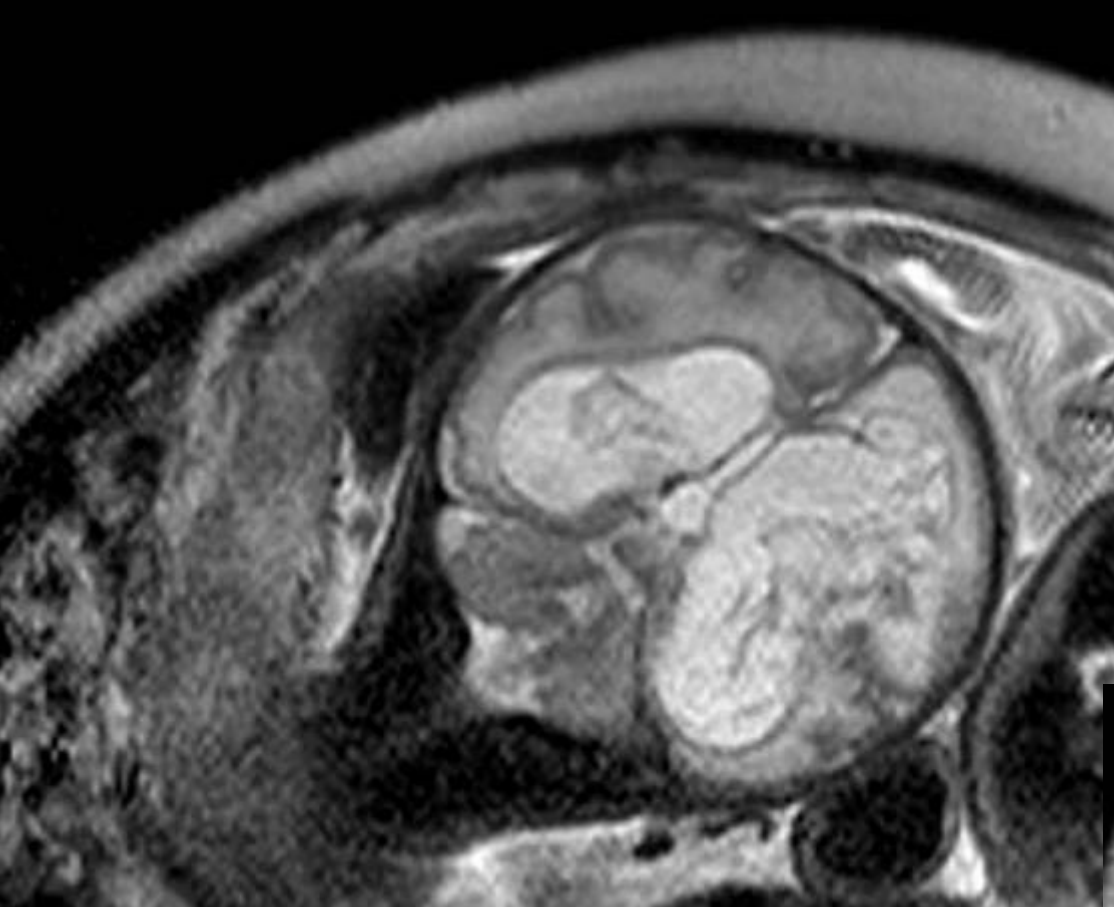
*Sviluppo lesioni cerebrali*

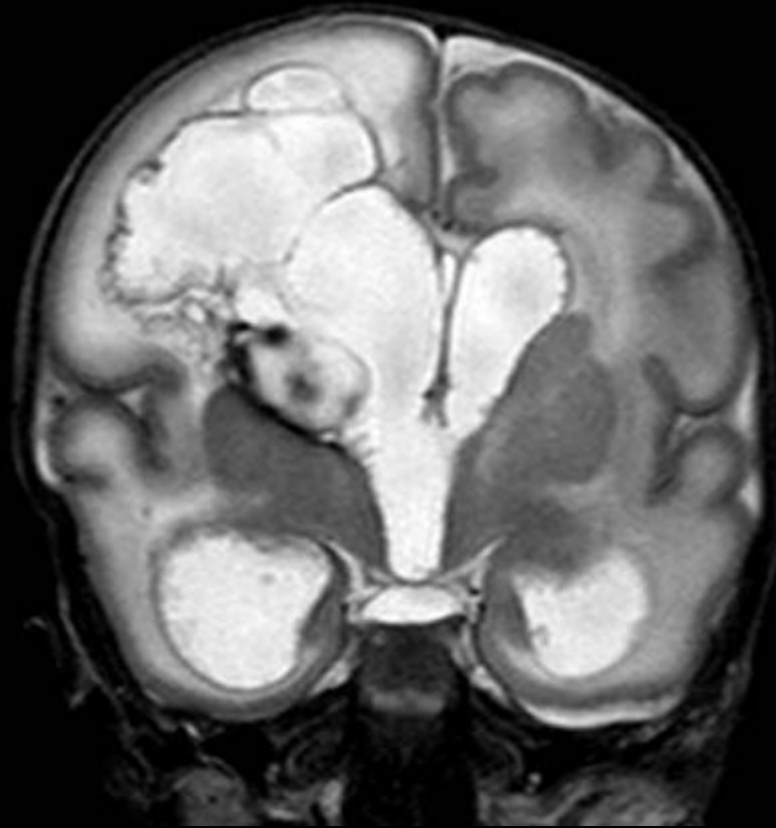
*Sviluppo encefalo*

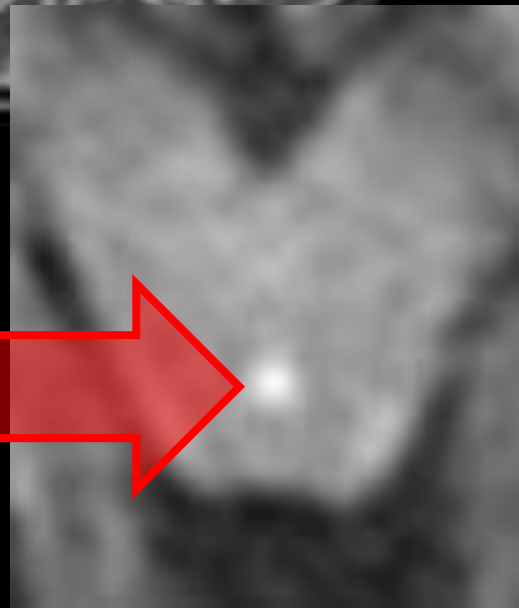
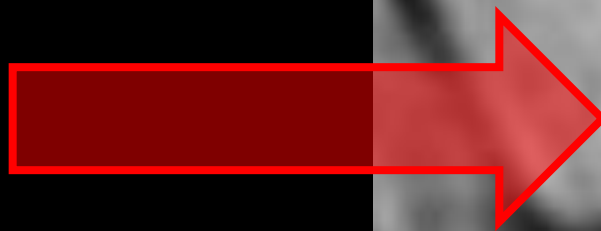
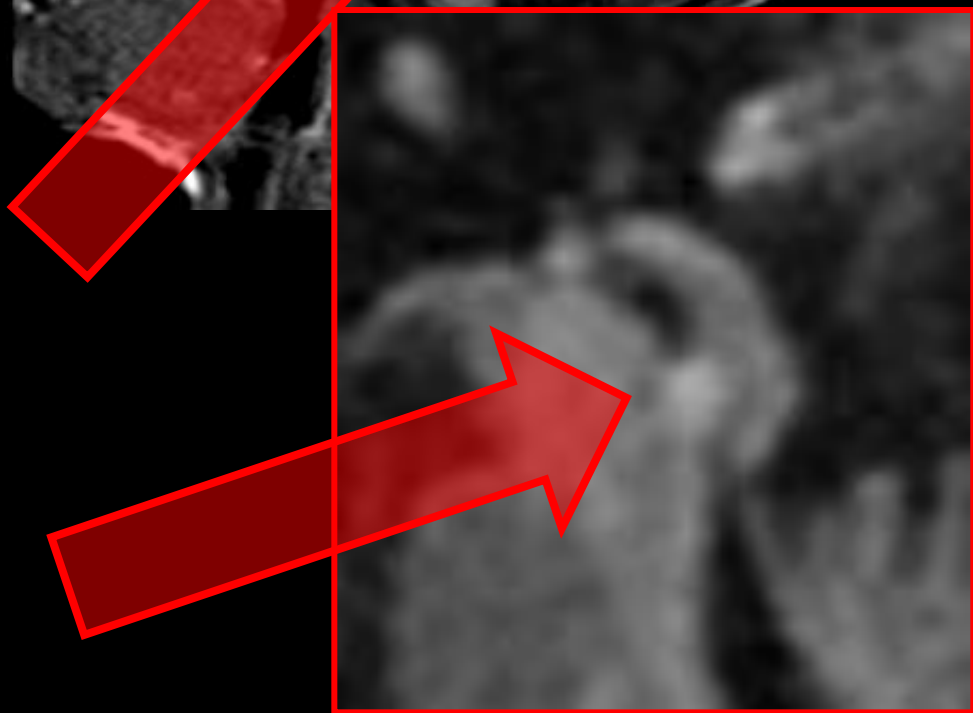
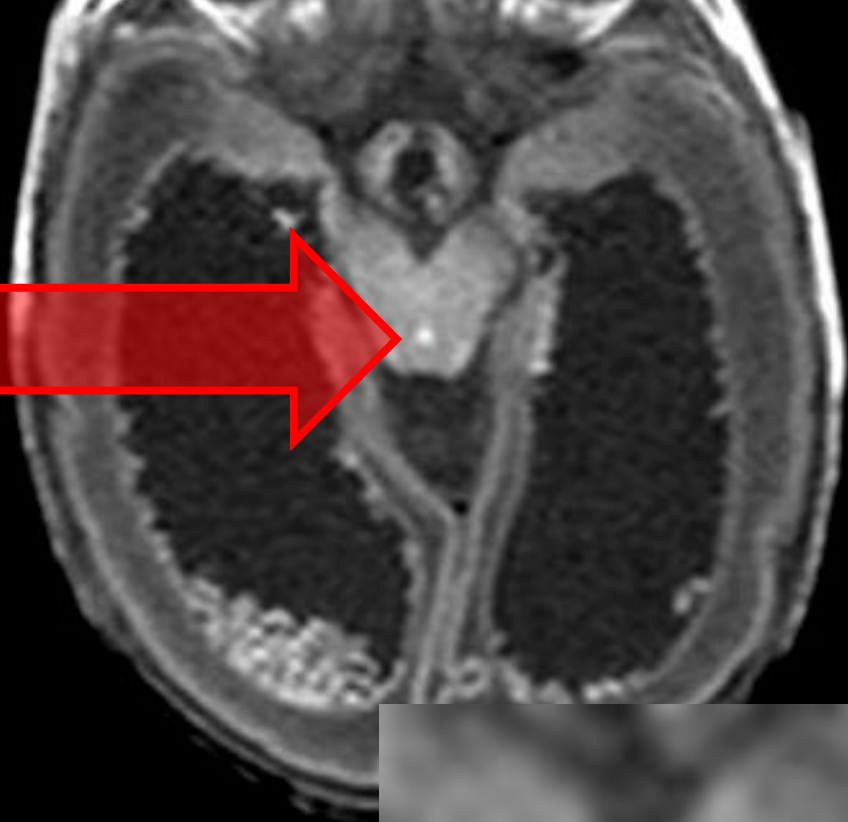
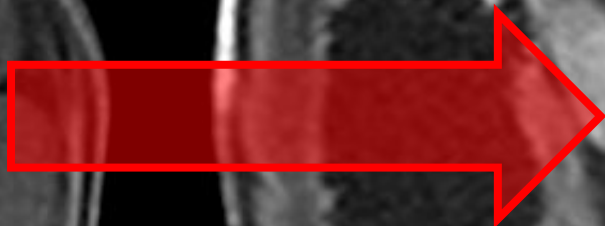
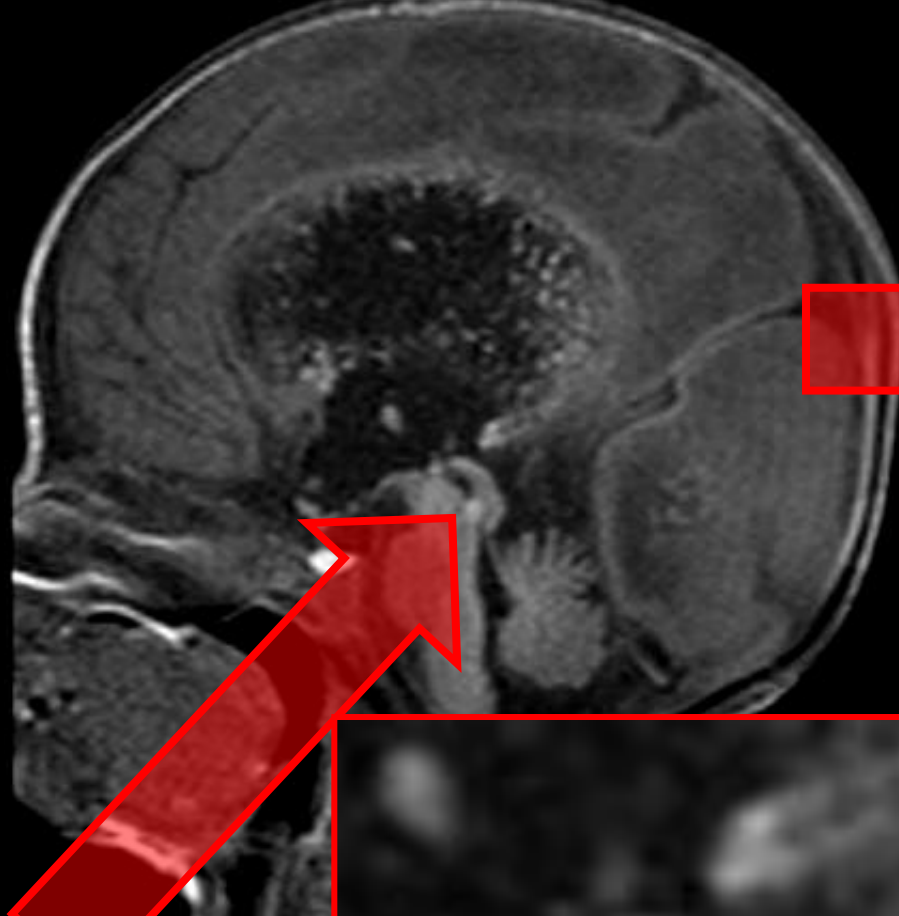
*Influenze ambientali*



# NEUROPROTEZIONE COME TIMING DEL PARTO

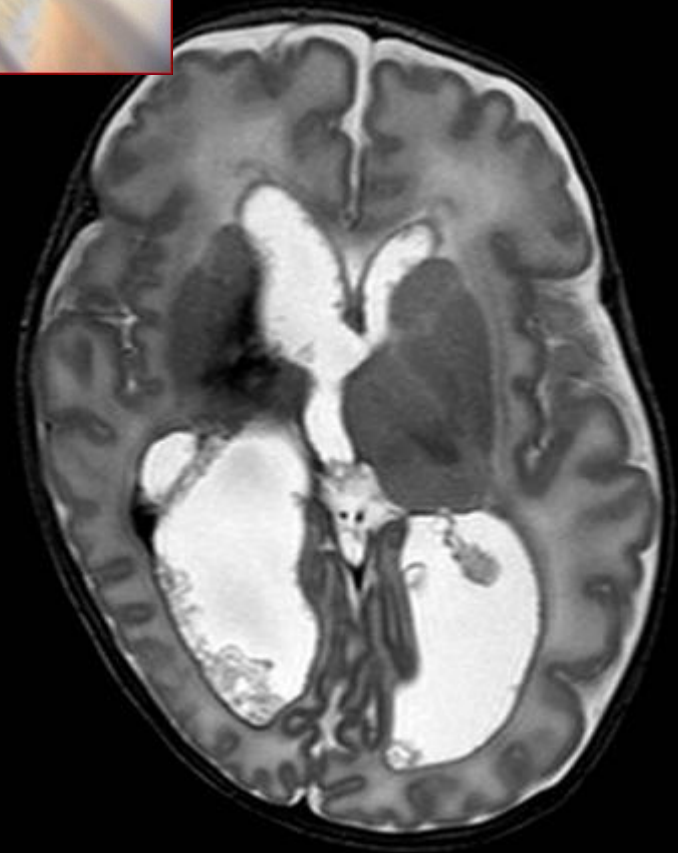






13/11/2013

19/12/2013

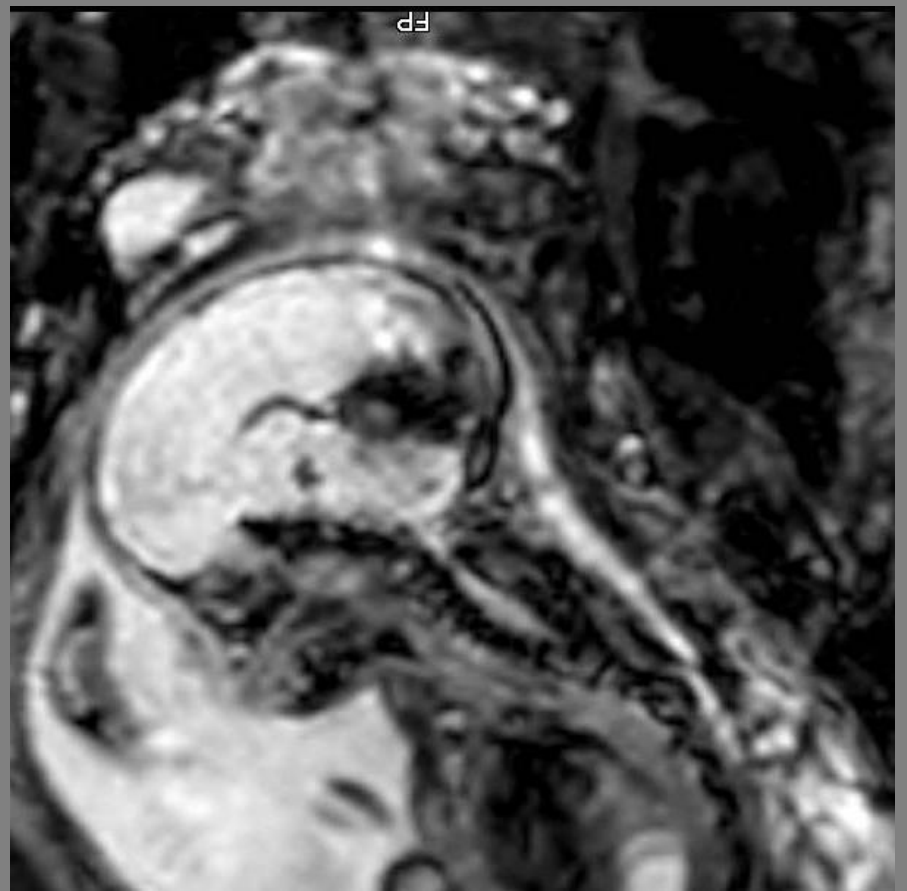




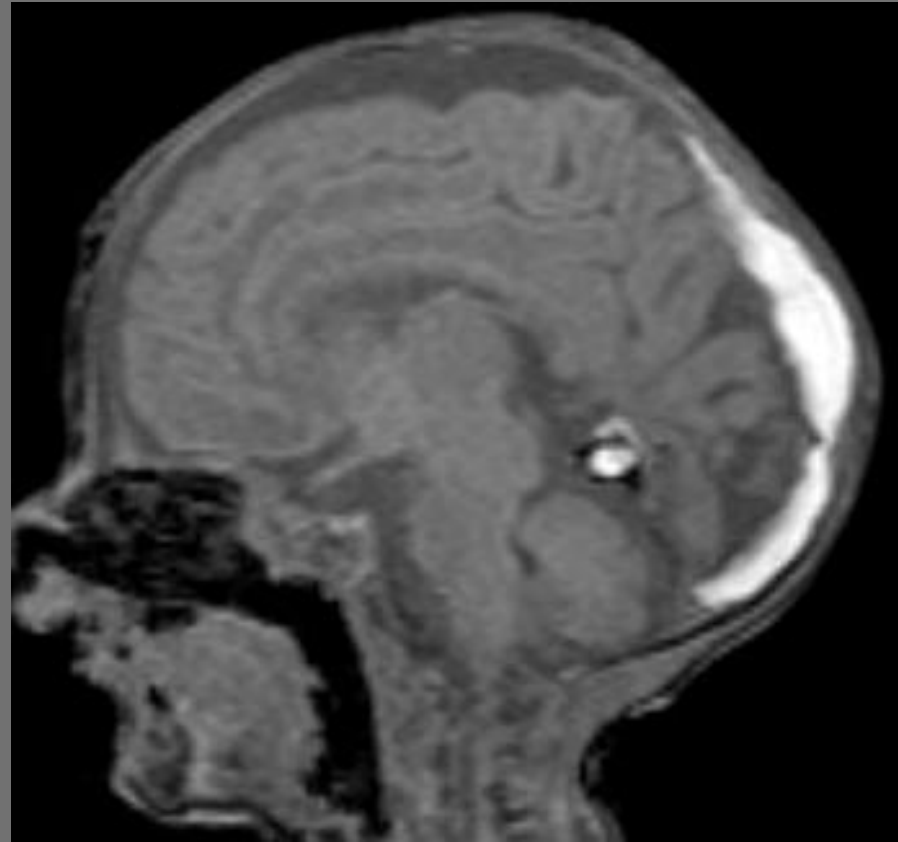




25 wks



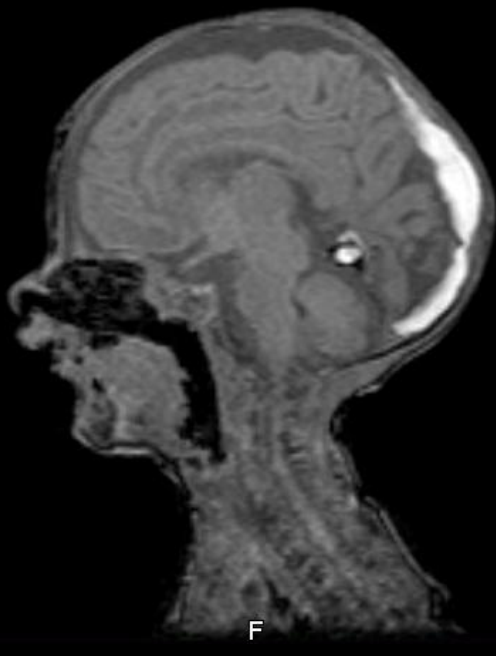
31 wks



32 wks

34 wks

On day 4 started on LMVH



F

Con parula : Rapporto = 10.10

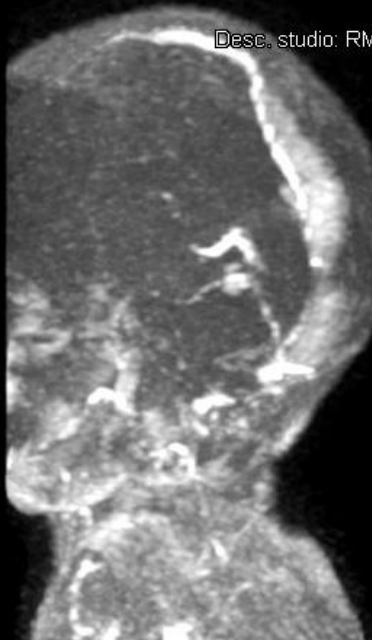


RAIN

F

Con parula : Rapporto = 5.16

Desc. studio: RM ENCEFALO (S



Desc. studio: RM ENCE

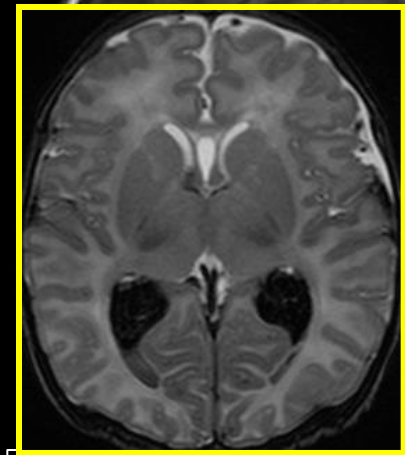


F

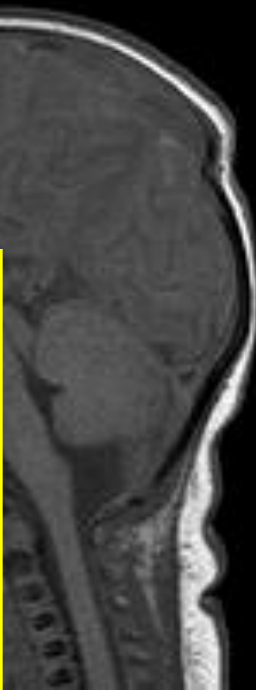
Con parula : Rapporto = 0.88

Desc. studio: RM ENCEFALO (S

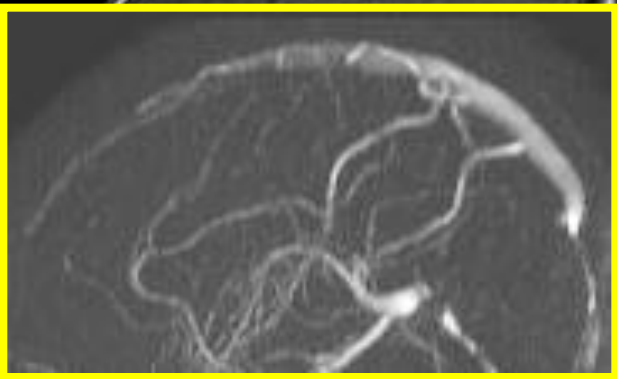
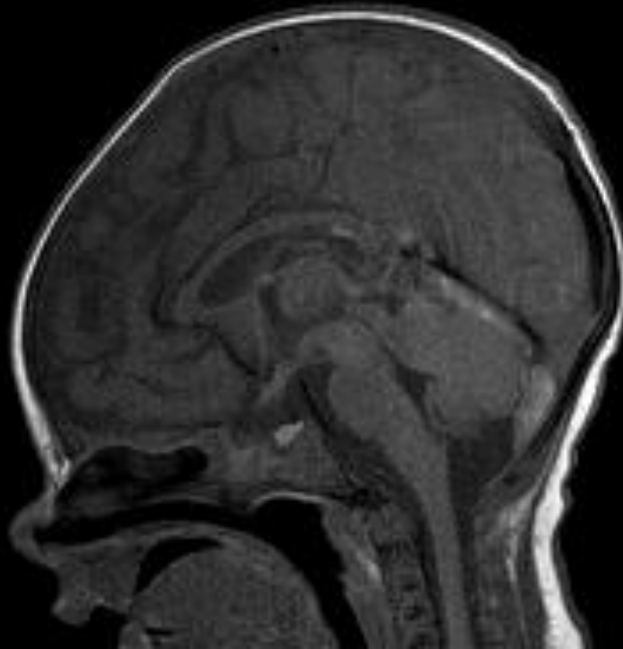
**NEUROPROTEZIONE COME  
GESTIONE DELL'IMMEDIATO  
POST-PARTUM**



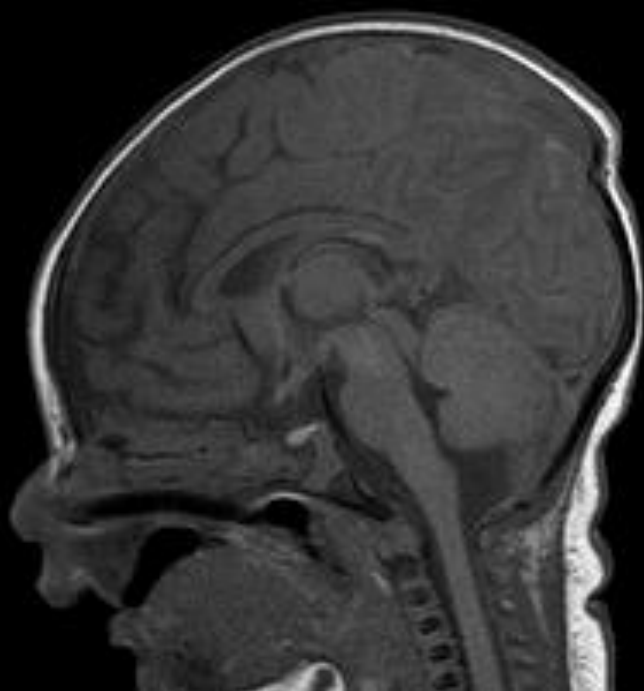
48 hrs



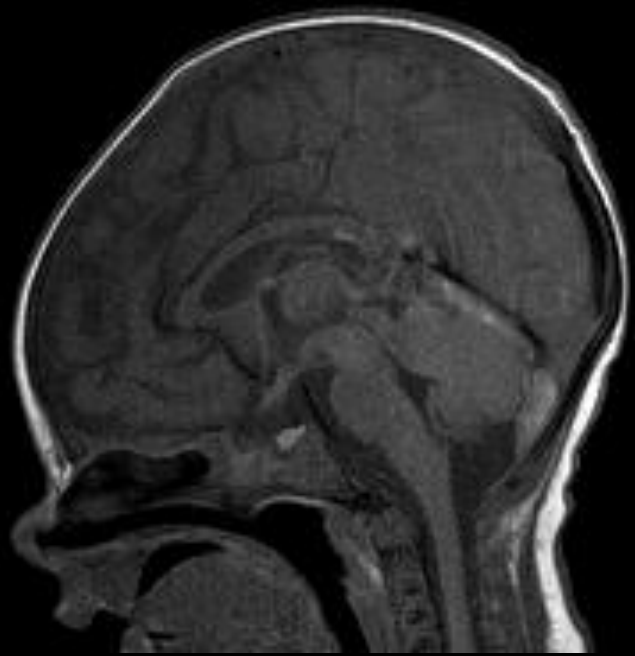
120 hrs



***an encephalopathic  
baby  
with mild IVH***



48 hrs



120 hrs



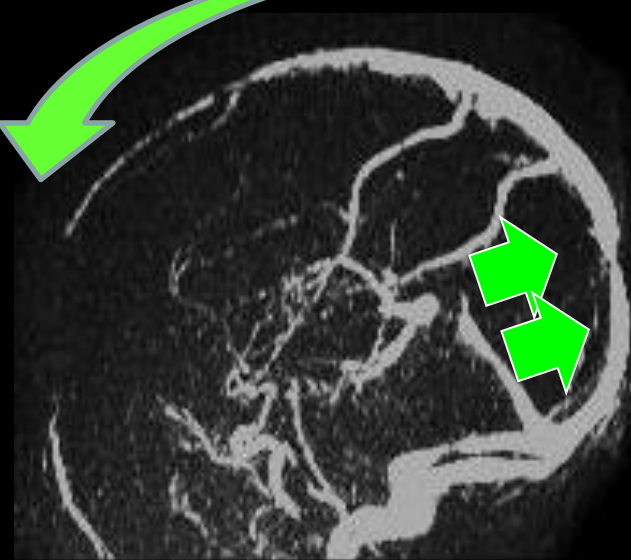


120 hrs





48 hrs



120 hrs



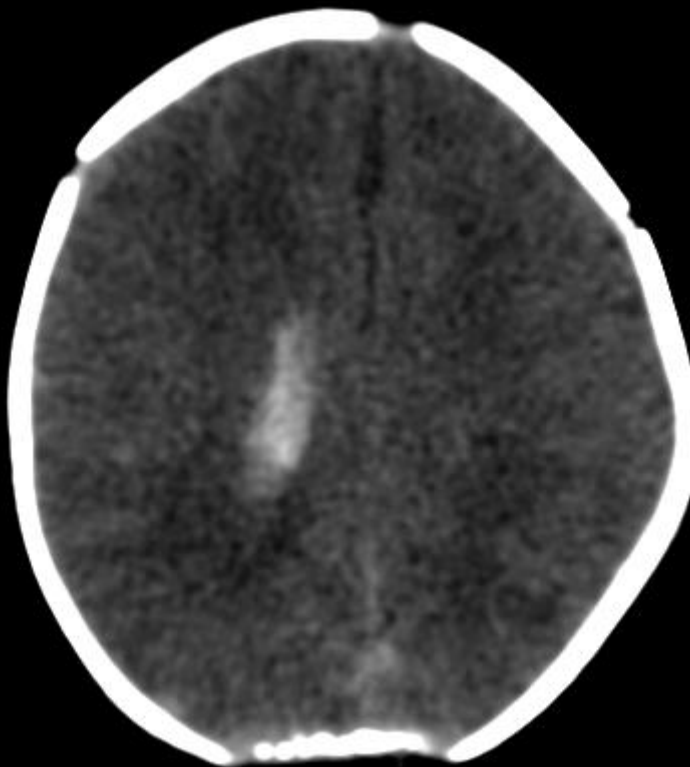
What have we done ?



48 ore



sagittale



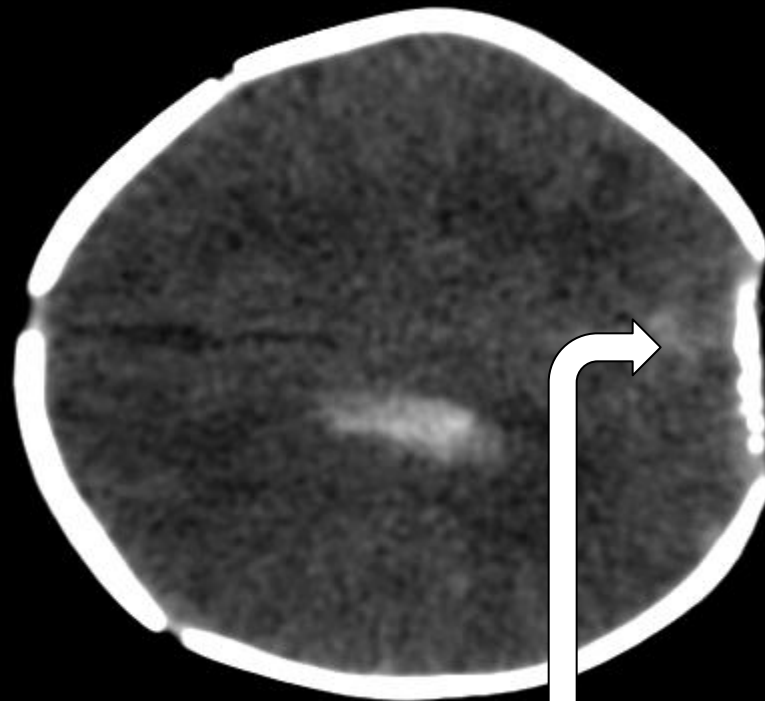
TAC assiale

Osso  
occipitale

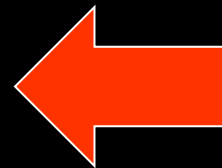
48 ore



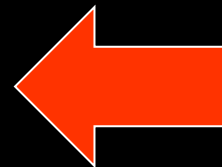
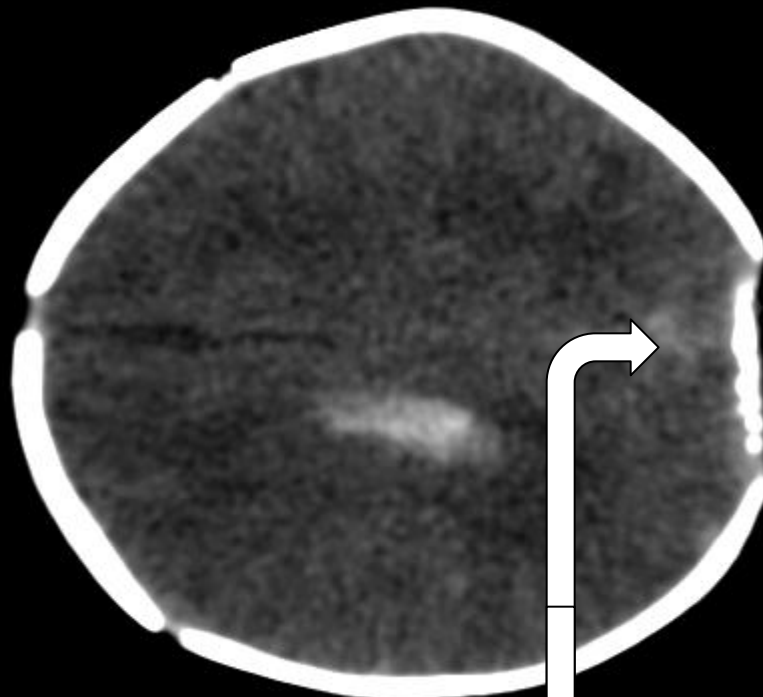
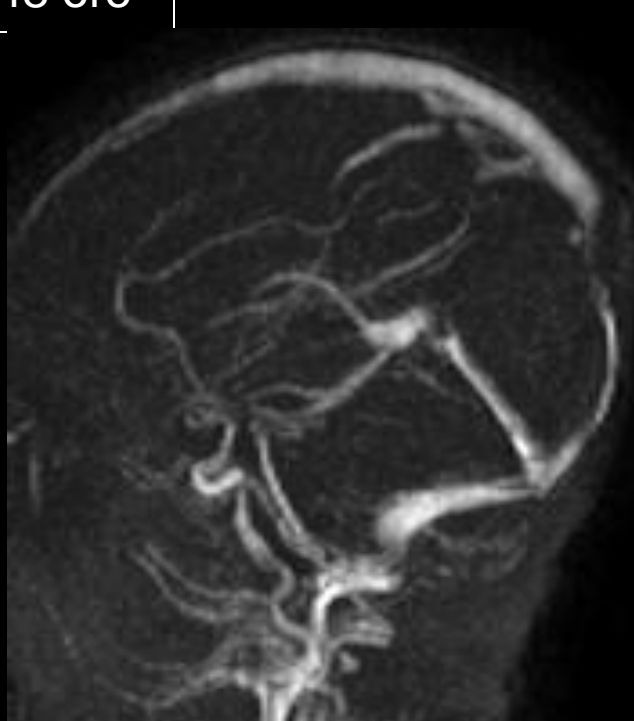
sagittale



Osso  
occipitale

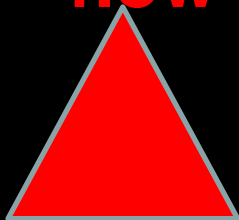


48 ore

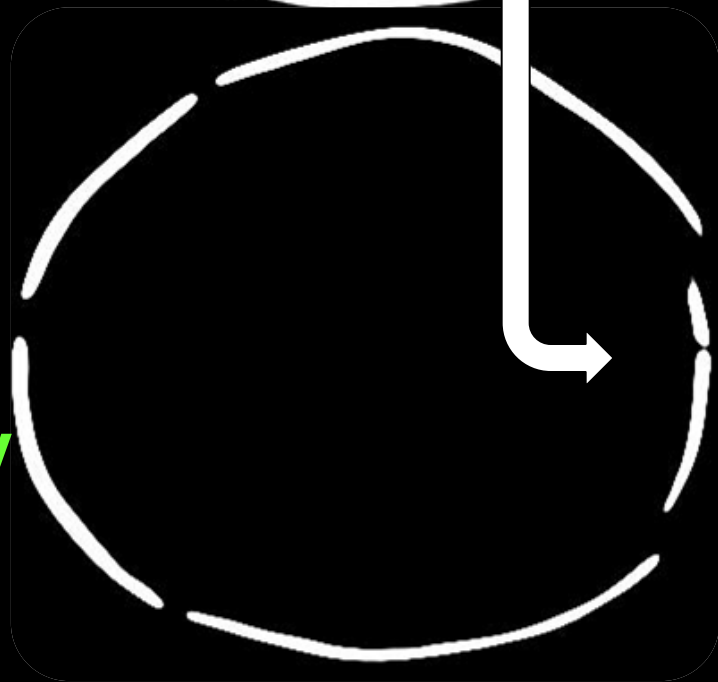


**Stasis of blood flow**

**Vessel injury**



**Hyper coagulability**

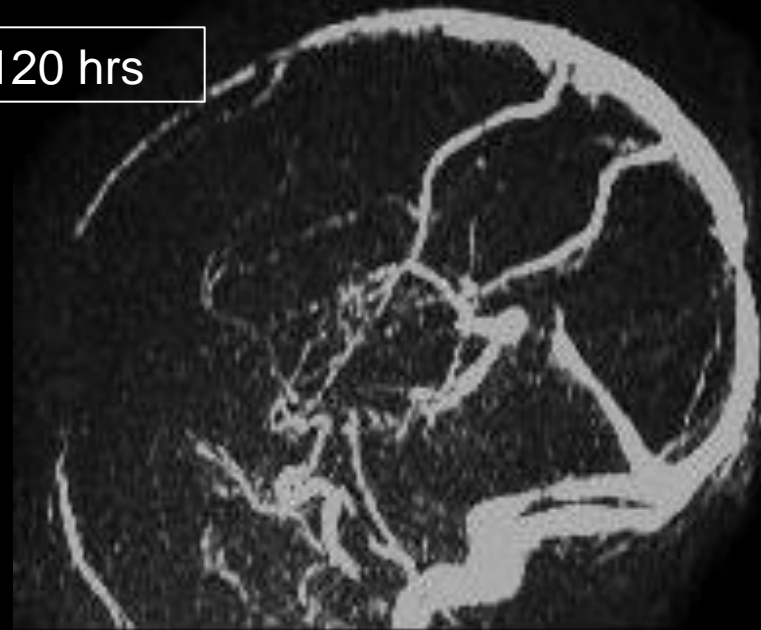


# Improvement in the venogram

48 hrs



120 hrs



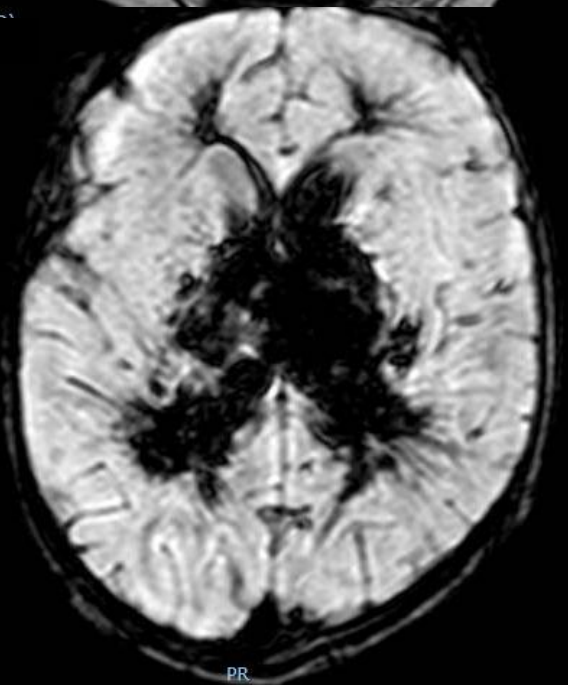
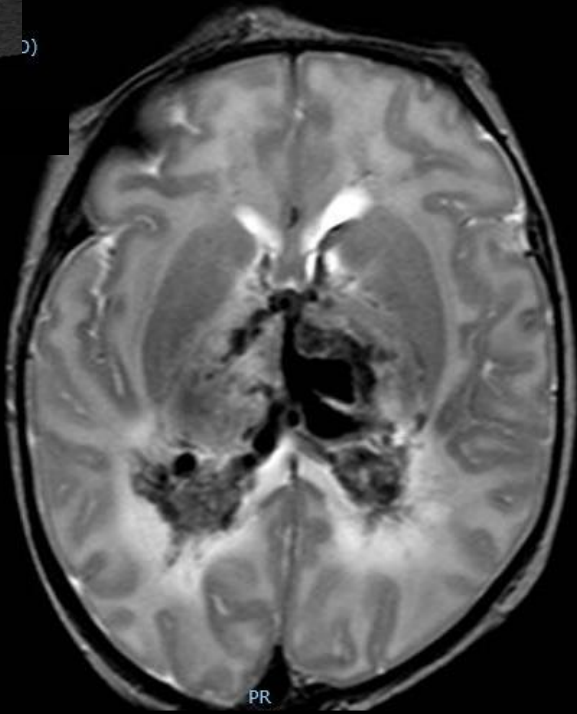
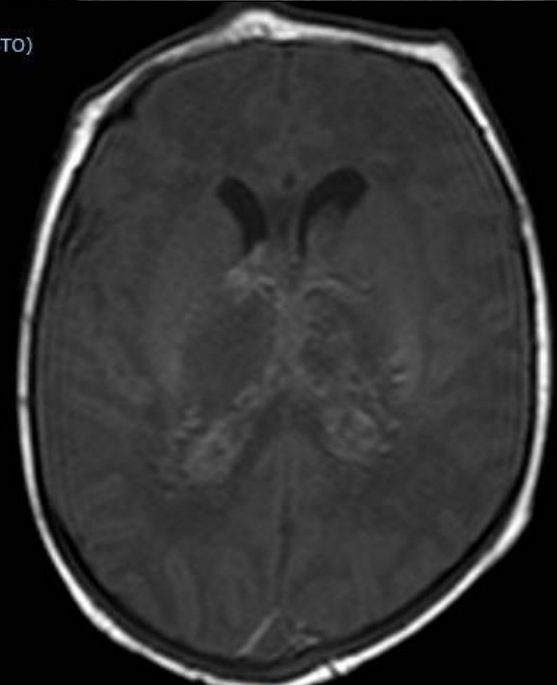
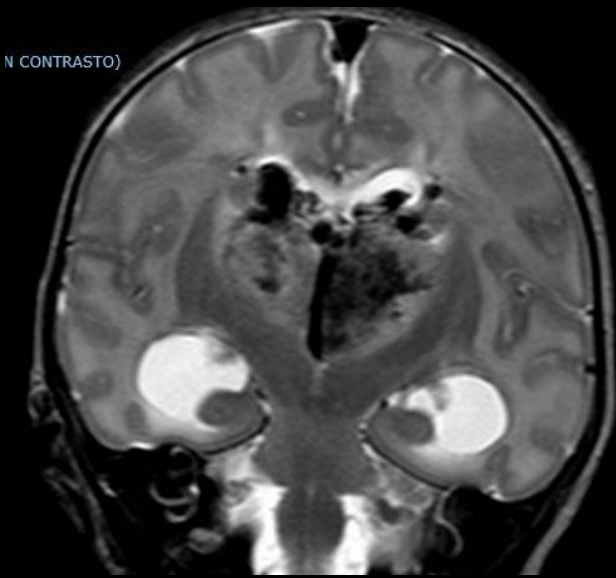
Posture  
+ Hyper hydration

NEUROPROTEZIONE COME  
DIAGNOSI DI PATOLOGIE  
CEREBRALI A PROGNOSE  
«MODIFICABILE»

**Nato a termine**  
**3° giorno di vita**

*Vomito - convulsione*

# CVST ?

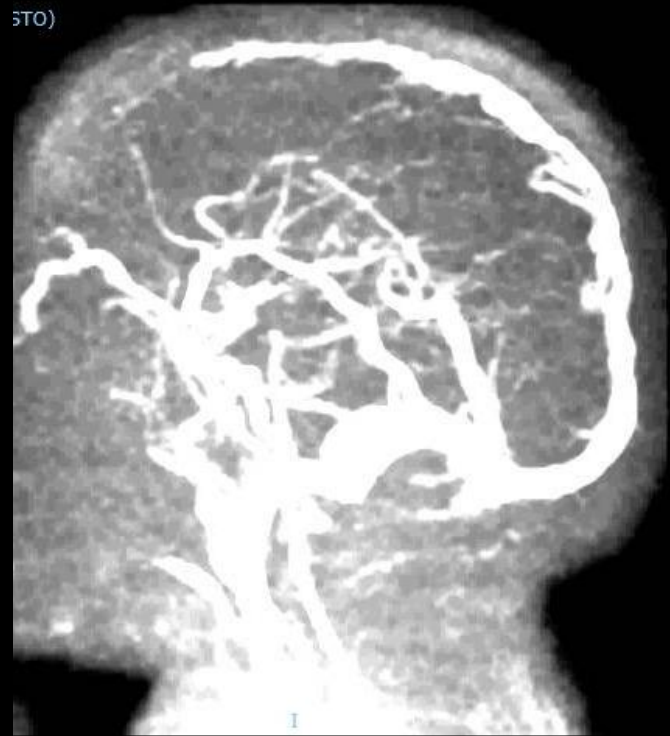


RASTO)



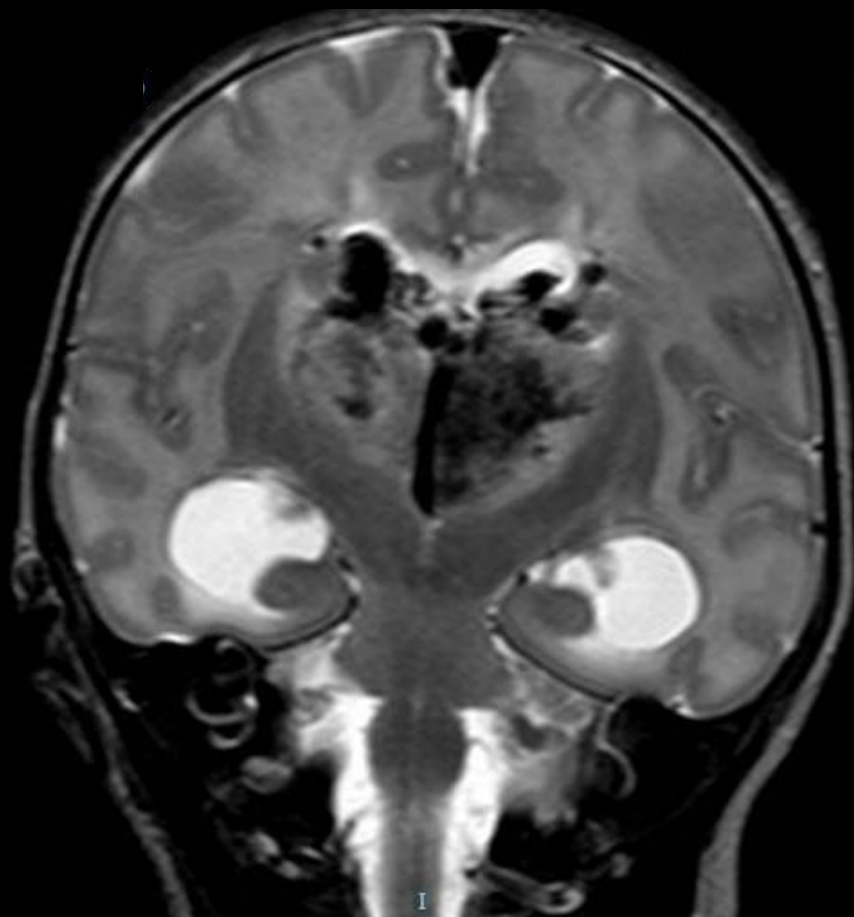
**6 giorni di vita**

STO)

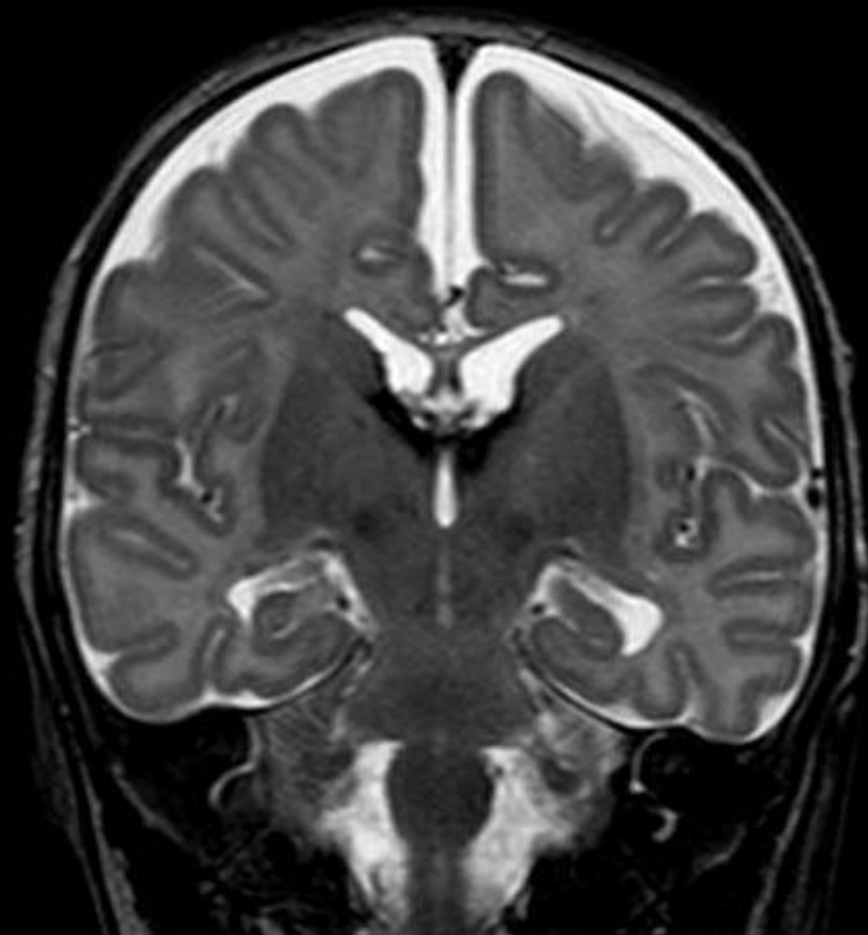


**37 giorni dopo**

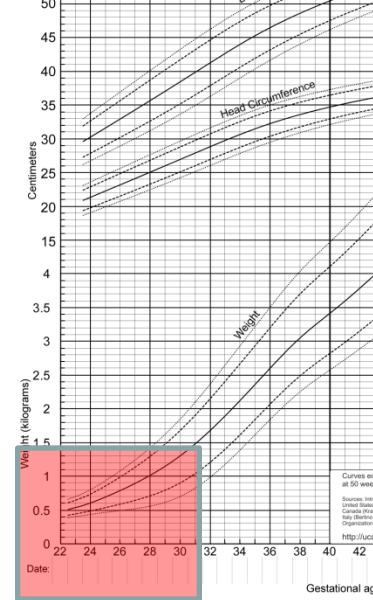
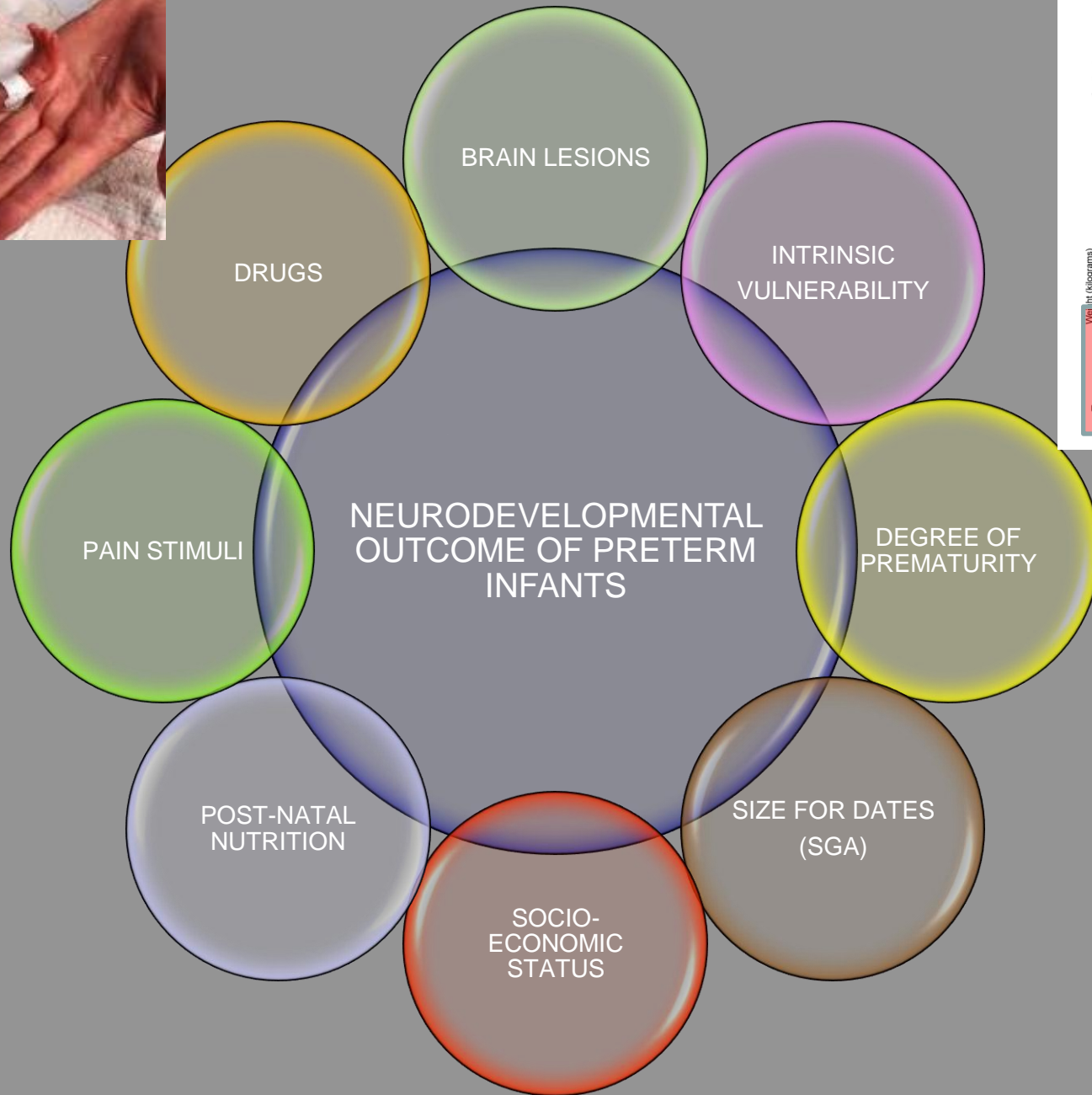


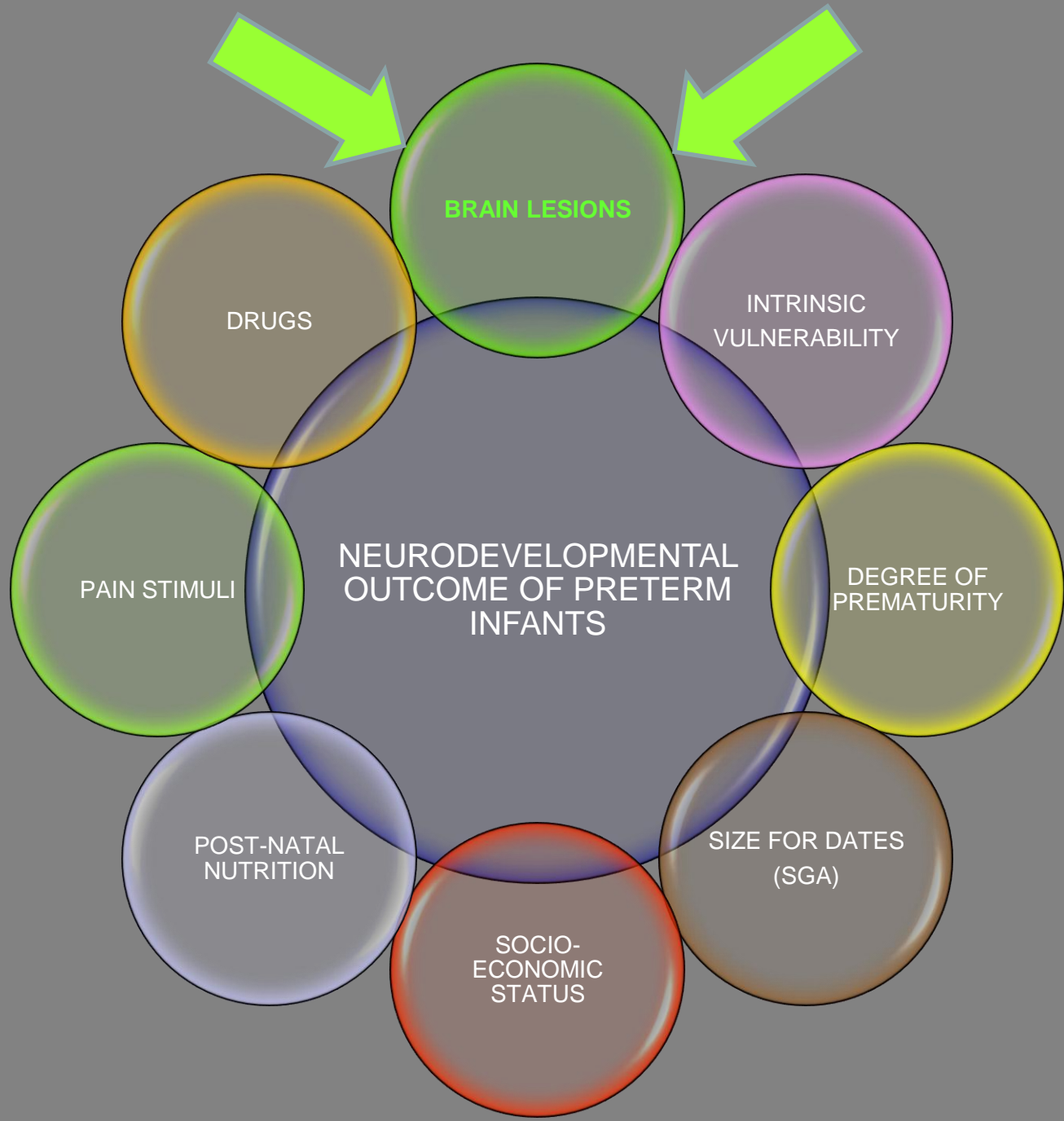


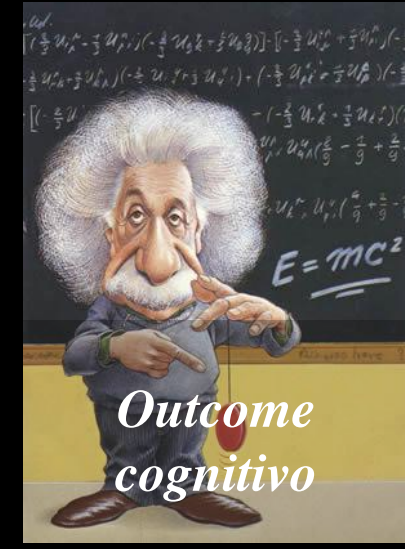
**6 giorni di vita**



**37 giorni dopo**



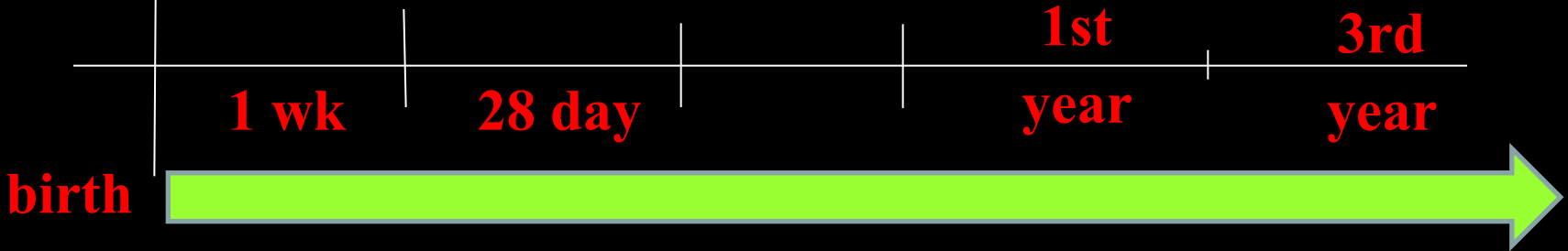




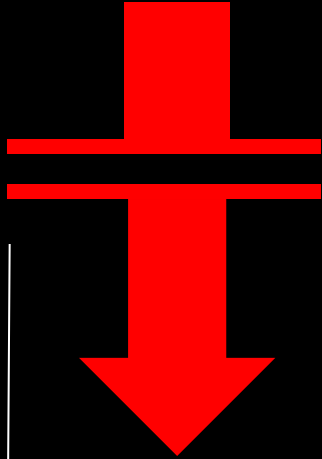
*Sviluppo lesioni cerebrali*

*Sviluppo encefalo*

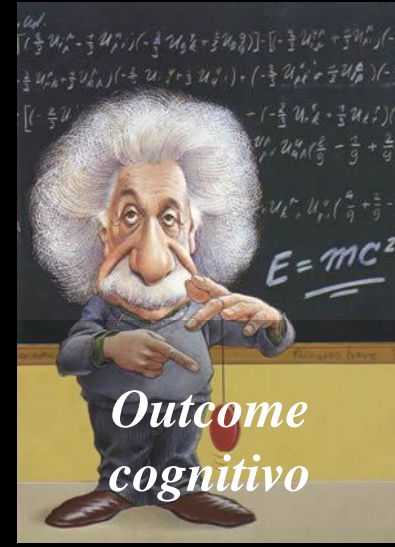
*Influenze ambientali*



# CONTRASTARE



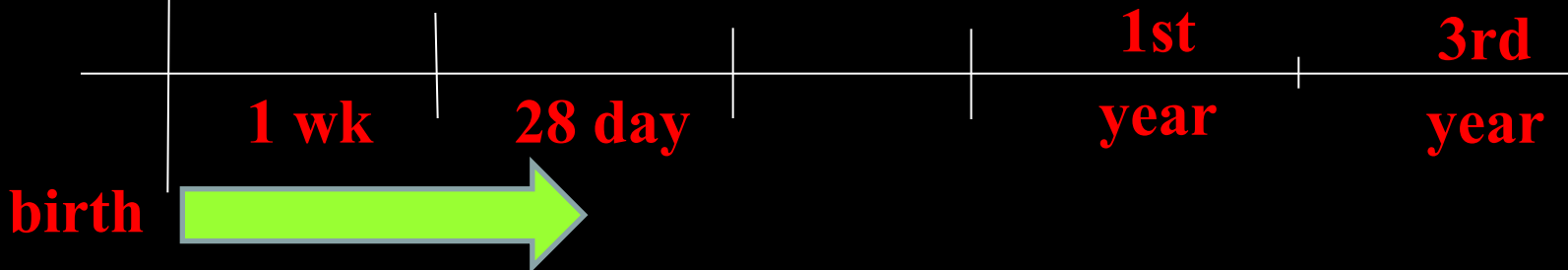
*Outcome motorio*



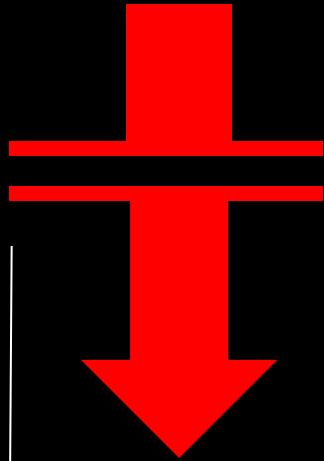
*Outcome cognitivo*

*Sviluppo lesioni cerebrali*

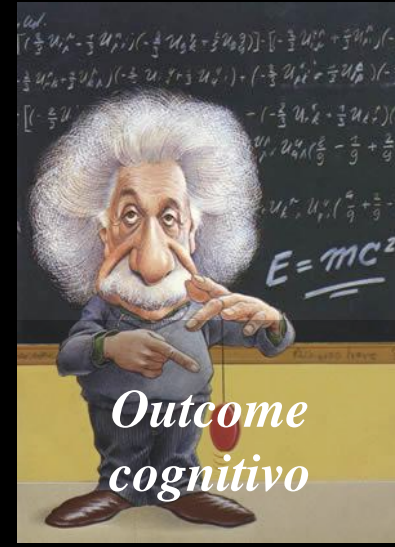
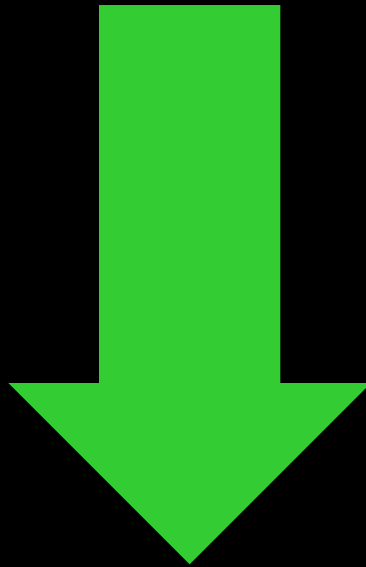
*Sviluppo encefalo*



# CONTRASTARE

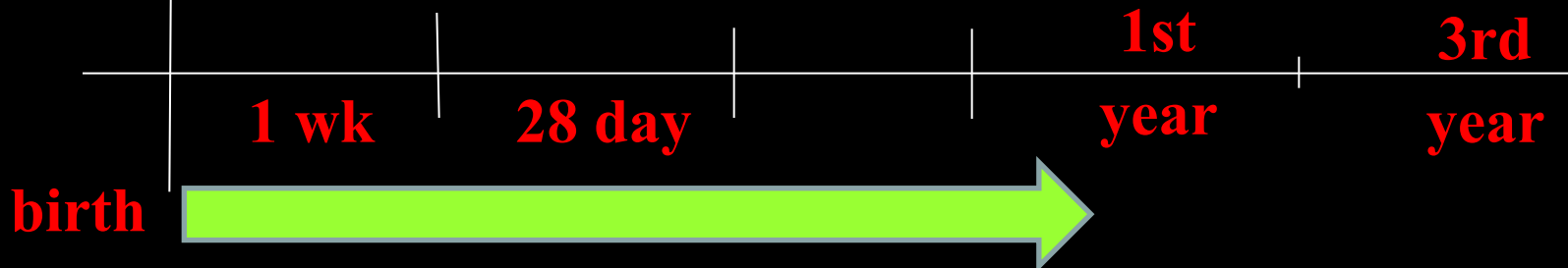


# FAVORIRE



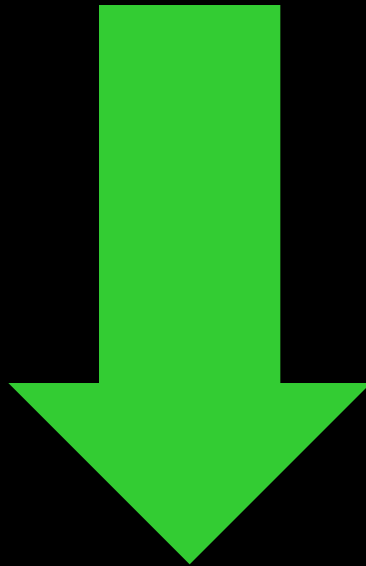
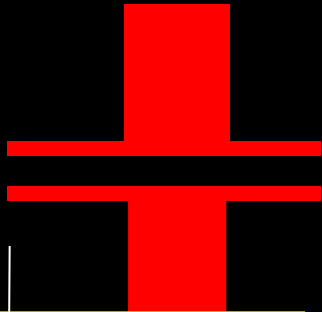
*Sviluppo  
lesioni cerebrali*

*Sviluppo  
encefalo*

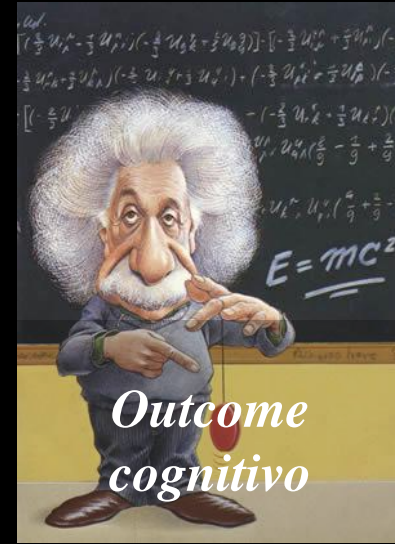


# CONTRASTARE

# FAVORIRE



*Outcome motorio*



*Outcome cognitivo*



*Sviluppo  
lesioni cerebrali*

*Sviluppo  
encefalo*

?

1 wk

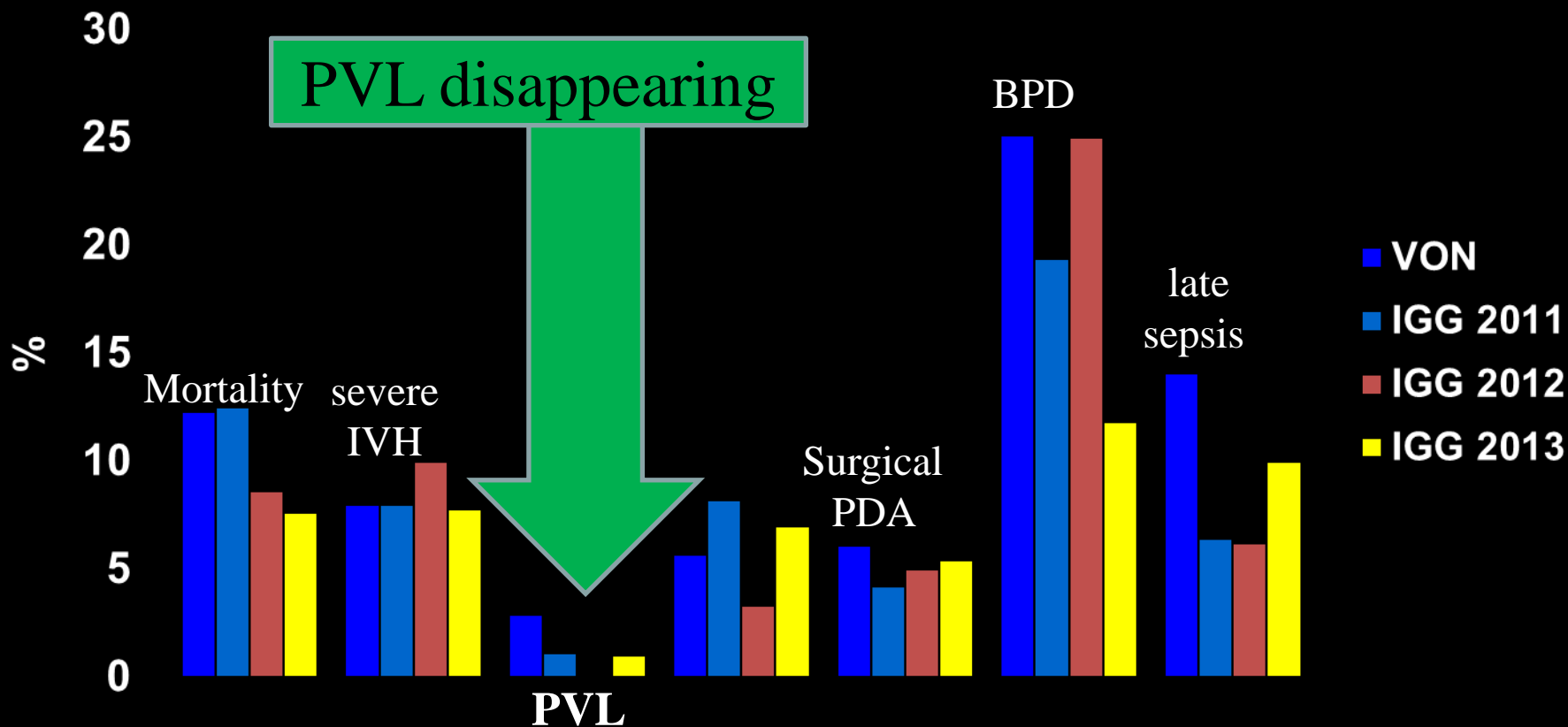
28 day

1st  
year

3rd  
year

birth





VON = Vermont Oxford Network (> 60000 neonati)

IGG 2011 = 102 VLBW

IGG 2012 = 112 VLBW

IGG 2013 = 98 VLBW

IGG = Istituto Giannina Gaslini  
IRCCS Genoa





• W.J. Little “*On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities*”

Transaction of the Obstetrical Society of London (1862)

*47 children with spastic affection of the limbs....  
..in all of them the generalised spastic rigidity was preceded by  
some abnormal circumstances connected with parturition....*

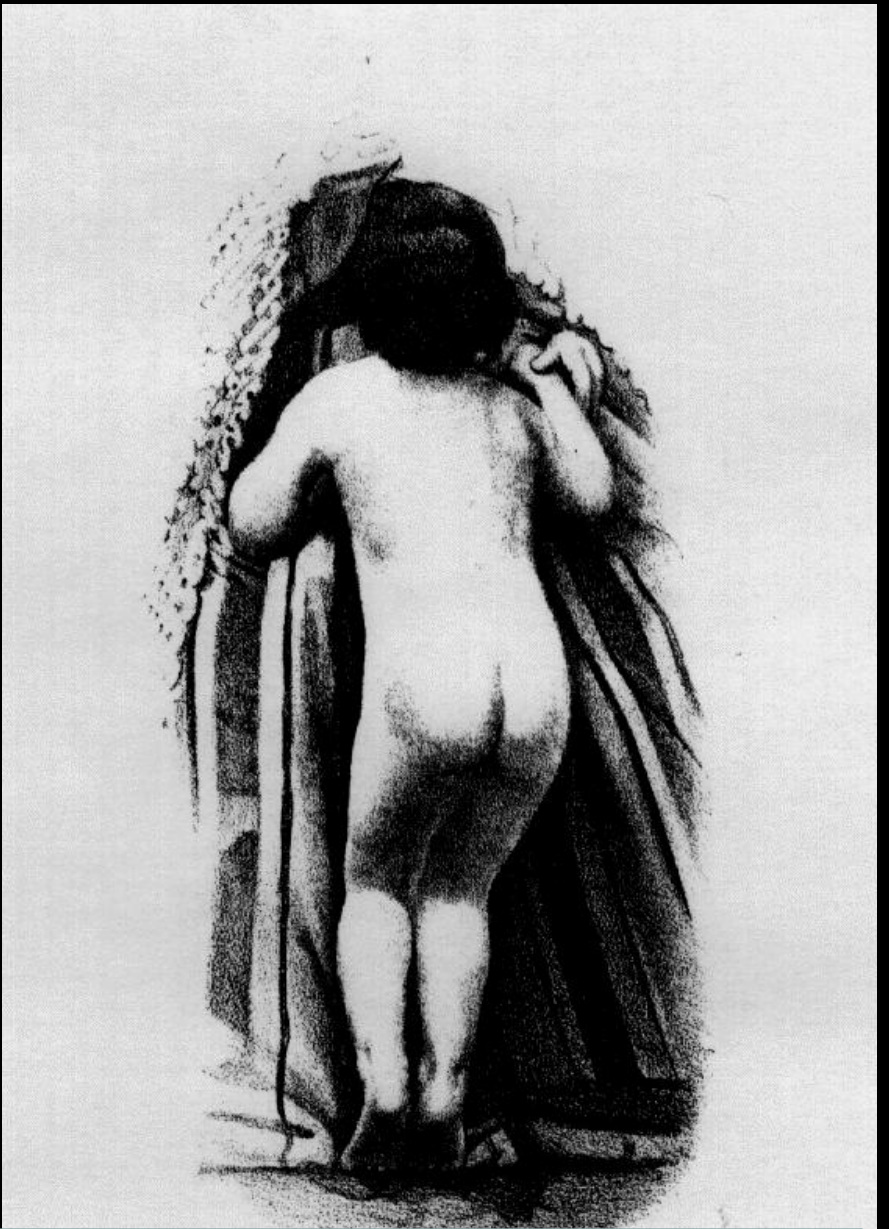
• W.J. Little “*On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities*”

Transaction of the Obstetrical Society of London (1862)

*47 children with spastic affection of the limbs....  
..in all of them the **generalised spastic** rigidity was preceded by  
some **abnormal circumstances** connected with **parturition**....*



Figure 66 William John Little (1810-1894)



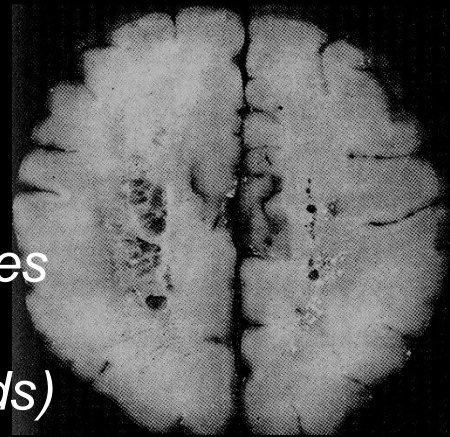
*" Morbo di Little "* 1862

# •Betty Banker Jeanne Claude Larroche

*to draw attention to a unique disease of cerebral white matter which has been encountered with great frequency among infants who died at the Children's Hospital Medical Center, Boston...periventricular leukomalacia*



## Annals of Neurology (1962)



*51 infants of which 26 were males and 25 were females  
**the incidence of prematurity was 74.4%***

***59.5% had birth weight below 2500 grams (5 ½ pounds)***

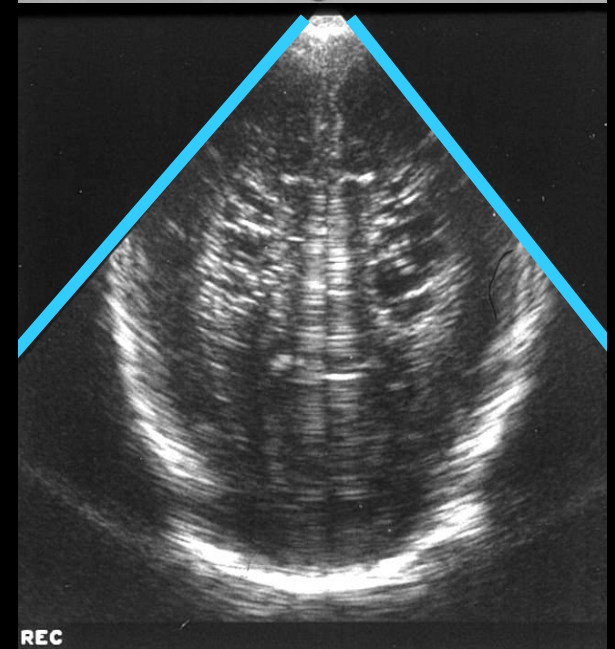
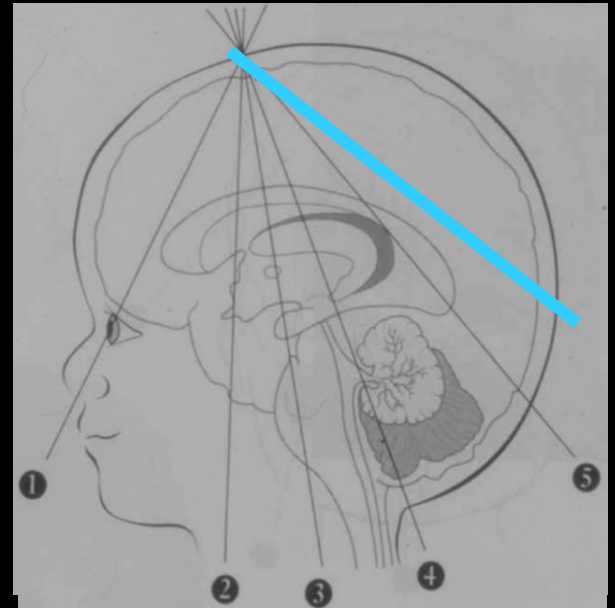
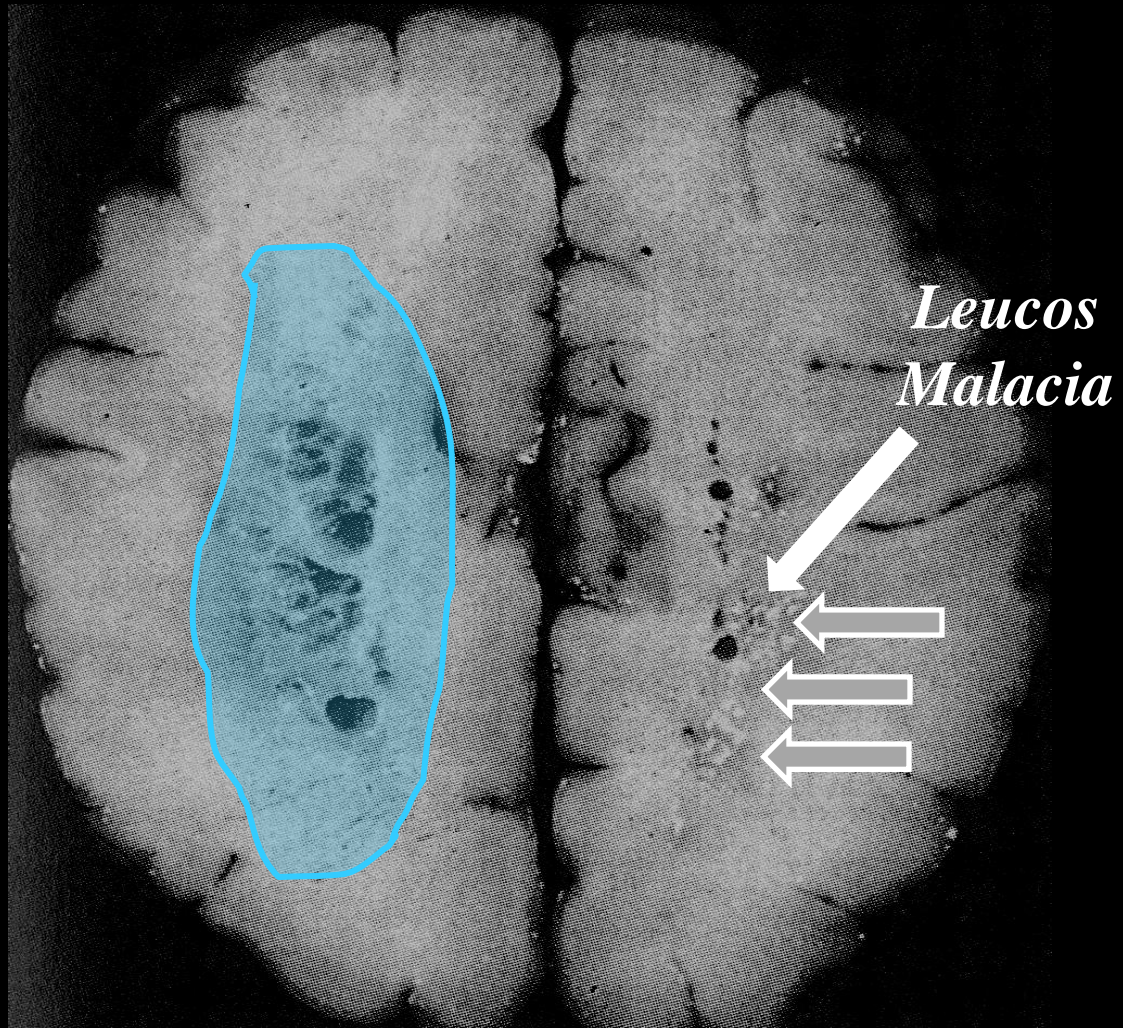
*Anoxia ..this was present in every infant in this series....*

*The anoxic episode was always severe in degree and did not merely constitute a terminal event...*

*The majority of infants had a period of apnea or cardiac arrest requiring resuscitation*

*20/51 had apnea at birth **what we would call today asphyxia !!!!!***


# "In vivo" Ultrasound diagnosis of PVL



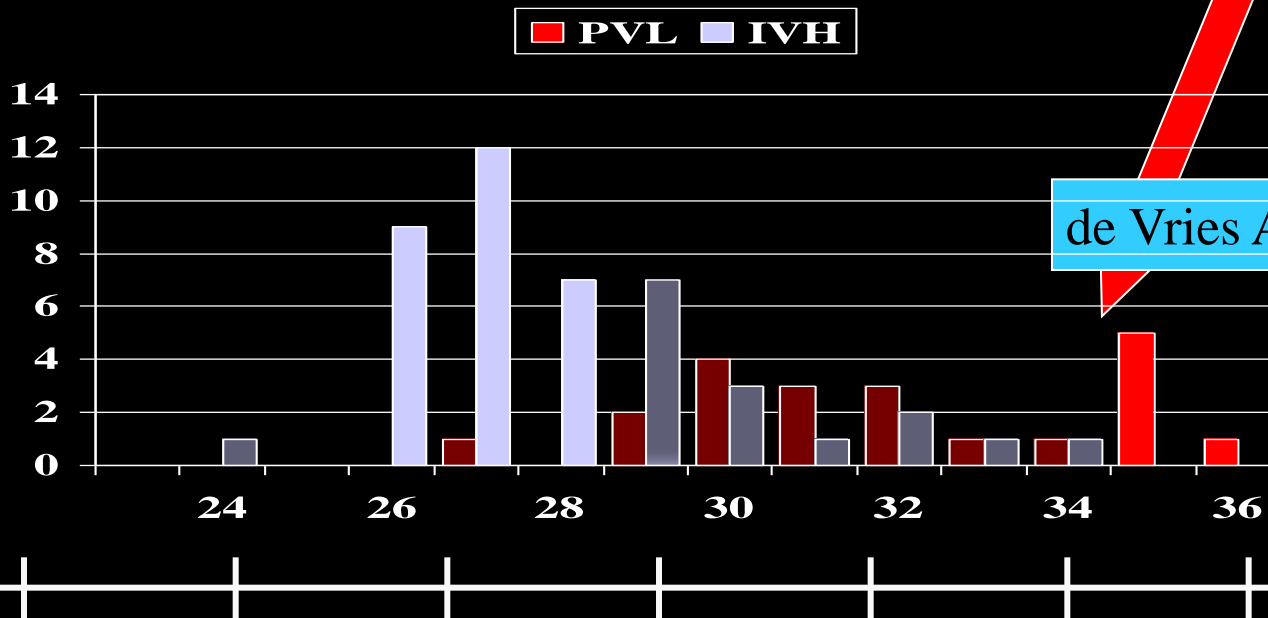
Banker-Larroche *Ann Neurol* 1962

Pape et al *Lancet* 1979

Table III. Cystic PVL by birth year period in newborn infants age 24 to 27 weeks and 28 to 35 weeks at birth

Year	Total at risk age 24-27 wk	Cystic PVL	Total at risk Age 28-35 wk	Cystic PVL
1992-1993	113	6 (5.3%)		4 (0.9%)
1994-1996	183	5 (2.7%)		5 (0.7%)
1997-1999	189	2 (1.1%)		3 (0.4%)
2000-2002	185	0		2 (0.3%)

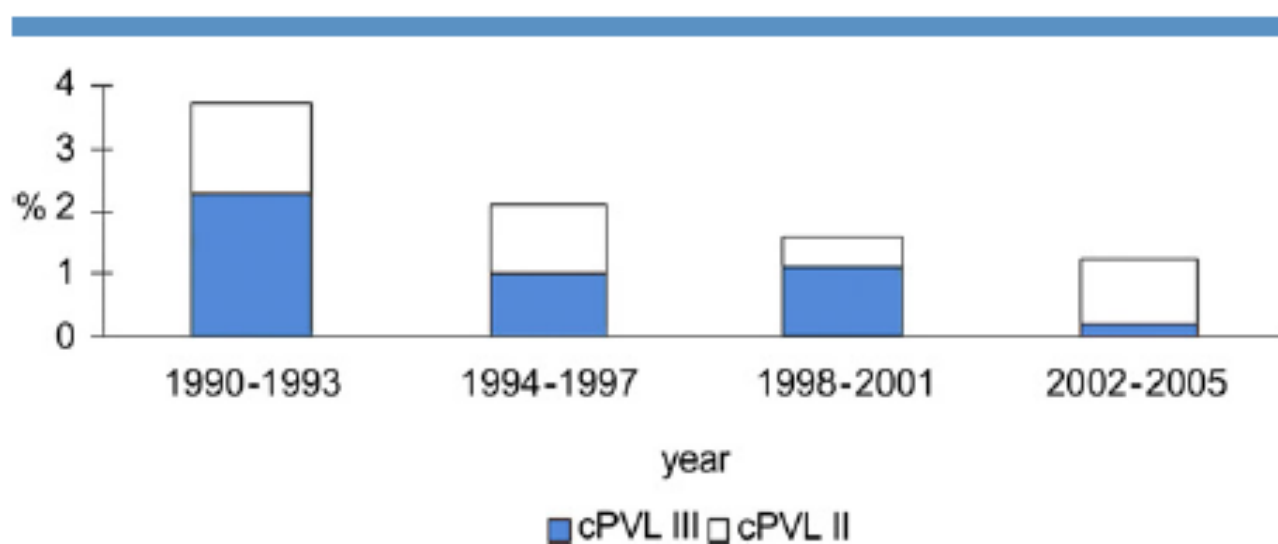
Hamrick et al *J Pediatr* 2004;145:593-9



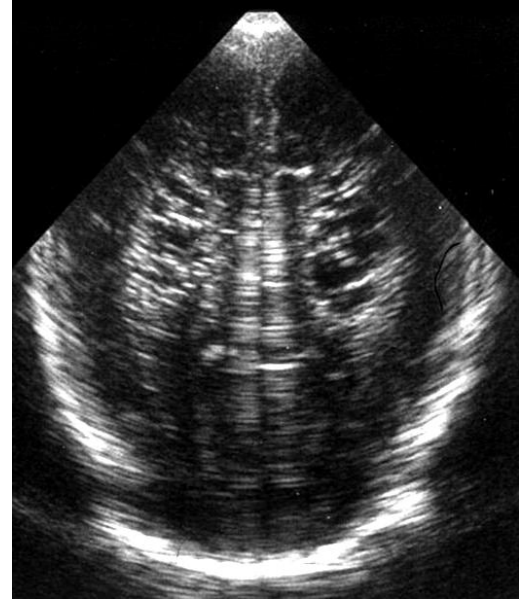
de Vries ADC 1986

## Decreasing Incidence and Severity of Cerebral Palsy in Prematurely Born Children

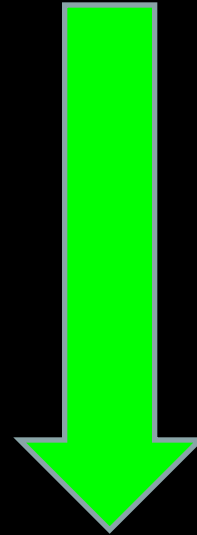
Ingrid C. van Haastert, MA, Floris Groenendaal, MD, PhD, Cuno S. P. M. Uiterwaal, MD, PhD, Jacqueline U. M. Termote, MD, PhD, Marja van der Heide-Jalving, MD, Maria J. C. Eijsermans, PPT, Jan Willem Gorter, MD, PhD, Paul J. M. Helders, MSc, PhD, Marian J. Jongmans, MSc, PhD, and Linda S. de Vries, MD, PhD



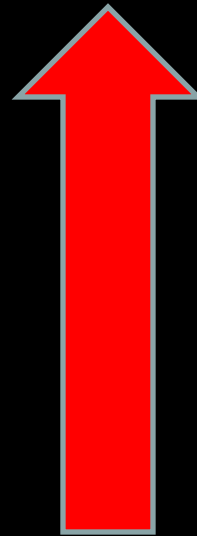
(*J Pediatr* 2011;159:86-91)



**Figure 4.** C-PVL grade II and III within total cohort.

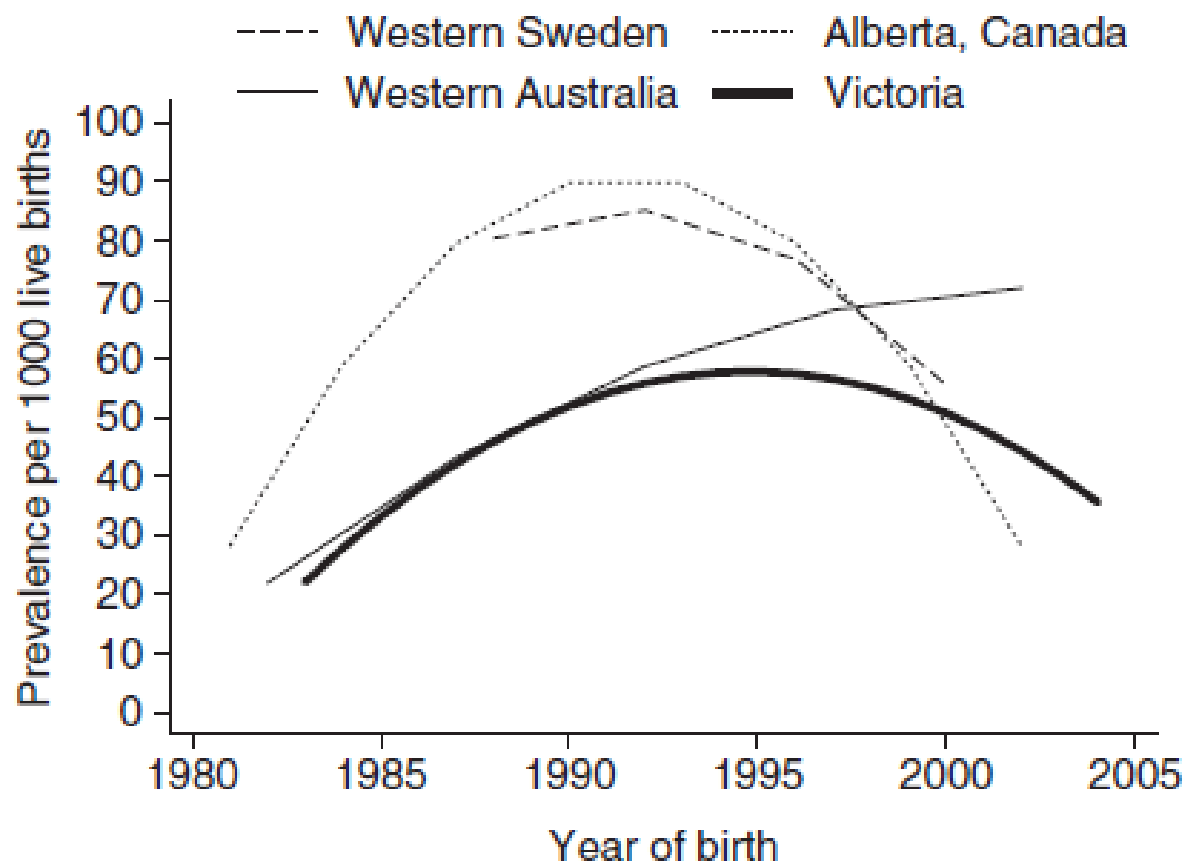


*PVL like lesions  
With obvious  
spasticity*

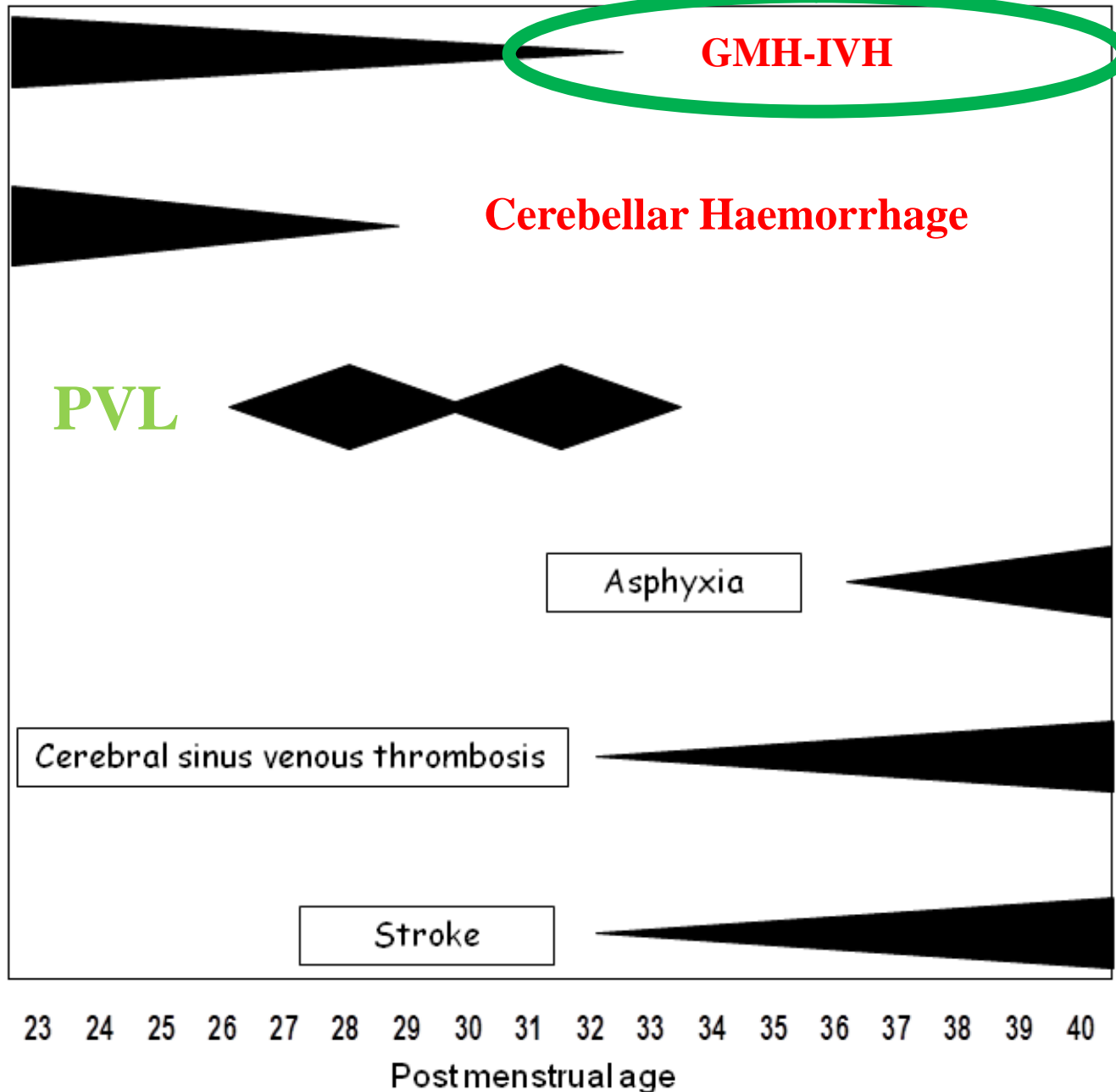


*Very prem with less  
overt brain lesions  
and cognitive  
problems*





**Figure 3:** Trends in the rates of cerebral palsy (CP) per 1000 live births from four CP registries for extremely preterm births (<28wks) for the period 1980–2004.



Sannia et al. (2012) Different gestational ages and changing vulnerability of the premature brain



**Table 3.** Risk of GMH-IVH according to selected clinical and genetic characteristics in a multivariate analysis.

	Risk Ratio*	95% Confidence Interval
GA (weeks)	0.83	0.72 - 0.97
Apgar at 5' $\leq 5$	2.30	1.02 - 5.18
Hypotension	2.05	0.74 - 5.69
Pro-thrombotic mutations	2.65	1.23 - 5.72

*\*Risk ratio calculated with Poisson regression with robust standard error; each variable adjusted for the others in the table.*

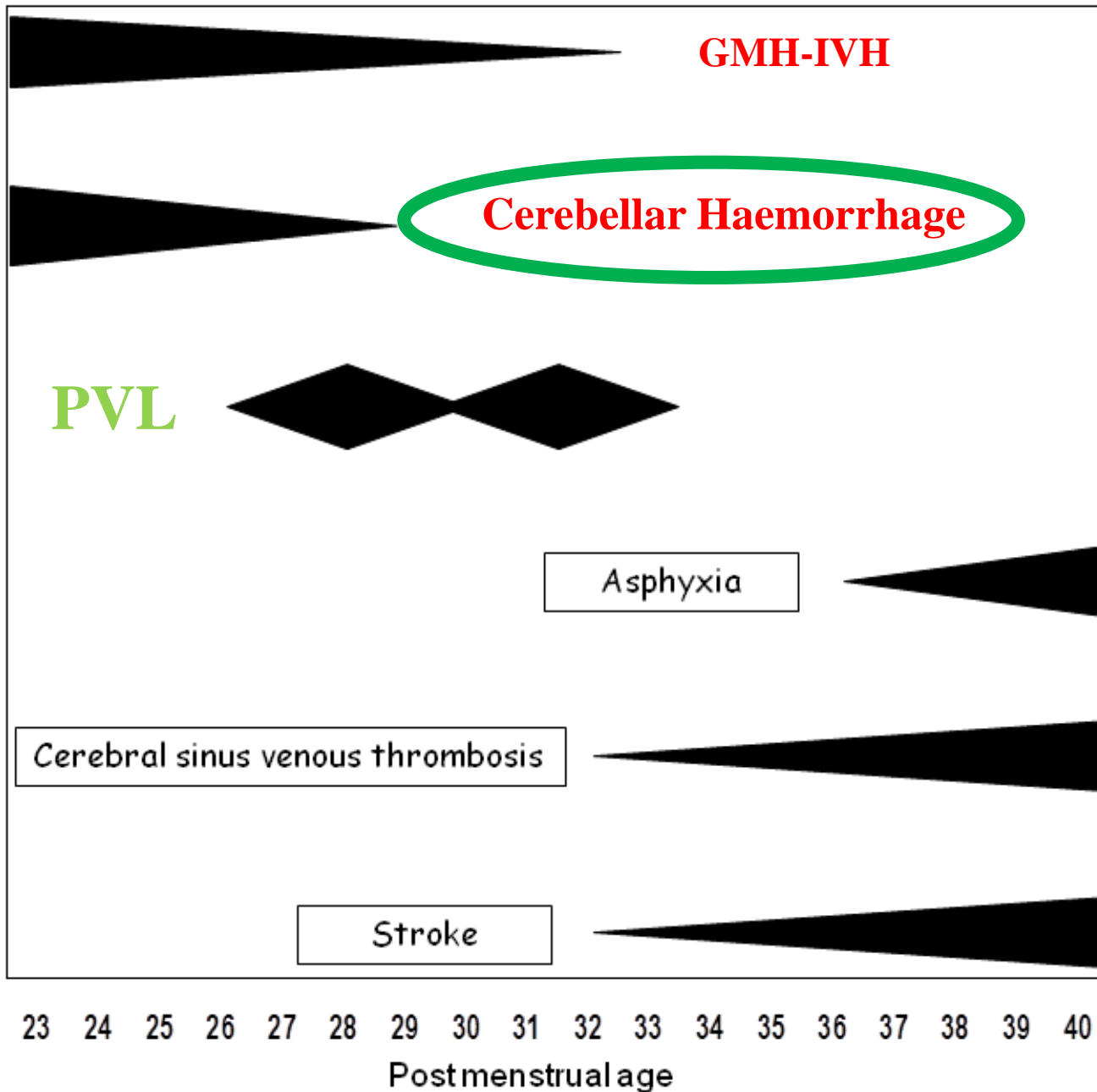
***Ramenghi et al. Germinal-Matrix Intraventricular Hemorrhage in VLBW infants: the independent role of inherited thrombophilia (Stroke 2011)***

**Table 3.** Risk of GMH-IVH according to selected clinical and genetic characteristics in a multivariate analysis.

	Risk Ratio*	95% Confidence Interval
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Hypotension 	2.05	0.74 - 5.69
Genetic mutations influence !!! 	2.65	1.23 - 5.72

*\*Risk ratio calculated with Poisson regression with robust standard error; each variable adjusted for the others in the table.*

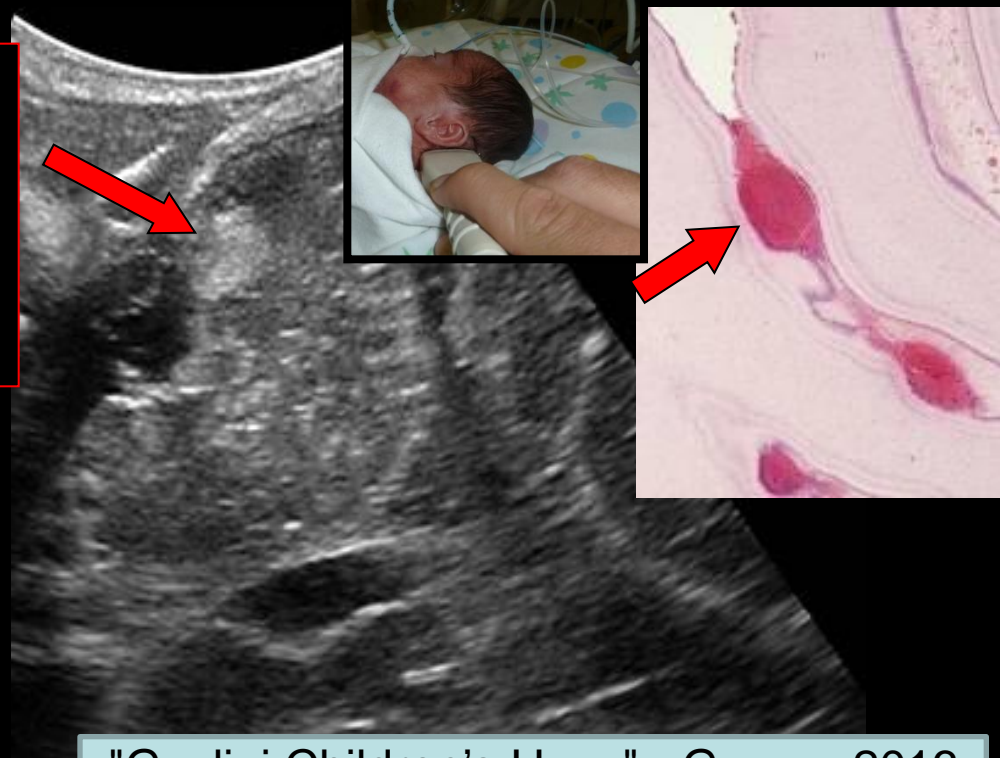
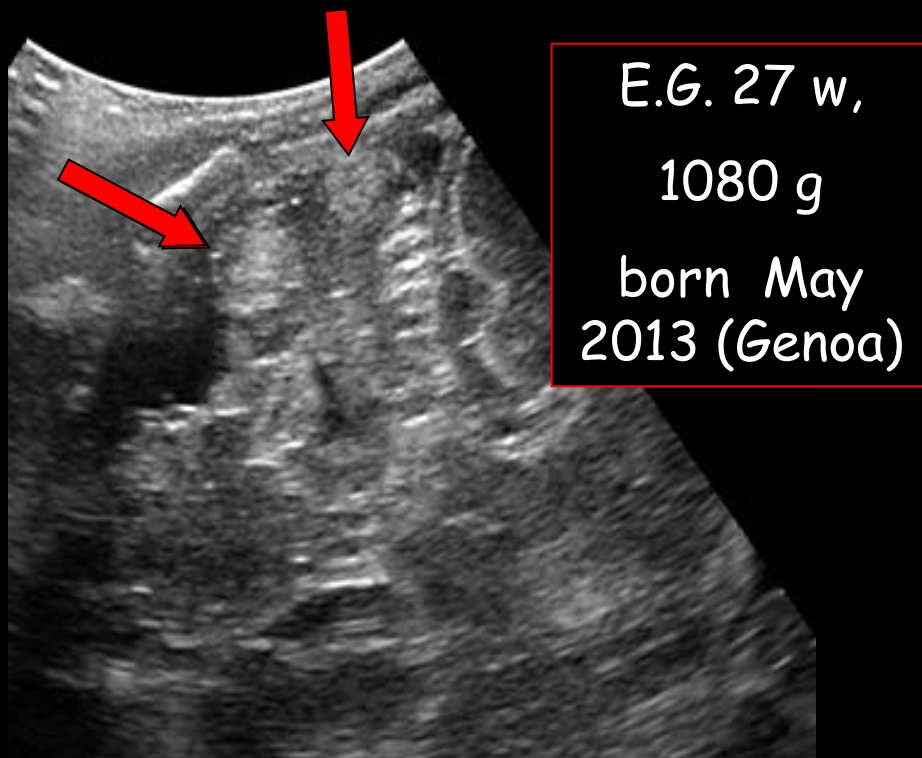
(Ramenghi et al *Stroke*. 2011)



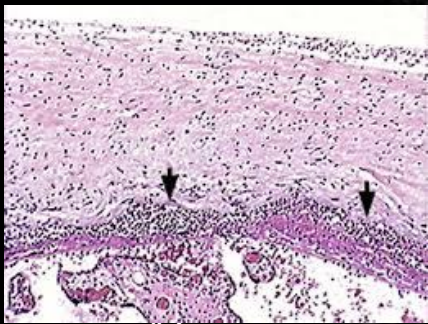
Sannia et al. (2012) Different gestational ages and changing vulnerability of the premature brain



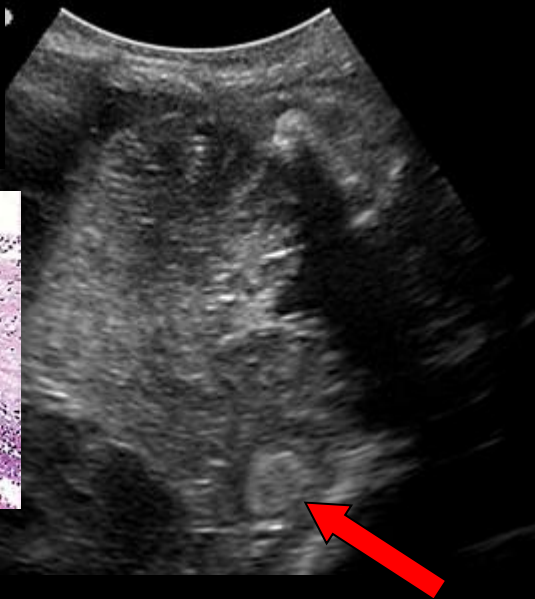
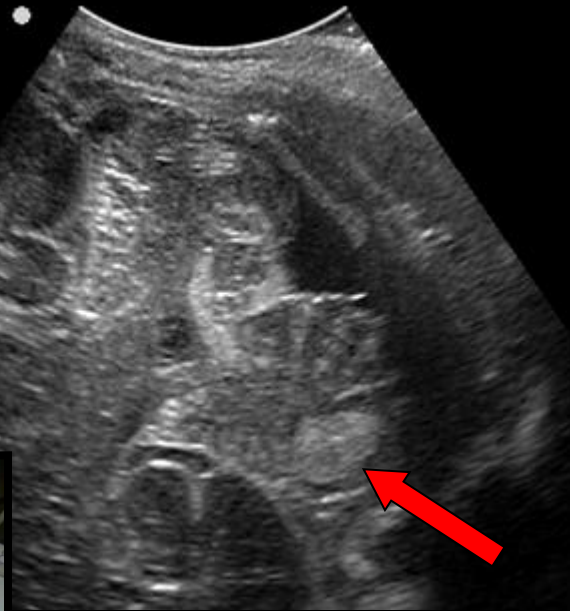
Cerebellar hemorrhage originating from external granular layer of cerebellar cortex



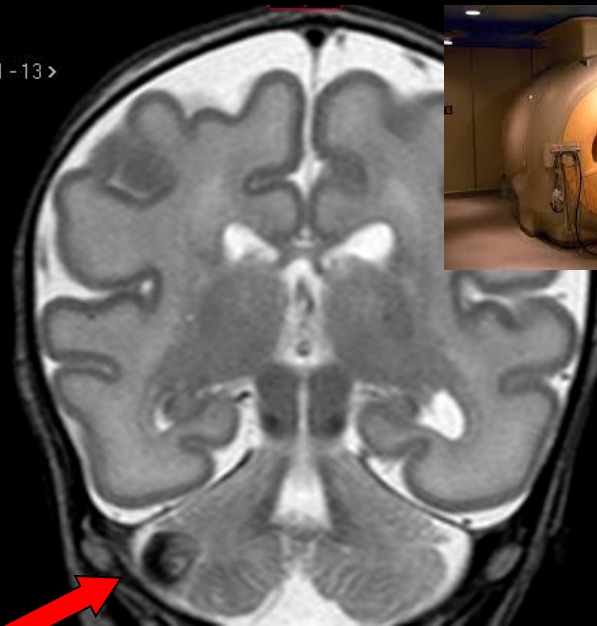
GA. 31 w,  
1570 g  
born  
Aug 2013



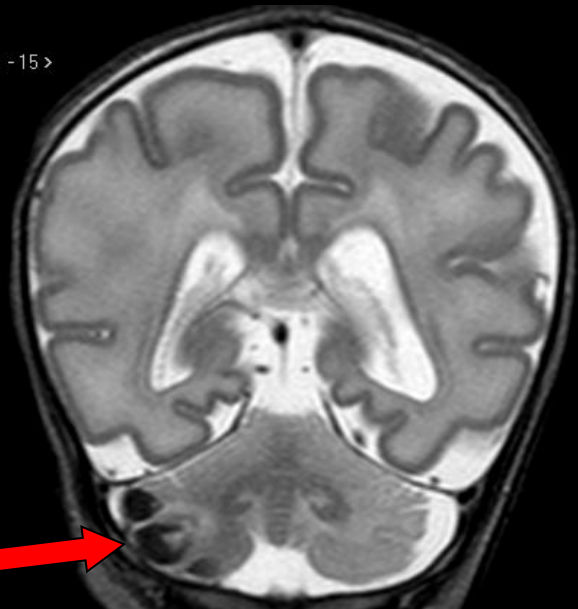
47



11-13 >



1-15 >



PLF = MF

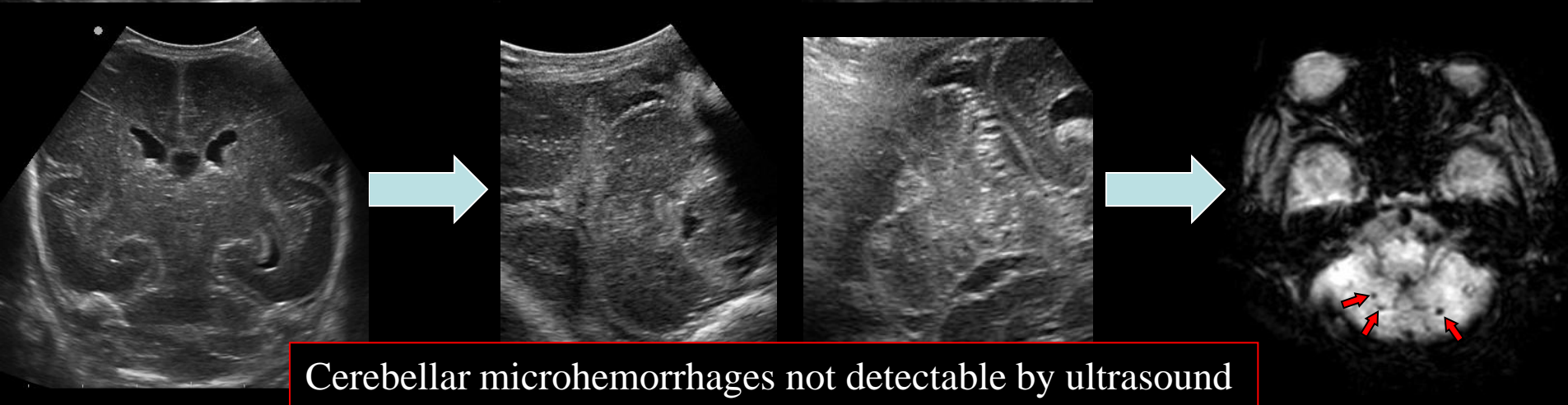
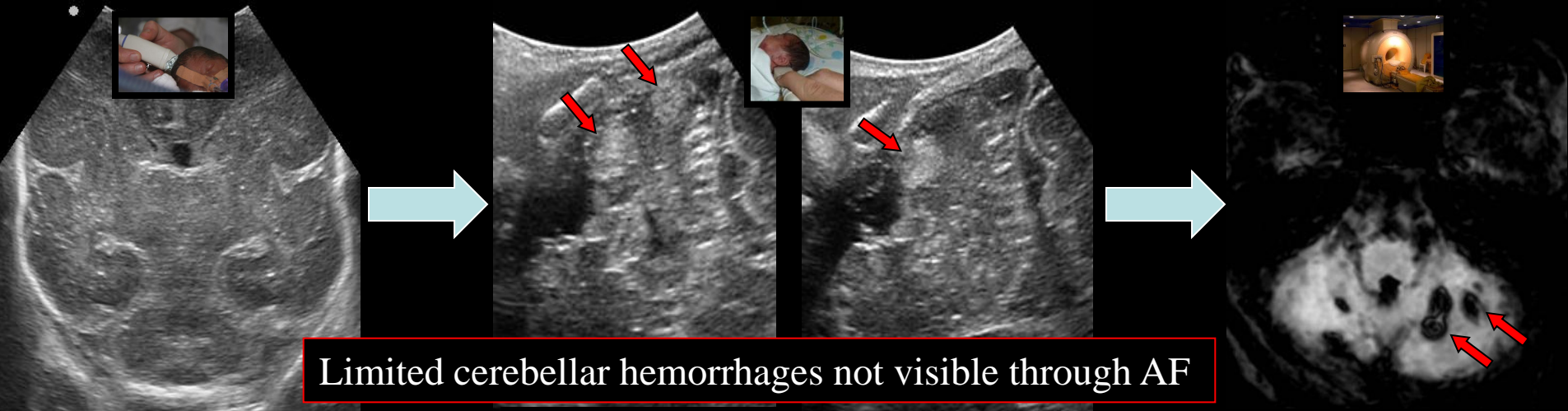
Postero-lateral = mastoid

AF = anterior fontanelle



Cerebellar haemorrhage size	AF	PLF	SWI
Massive cerebellar hemorrhages (>1/3 of cerebellum)	2/128 (1,6%)	2/128 (1,6%)	2/128 (1,6%)
Limited cerebellar hemorrhages (size $\geq$ 5 mm and <1/3 of cerebellum)	2/128 (1,6%)	5/128 (3,9%)	5/128 (3,9%)
Cerebellar microhaemorrhages (microCBH) (size <5 mm)	0/128 (0%)	0/128 (0%)	20/128 (15,6%)
All cerebellar haemorrhages	4/128 (3,1%)	6/128 (4,7%)	26/128 (20,3%)

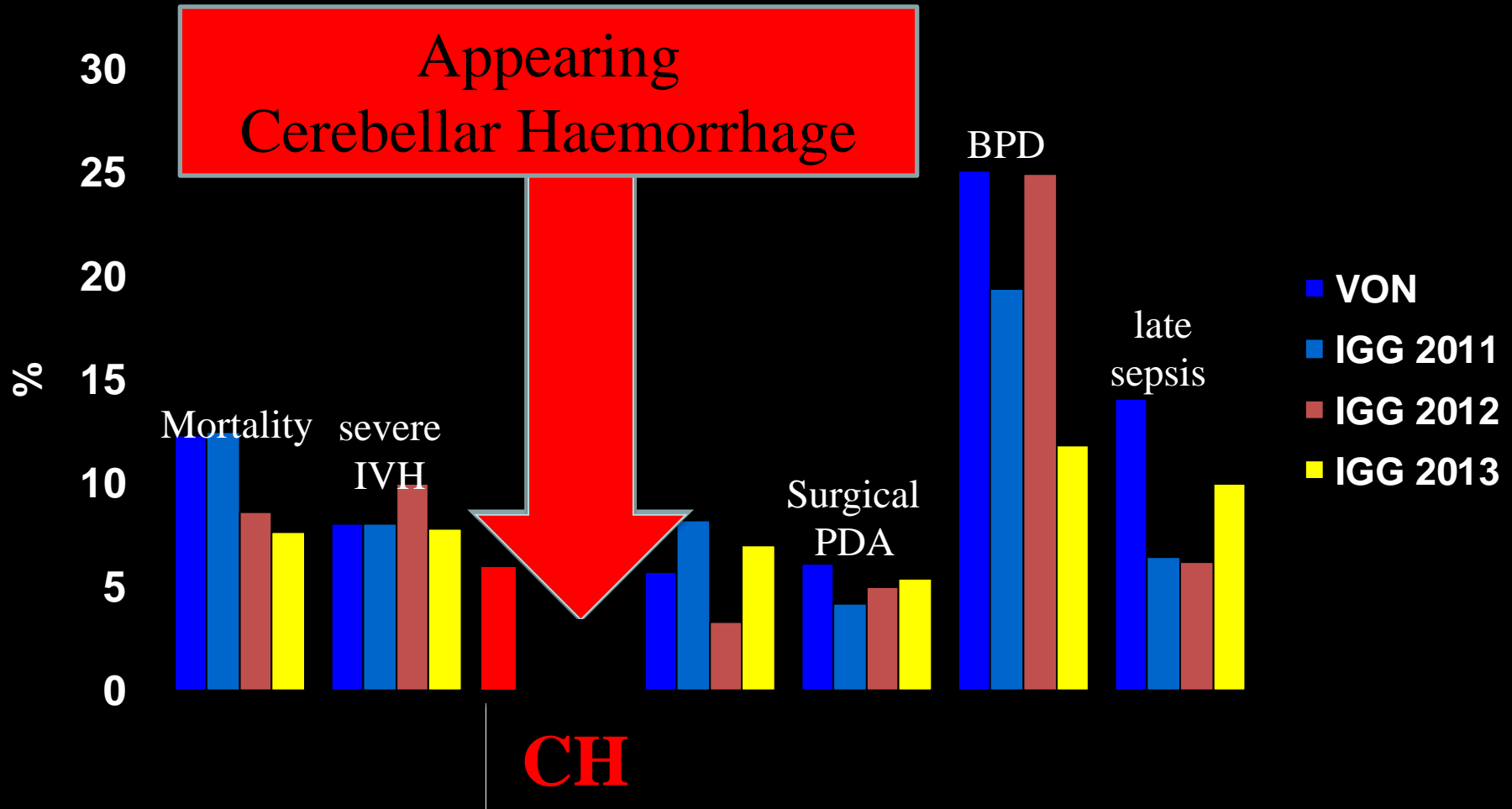




## Conclusions

- 1) Overall ultrasound sensitivity seems surprisingly low when microhemorrhages are included
- 2) Microhemorrhages proved to be undetectable by ultrasound
- 3) The routine use of MF allows a better detection of limited hemorrhages when compared to AF

# Major outcomes in VLBW



IGG 2011 = 102 VLBW

IGG 2012 = 112 VLBW

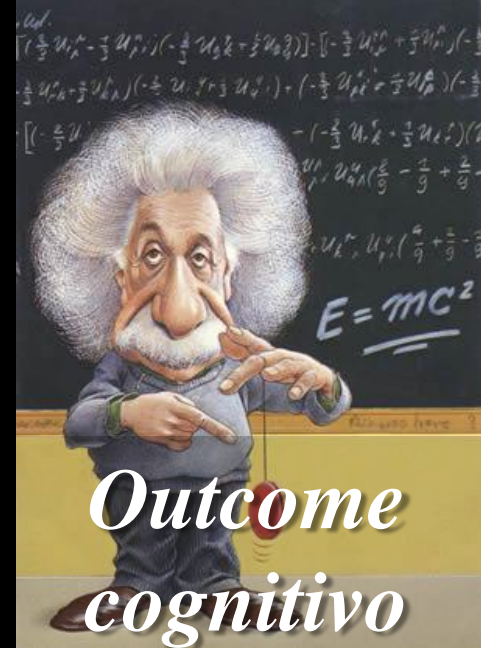
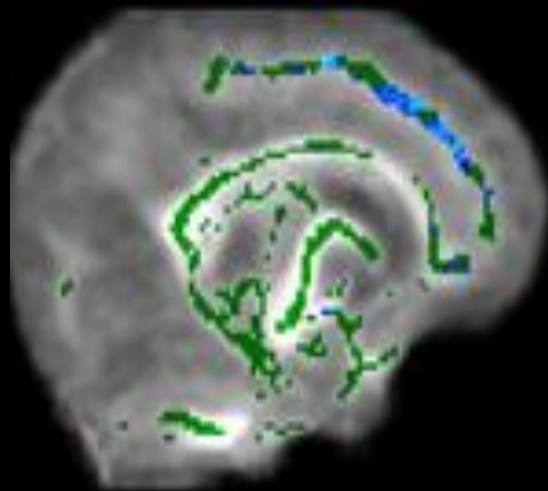
IGG 2013 = 98 VLBW

**IGG 2014 = 107 VLBW (ad oggi)**

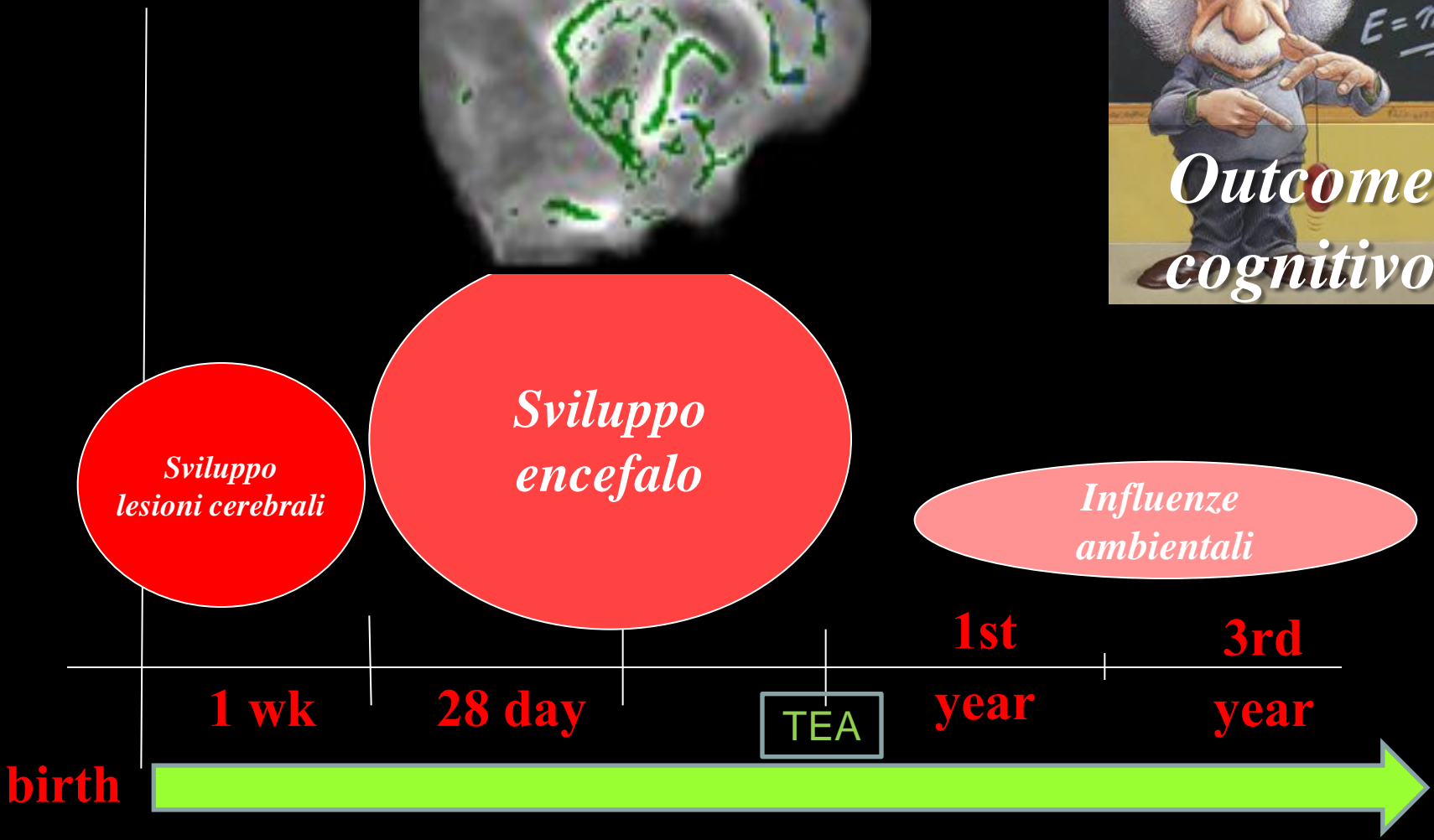
IGG  
Istituto Giannina Gaslini

The dream is .....

A baby without brain lesions



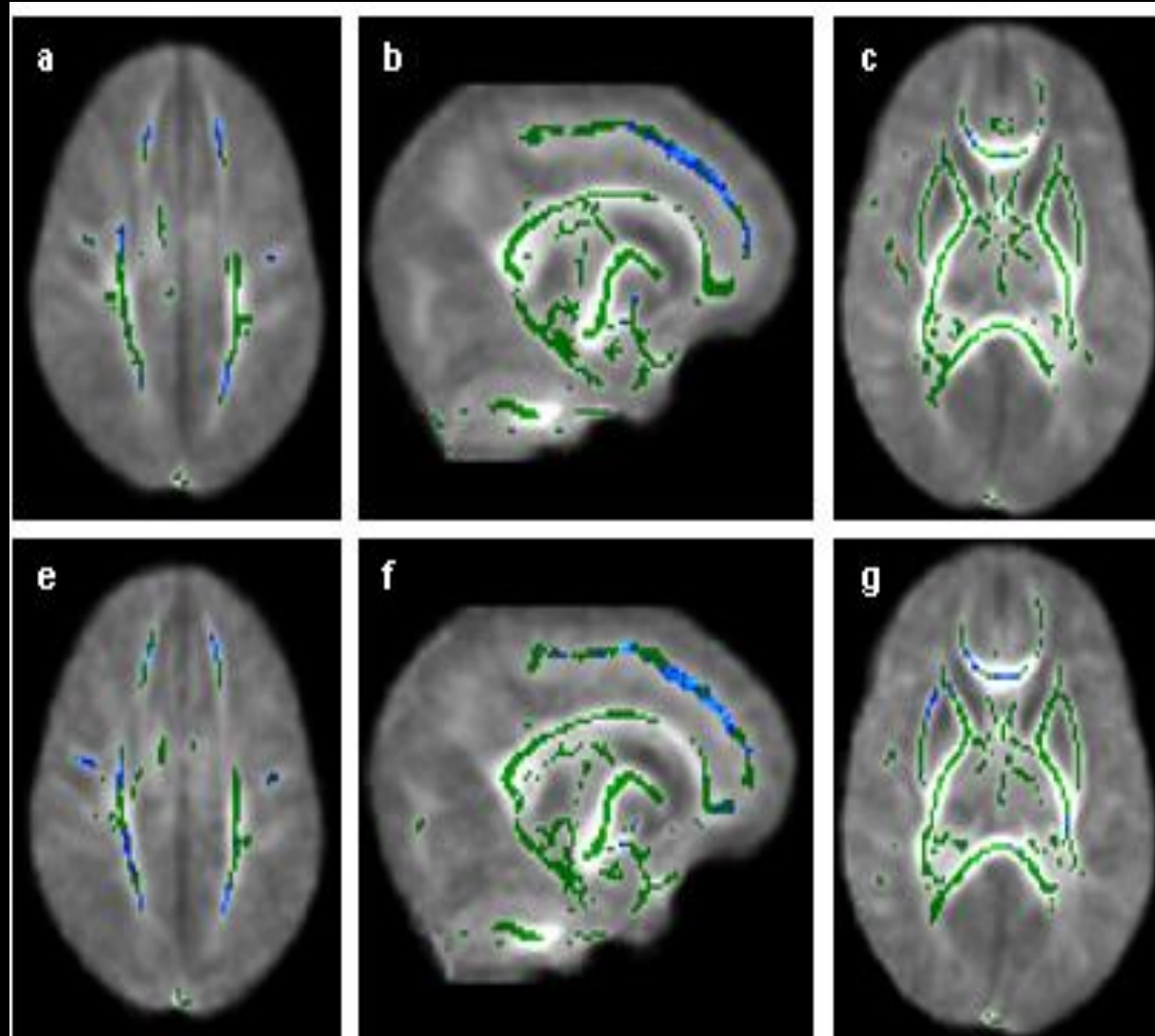
*Outcome  
cognitivo*



**TEA = Term Equivalent Age**

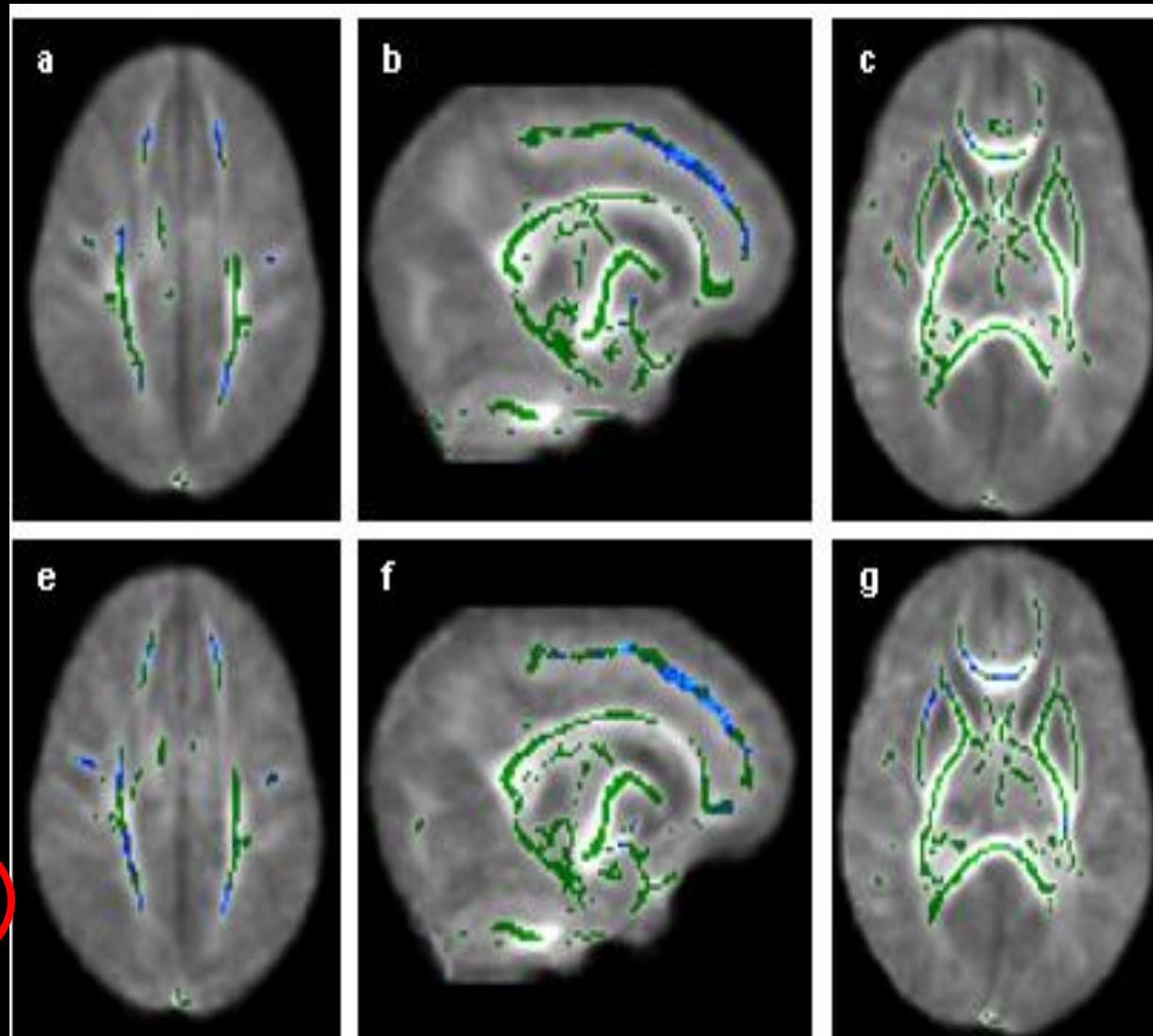
# DTI anisotropy maps at term equivalent age

White matter  
organisation  
when no focal  
lesions

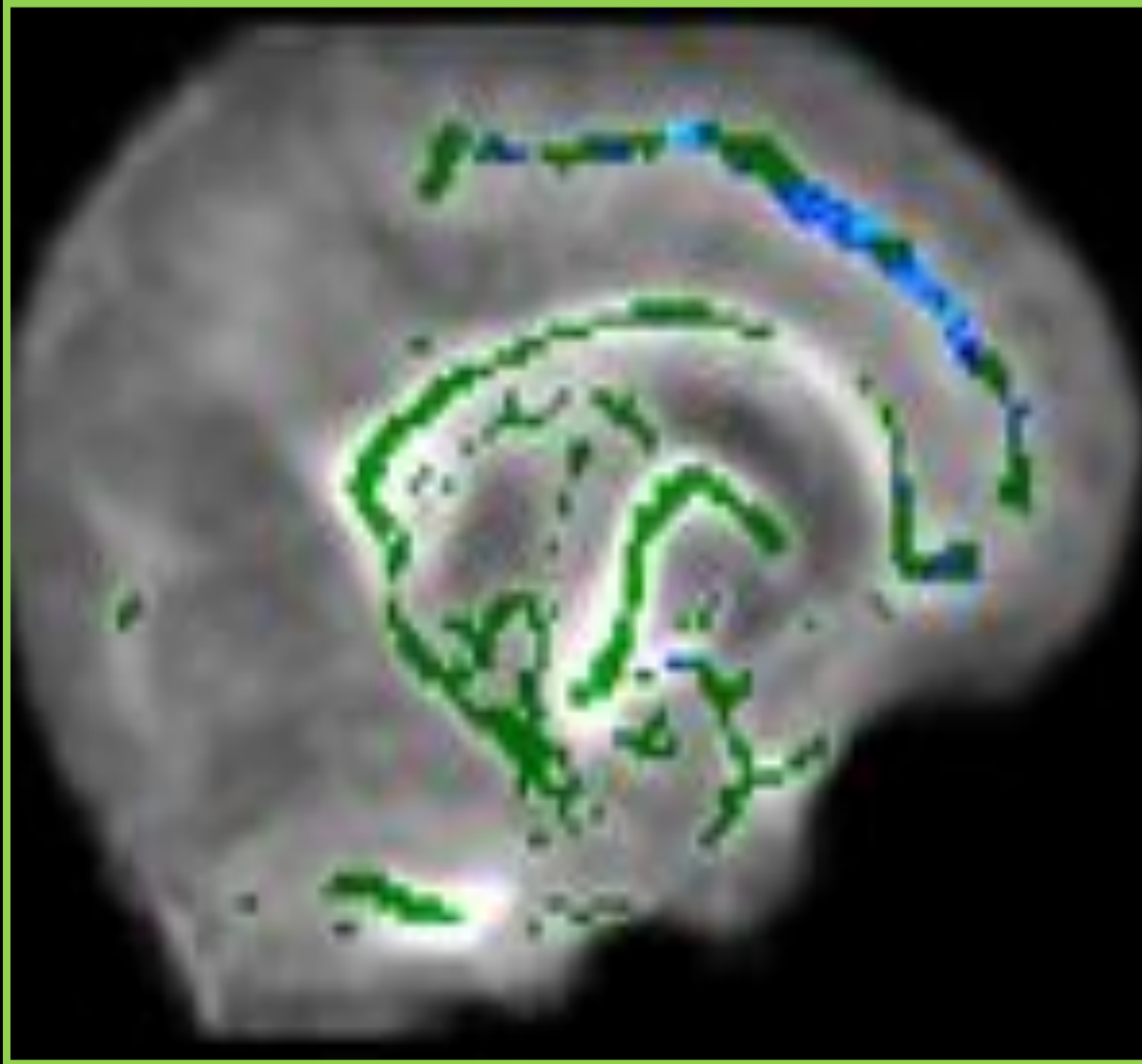


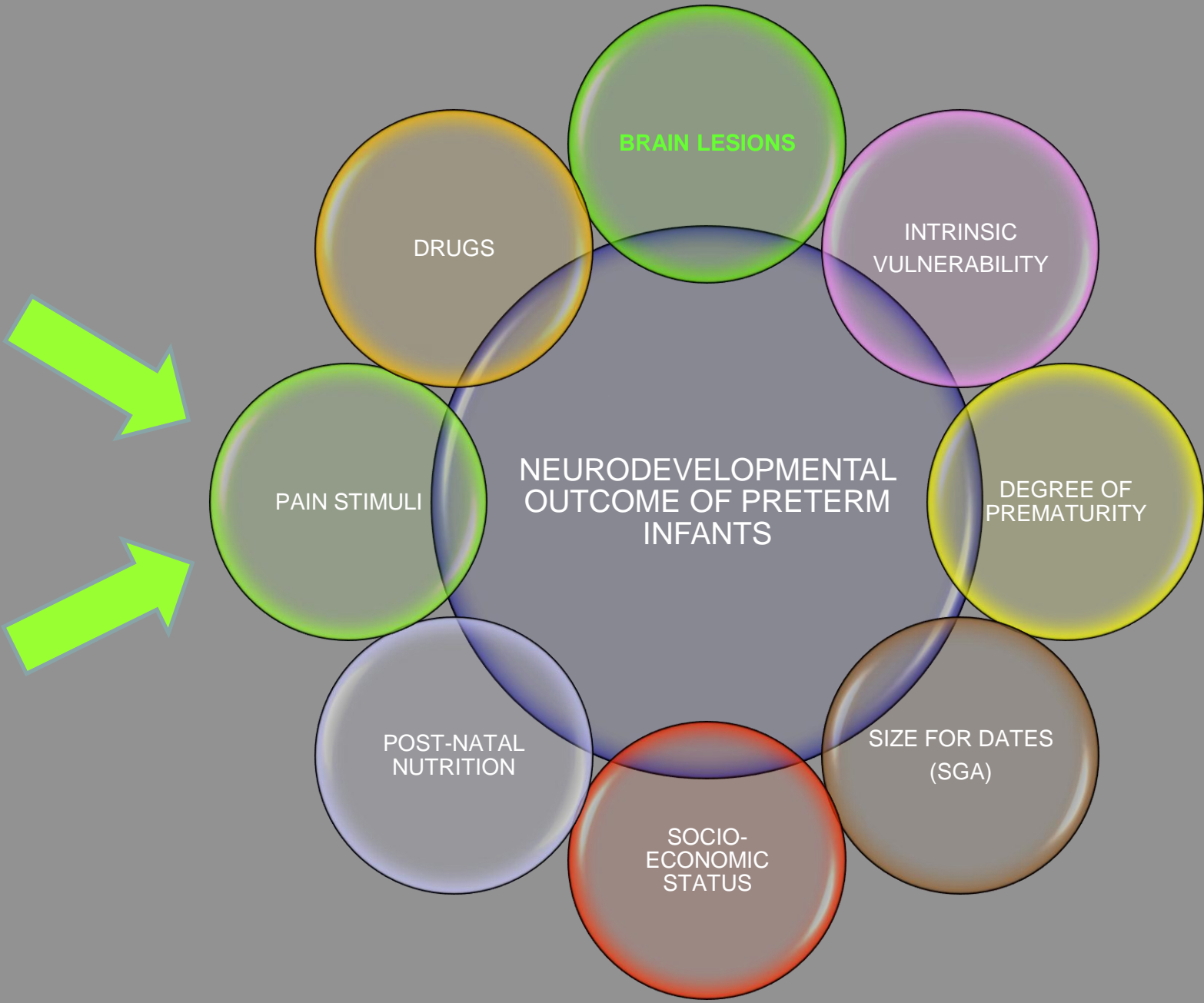
# DTI anisotropy maps at term equivalent age

- White matter organisation when no focal lesions
- Regional anisotropy lower than term control infants in many white matter tracts (blue).
- Greater changes in < 28 week infants



In the absence of brain lesions what are the mechanisms leading to this impairment in white matter development ?







# Procedural Pain and Brain Development in Premature Newborns

Susanne Brummelte, PhD,<sup>1,2</sup> Ruth E. Grunau, PhD,<sup>1,2</sup> Vann Chau, MD,<sup>1,2</sup>

Kenneth J. Poskitt, MDCM,<sup>1,2,3</sup> Rollin Brant, PhD,<sup>4</sup> Jillian Vinall, BA,<sup>1,2</sup> Ayala Gover, MD,<sup>1,2</sup>

Anne R. Synnes, MDCM,<sup>1,2</sup> and Steven P. Miller, MDCM<sup>1,2</sup>



**Interpretation:** Early procedural pain in very preterm infants may contribute to impaired brain development.

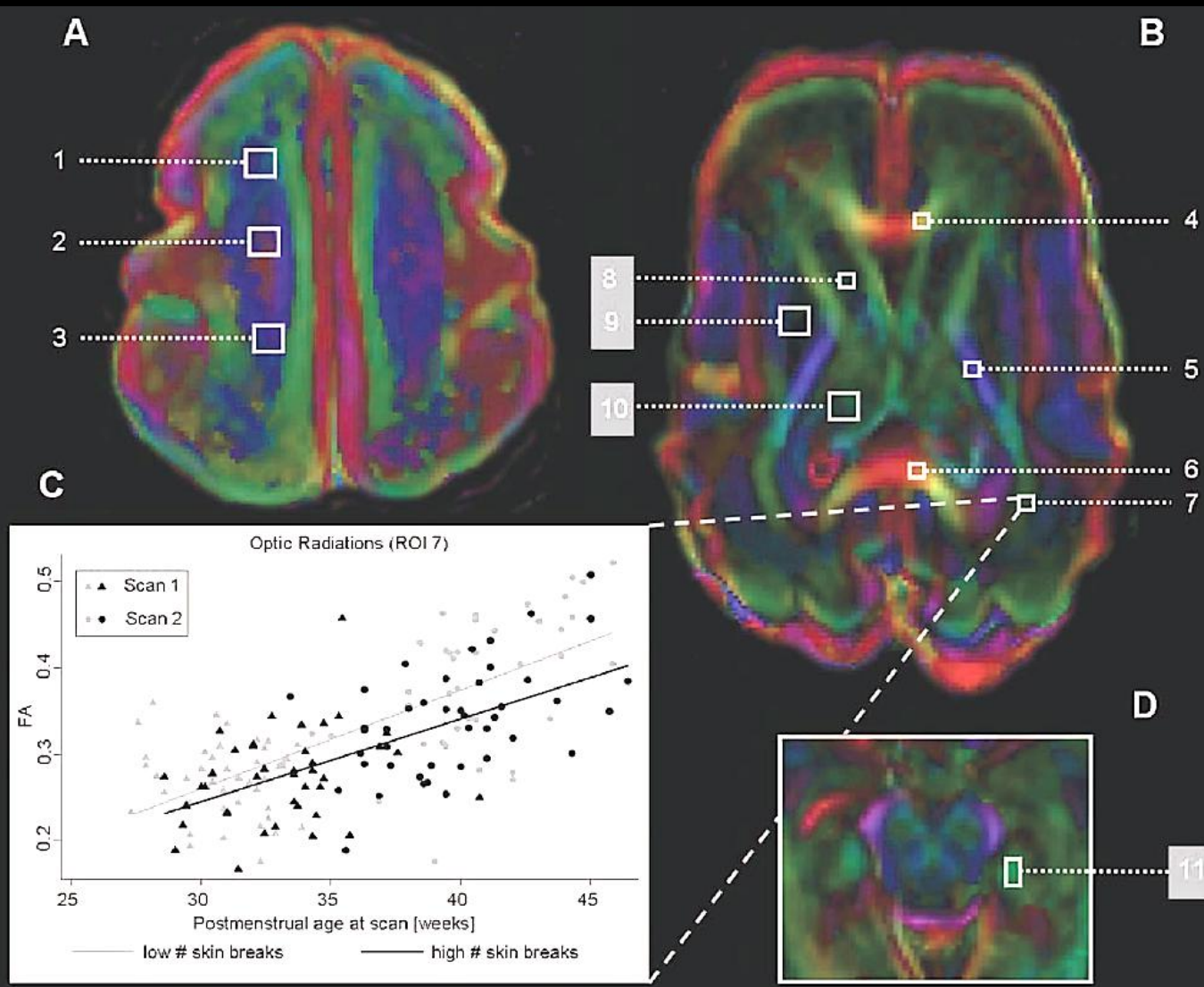
ANN NEUROL 2012;71:385–396

TABLE 1: Infant Characteristics for the Full Cohort and Separately for High and Low Pain Exposure (Median Split on Number of Skin Breaks)

Characteristic	Total, N = 86		Infants with Low Number of Skin Breaks, n = 42		Infants with High Number of Skin Breaks, n = 44		<i>p</i>
Mechanical ventilation					0.00055		0.98
Infection					-0.0464		0.16
NEC					-0.0170		0.55
Hypotension					-0.0561		0.05
Dexamethasone					0.0069		0.80
Midazolam			-0.0014	0.34	-0.0022		0.15
≥2 surgeries			0.0310	0.17	0.0329		0.20
Skin breaks	-0.00069	0.008 <sup>a</sup>	-0.00064	0.001 <sup>a</sup>	-0.00061		0.004 <sup>a</sup>

The effect size describes the expected change per unit in the outcome variable (FA) with a change in the predictor variable. For example, each additional skin break decreased FA by 0.00024 in the final model.

The number of skin breaks remained significant to negatively influence FA after adjusting for mechanical ventilation, hypotension, infection, NEC, dexamethasone, and midazolam.

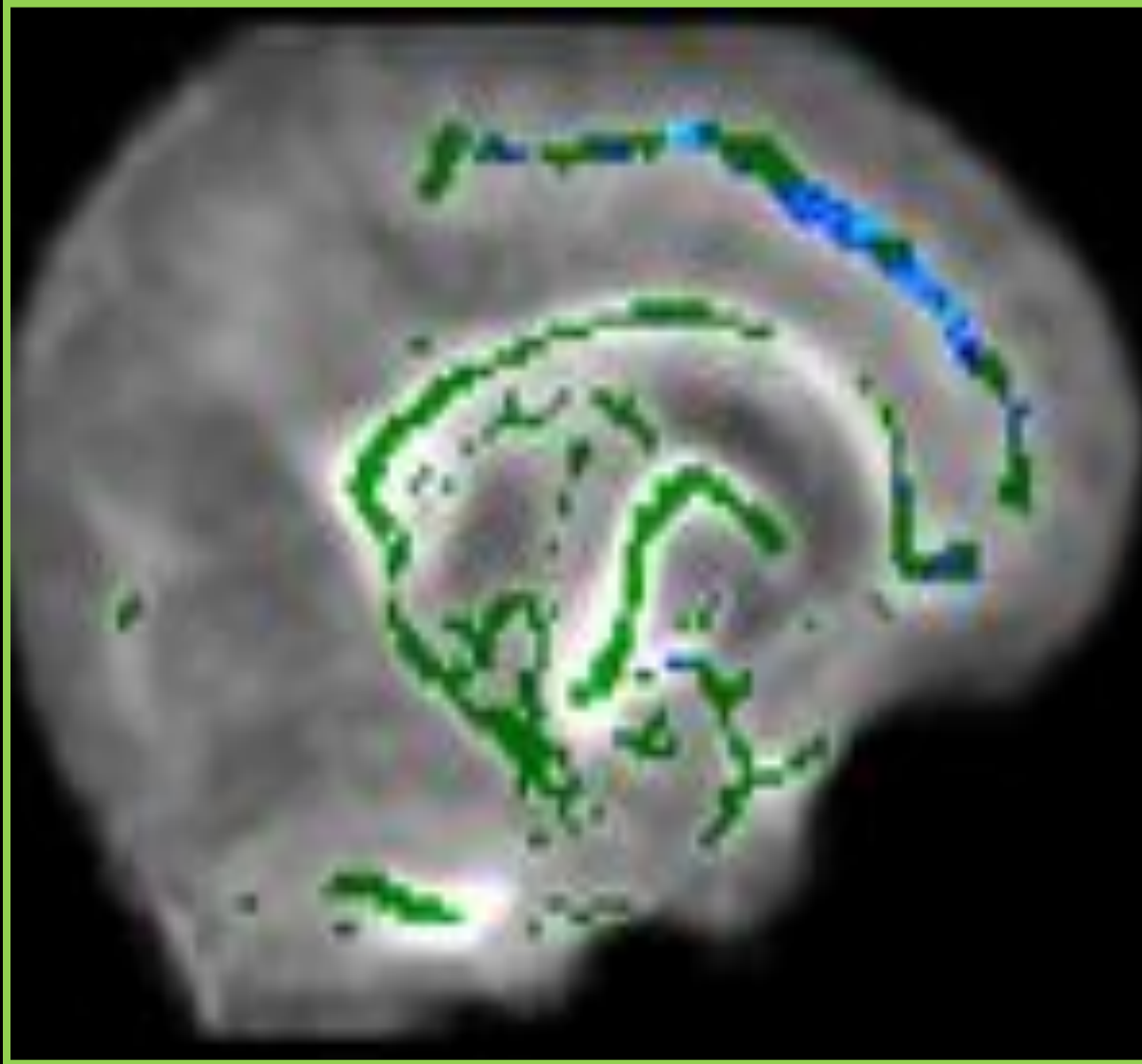


Significant association of the total number of skin breaks with mean FA.

**Early but not later pain exposure was a significant predictor of abnormal white matter microstructure.**



In the absence of brain lesions what are the mechanisms leading to this impairment in white matter development ?



**Infection/Inflammation**

**Hypoxia/Ischemia**

**PAMPs**

**DAMPs**

**TLRs**

**TLRs**



**Microglia**

**Microglial activation**

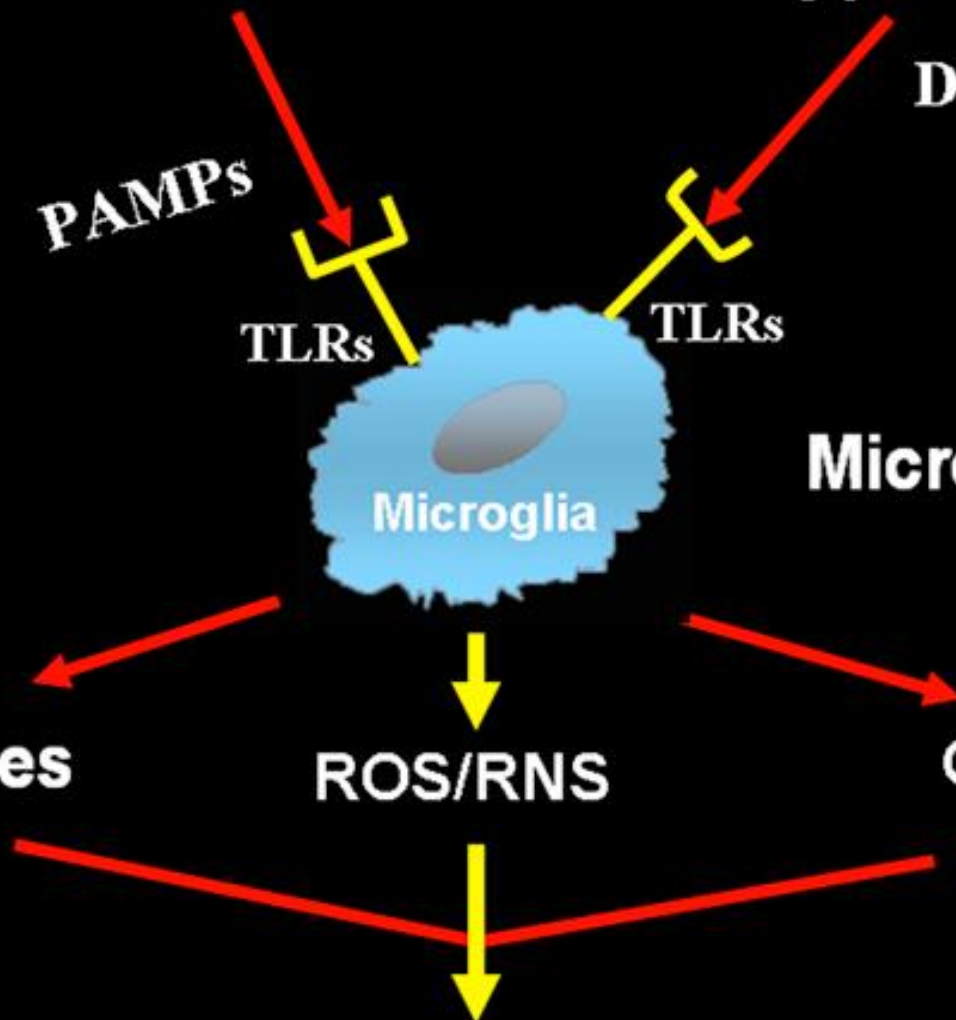
**Cytokines**

**ROS/RNS**

**Glutamate**

**Pre-OL Injury**

Courtesy of JJ Volpe



**Infection/Inflammation**

**Hypoxia/Ischemia**

**Premature  
Birth per se**

**PAMPs**

**DAMPs**

**TLRs**

**TLRs**

**Microglia**

**Microglial activation**

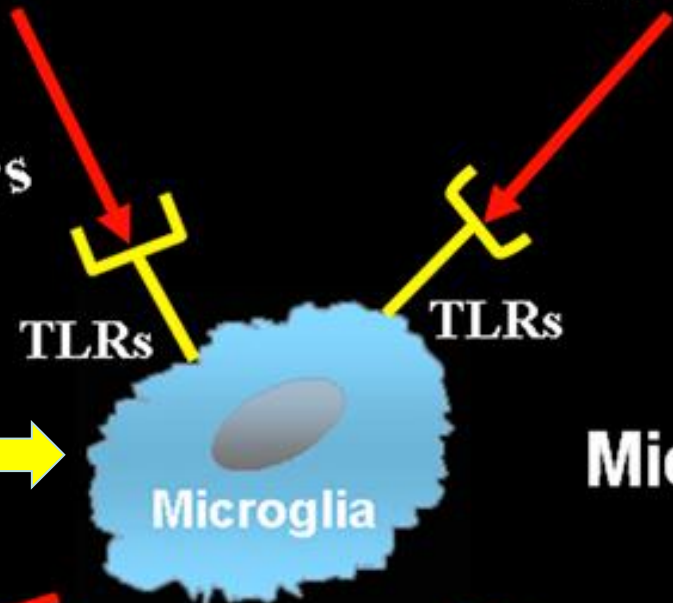
**Cytokines**

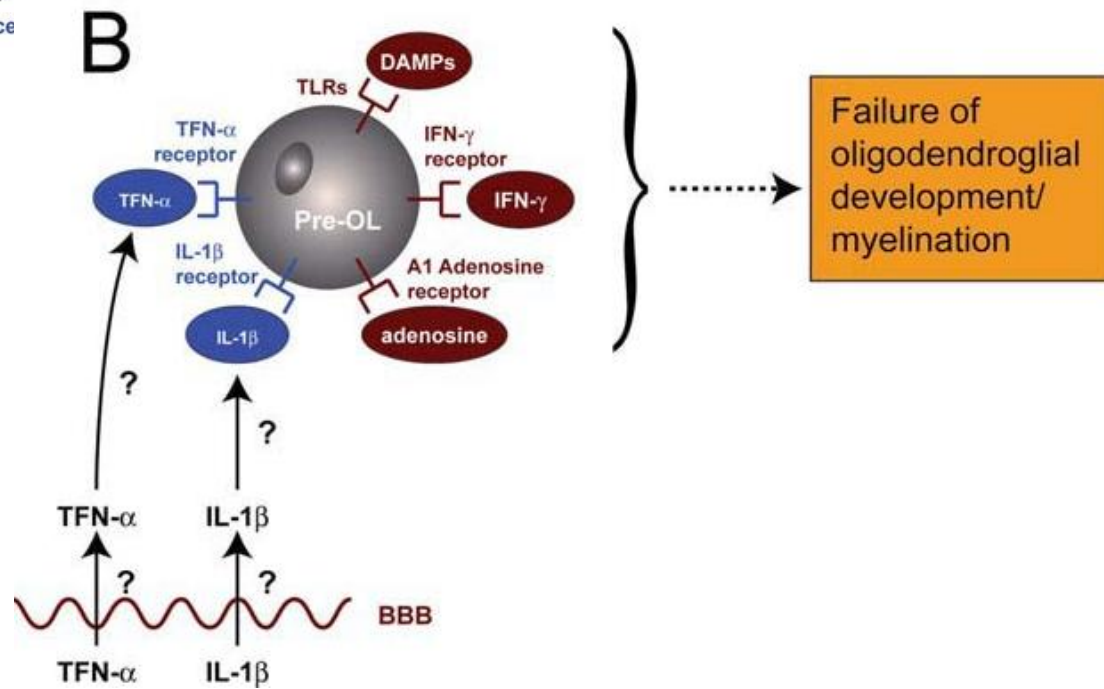
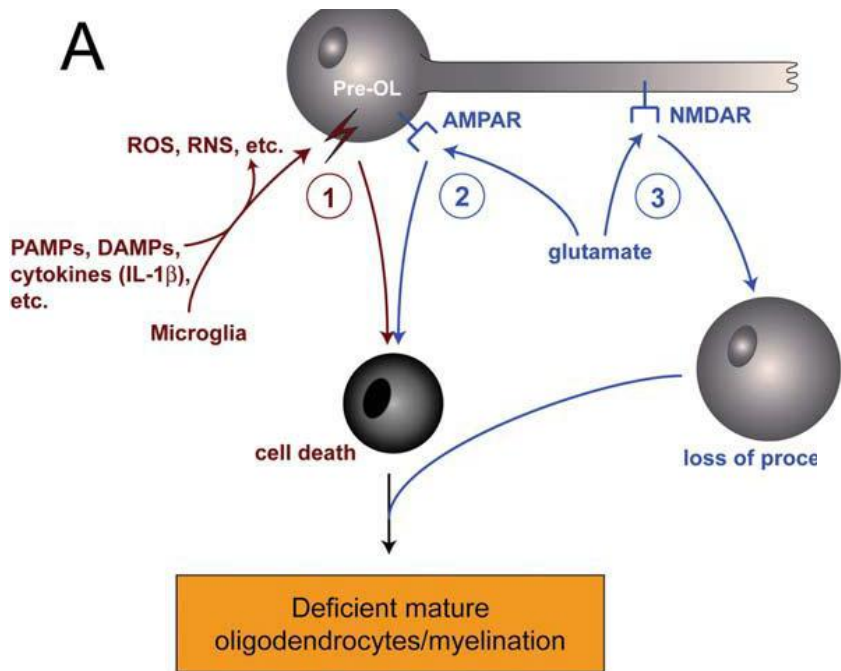
**ROS/RNS**

**Glutamate**

**Pre-OL Injury**

Courtesy of JJ Volpe



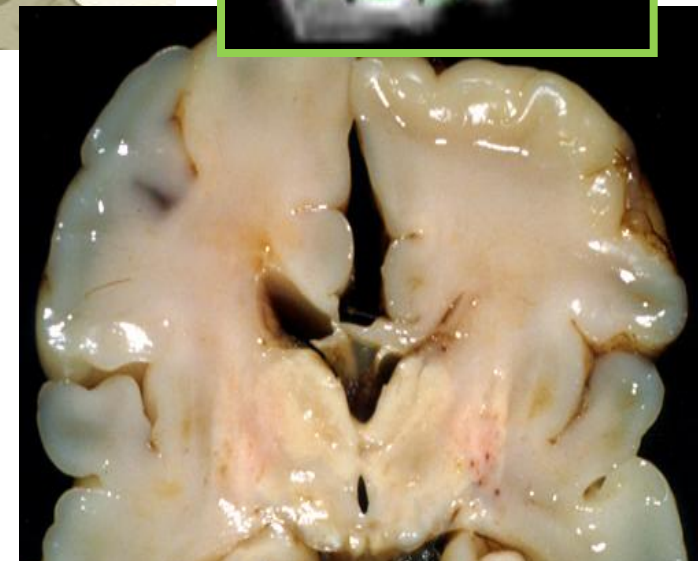
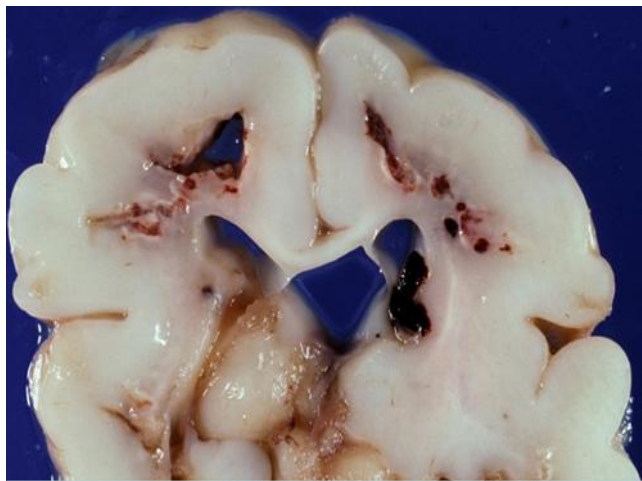
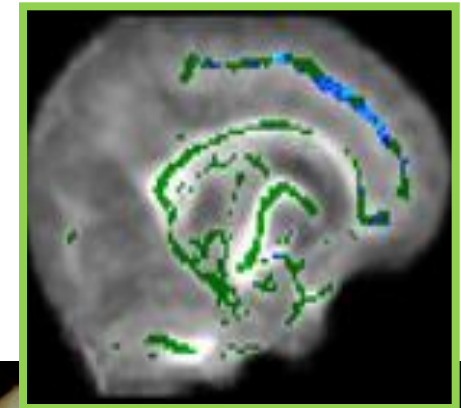
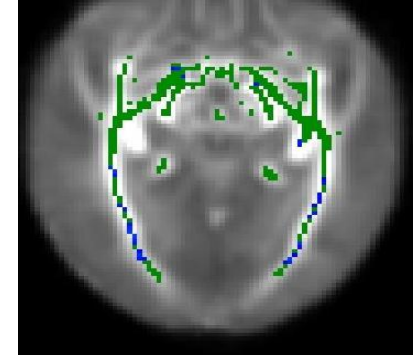
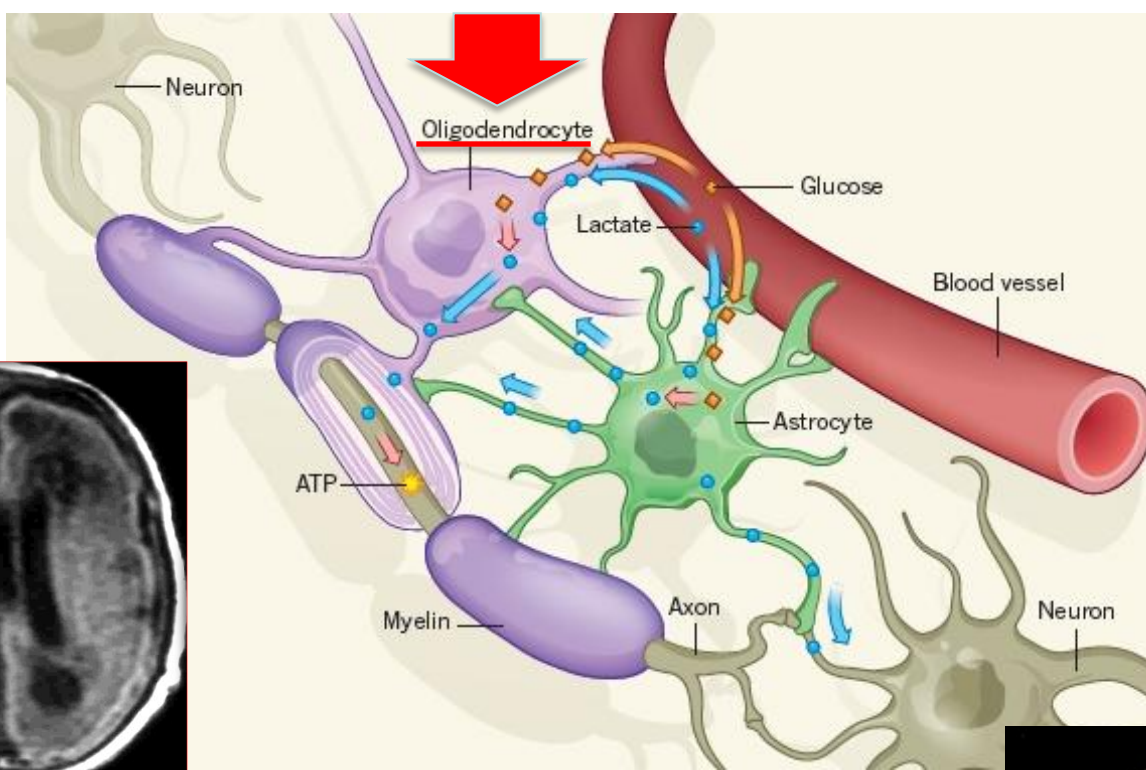




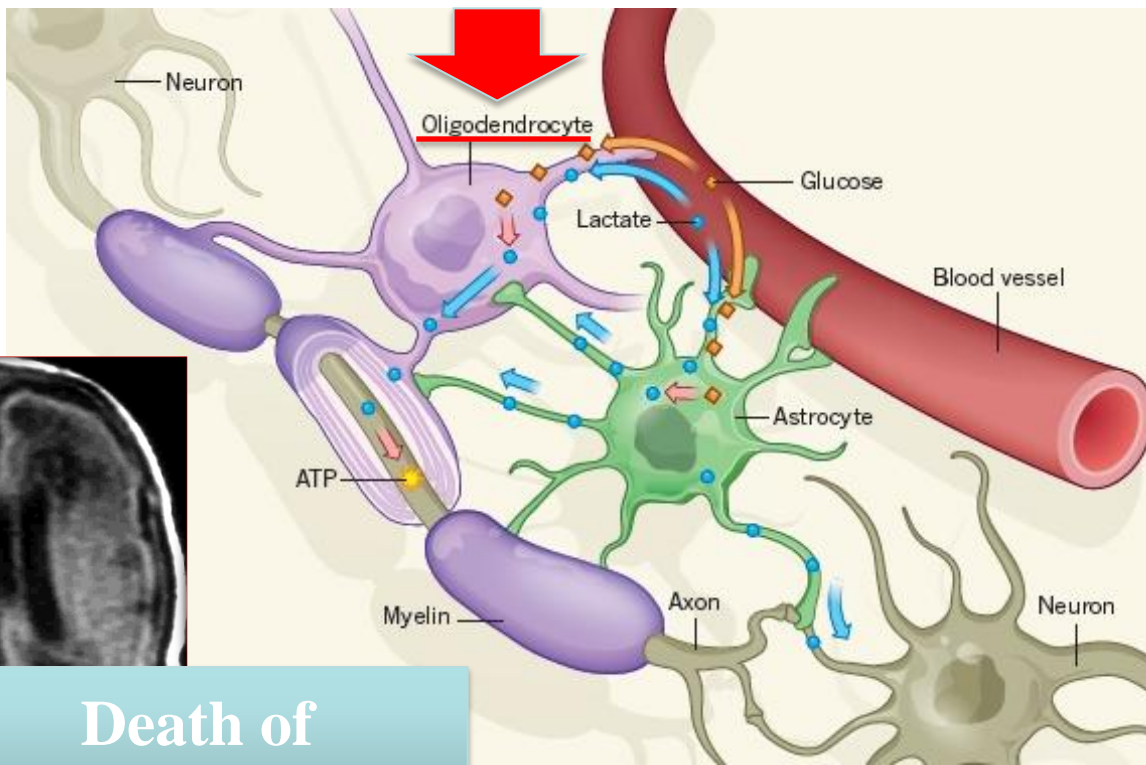
# Systemic Inflammation Disrupts the Developmental Program of White Matter

Géraldine Favrais, MD, PhD,<sup>1,2,3,4</sup> Yohan van de Looij, PhD,<sup>5,6</sup> Bobbi Fleiss, PhD,<sup>7</sup>  
Nelina Ramanantsoa, PhD,<sup>1,2,3</sup> Philippe Bonnin, MD, PhD,<sup>2,3,4,5,6,7,8</sup>  
Gisela Stoltenburg-Didinger, MD,<sup>9</sup> Adrien Lacaud, BS,<sup>10</sup> Elie Saliba, MD, PhD,<sup>4</sup>  
Olaf Dammann, MD,<sup>11,12,13</sup> Jorge Gallego, PhD,<sup>1,2,3</sup> Stéphane Sizonenko, MD, PhD,<sup>5</sup>  
Henrik Hagberg, MD, PhD,<sup>7,14</sup> Vincent Lelièvre, PhD,<sup>1,2,3,9</sup>  
and Pierre Gressens, MD, PhD<sup>1,2,3,14</sup>

Moderate perinatal systemic inflammation alters the developmental program of the white matter. This insult induces a long-lasting myelination deficit accompanied by cognitive defects and MRI abnormalities, further supporting the clinical relevance of the present data.



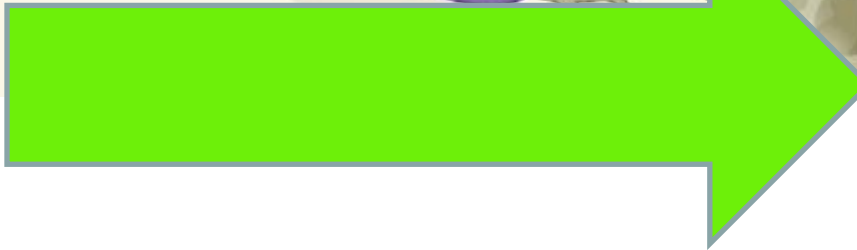
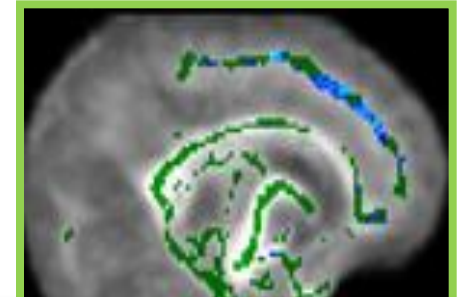
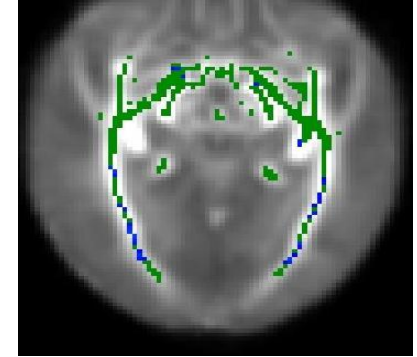
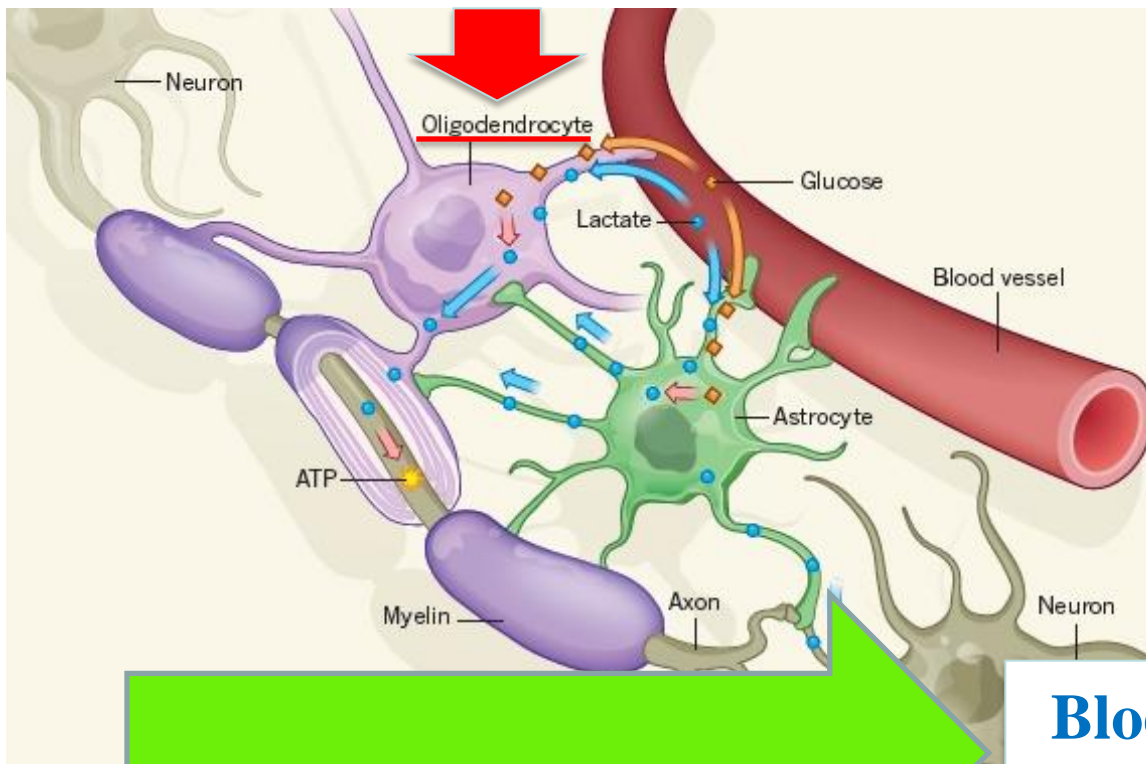
Disappearing  
Cystic PVL



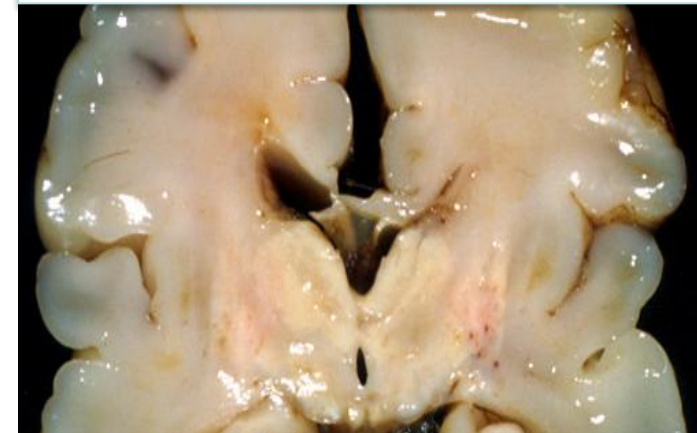
Death of oligodendrocyte



Disappearing Cystic PVL



**Blockade/impairment  
of pre-oligodendrocyte**



More diffuse  
White matter impairment

# Inflammation & cytokines

**amniotic infection**



**amniotic/systemic inflammation/  
Hypoxia-ischaemia/high prematurity**



**circulating pro-inflammatory cytokines**

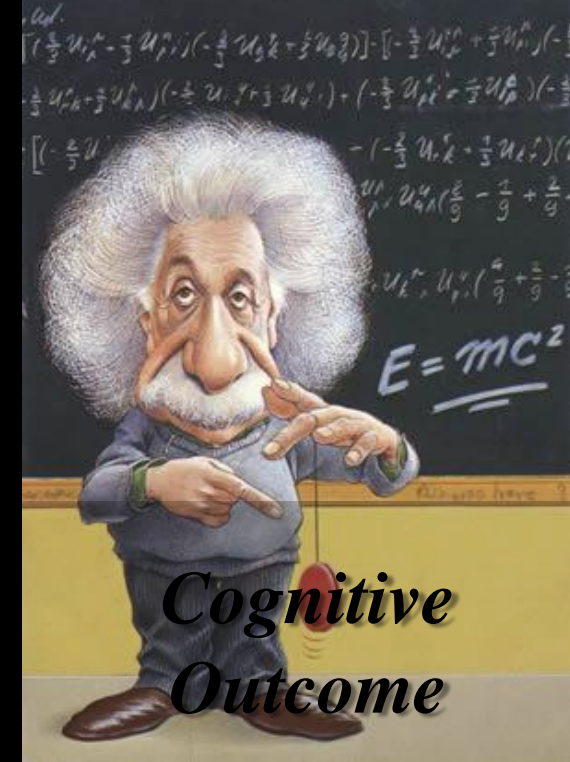
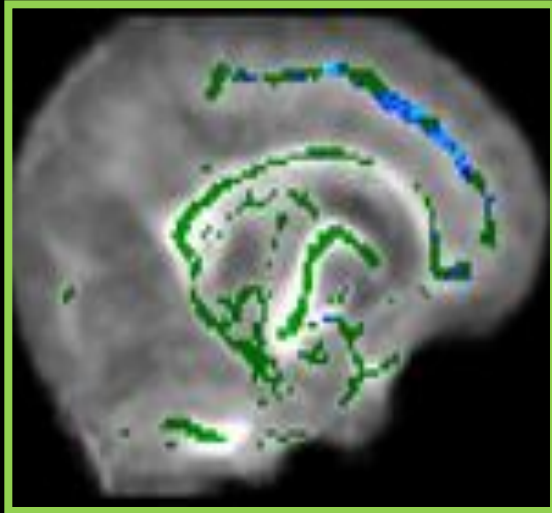


**Microglia activation**

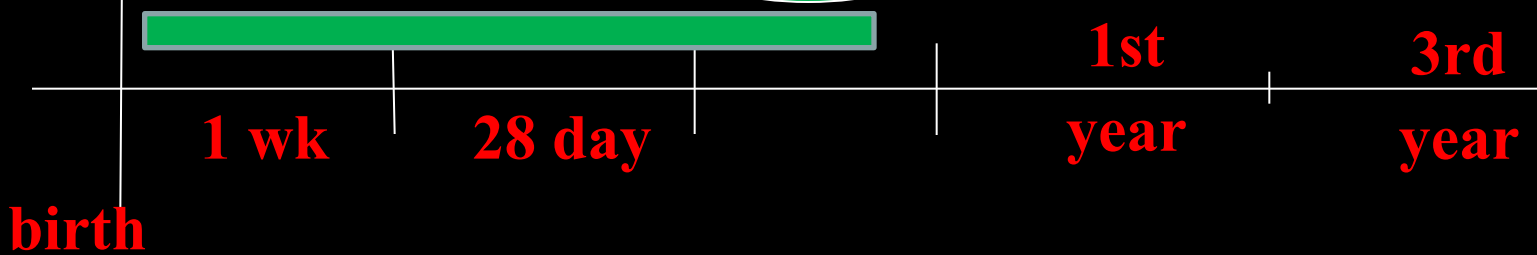


**oligo maturation blockade**

**TO FAVOUR**



*Brain  
development*



# Inflammation & cytokines

**amniotic infection**



**amniotic/systemic inflammation/  
Hypoxia-ischaemia/high prematurity**



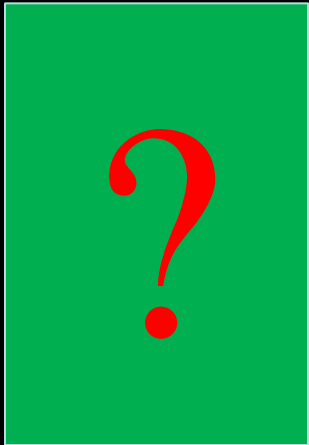
**circulating pro-inflammatory cytokines**



**Microglia activation**

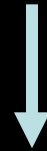


**oligo maturation blockade**

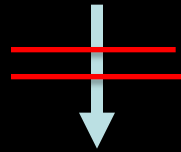


# Inflammation & cytokines

**amniotic infection**



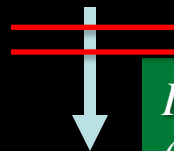
**amniotic/systemic inflammation/  
Hypoxia-ischaemia/high prematurity**



*Less aggressive and more tailored ven*

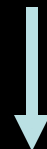
**circulating pro-inflammatory cytokines**

*Less infections*



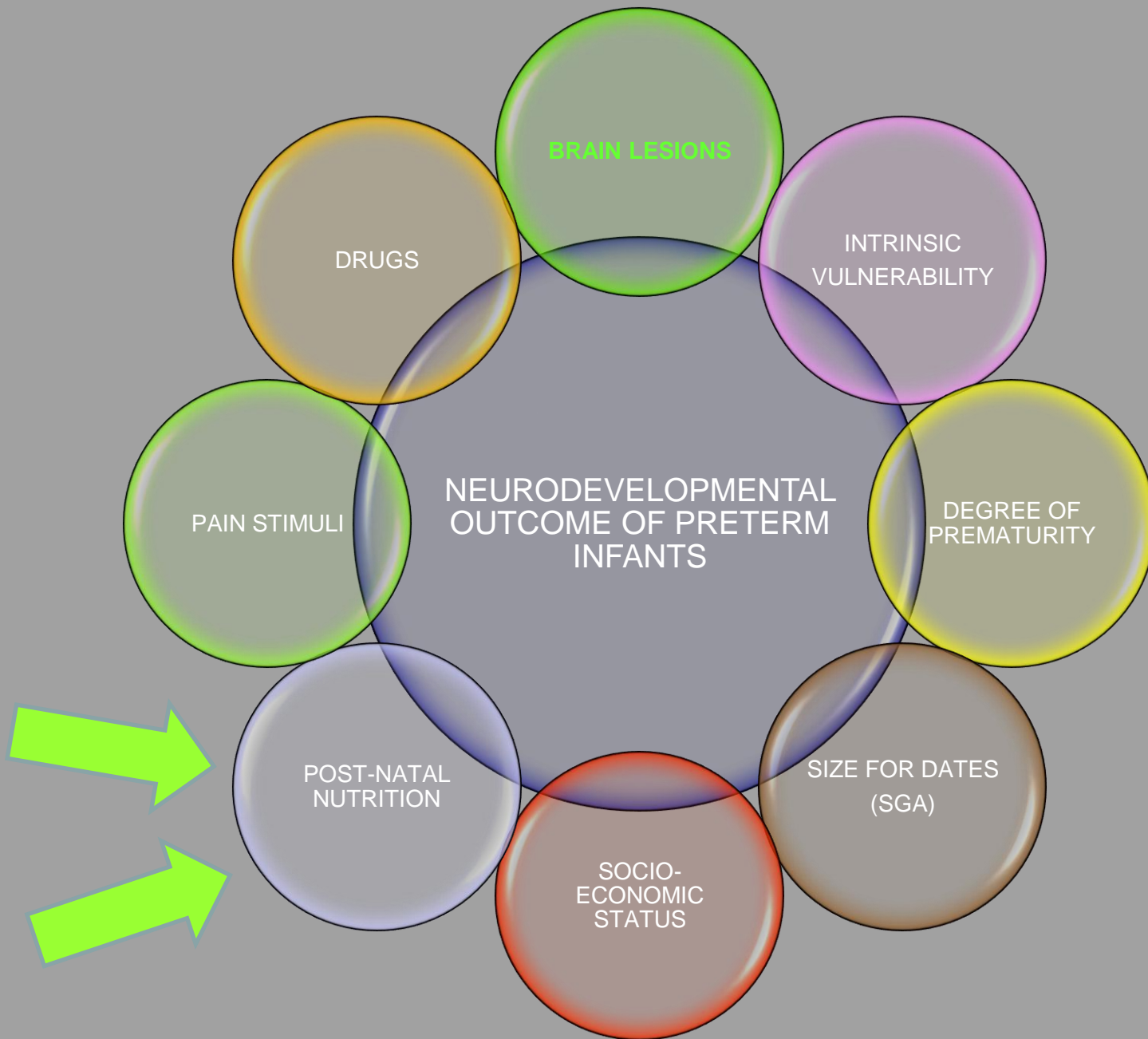
*Identify and test neuroprotective agents  
(Magnesium Sulphate, Epo, caffeine, melat.)*

**Microglia activation**



**oligo maturation blockade**





**Infection/Inflammation**

**Hypoxia/Ischemia**

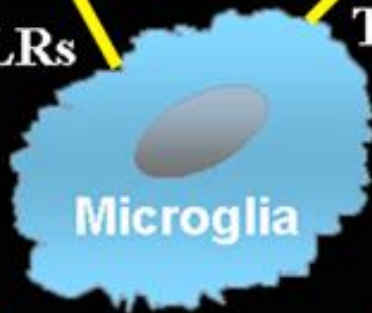
**PAMPs**

**DAMPs**

**TLRs**

**TLRs**

**a dietary n-3 PUFAs  
deficiency ?**



**Microglia**

**Microglial activation**

**Improvement  
nutrition ?**

**Cytokines**

**ROS/RNS**

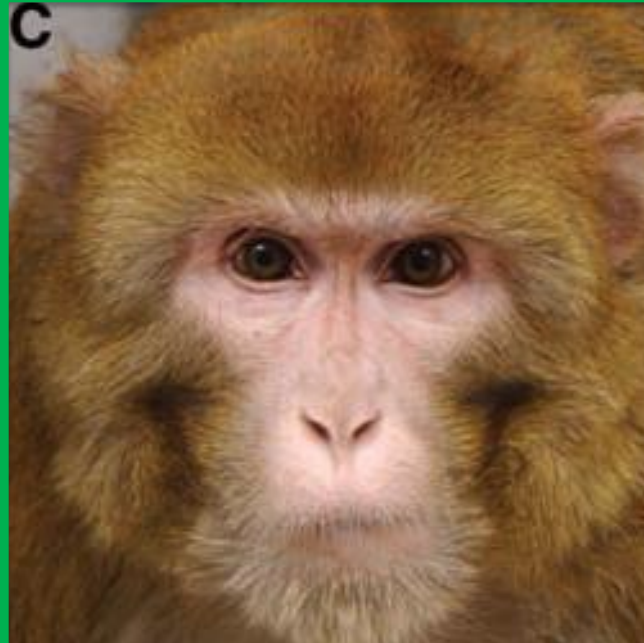
**Glutamate**

**Pre-OL Injury**

*“Providing nutrient intakes that permit  
the rate of postnatal growth  
and the composition of weight gain  
to approximate that of a normal fetus  
of the same postmenstrual age”*

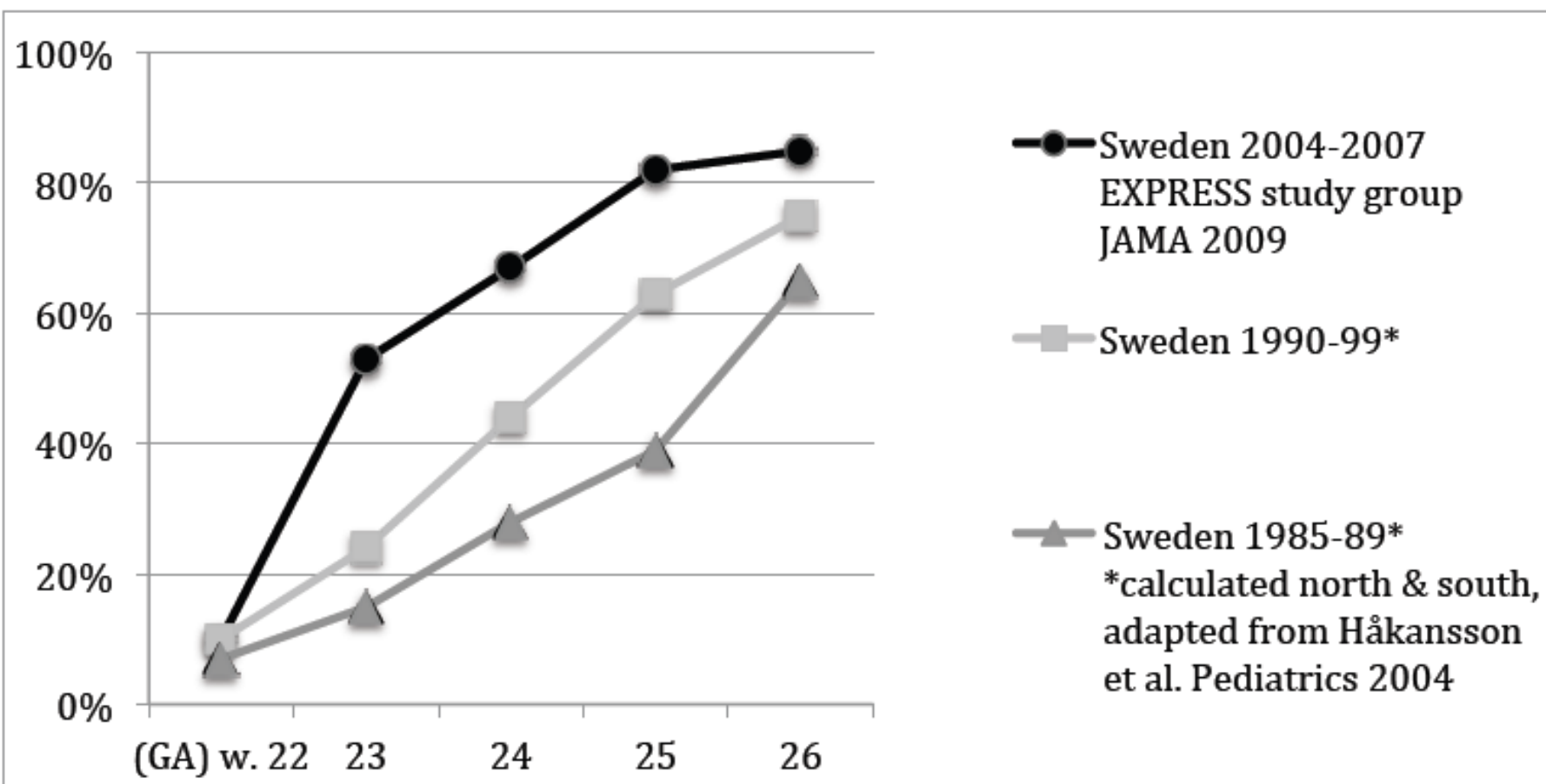
# Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys

Ricki J. Colman *et al.*  
*Science* **325**, 201 (2009);  
DOI: 10.1126/science.1173635



Both at 27.5 years

**CD was on caloric restriction !**



*Survival rates of extremely preterm infants in Sweden over the last twenty years*

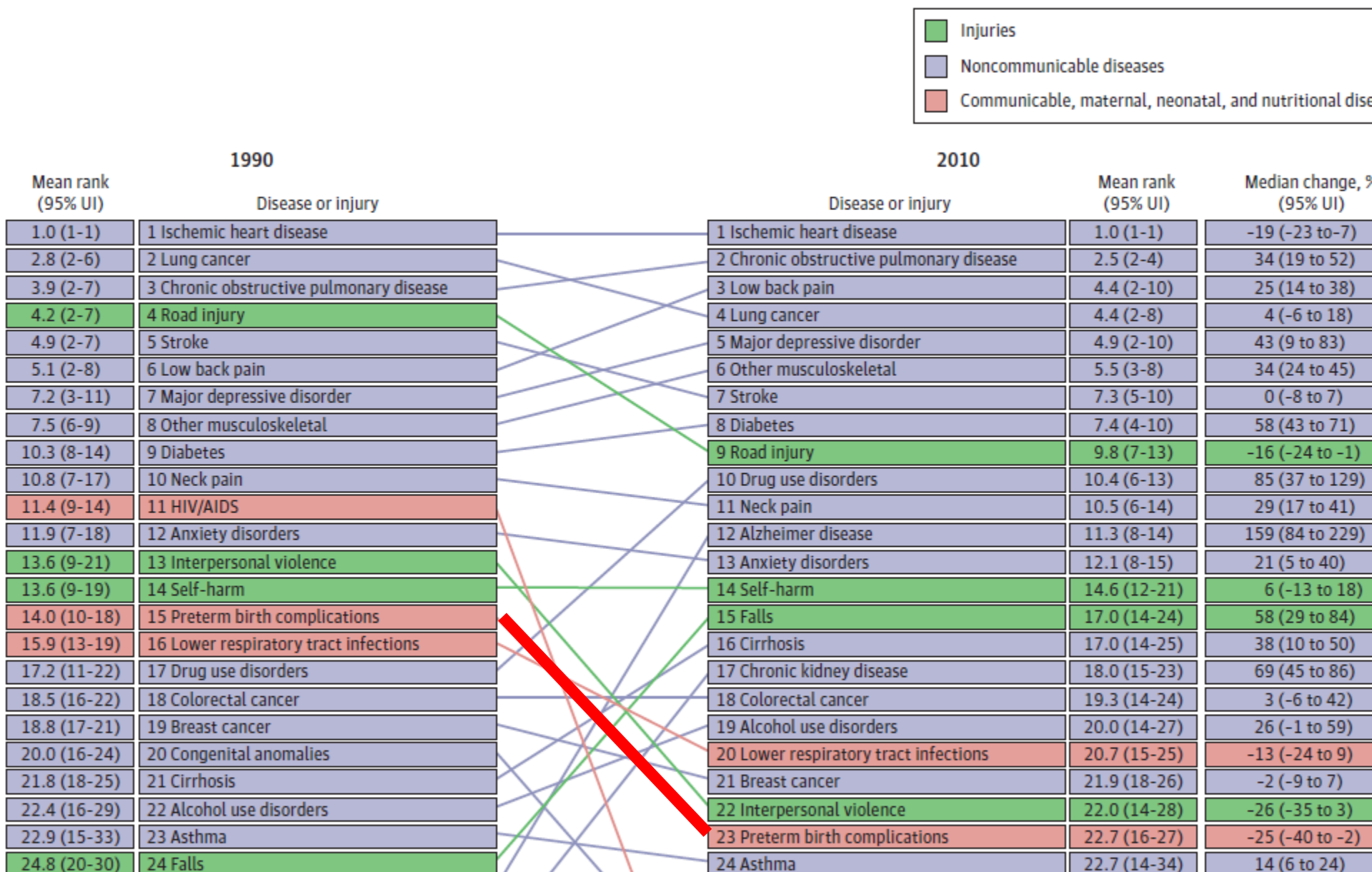
**BRAIN IMAGING AND OUTCOME IN EXTREMELY PRETERM INFANTS**

Candidate: Beatrice Skiold  
Opponent: Luca Ramenghi

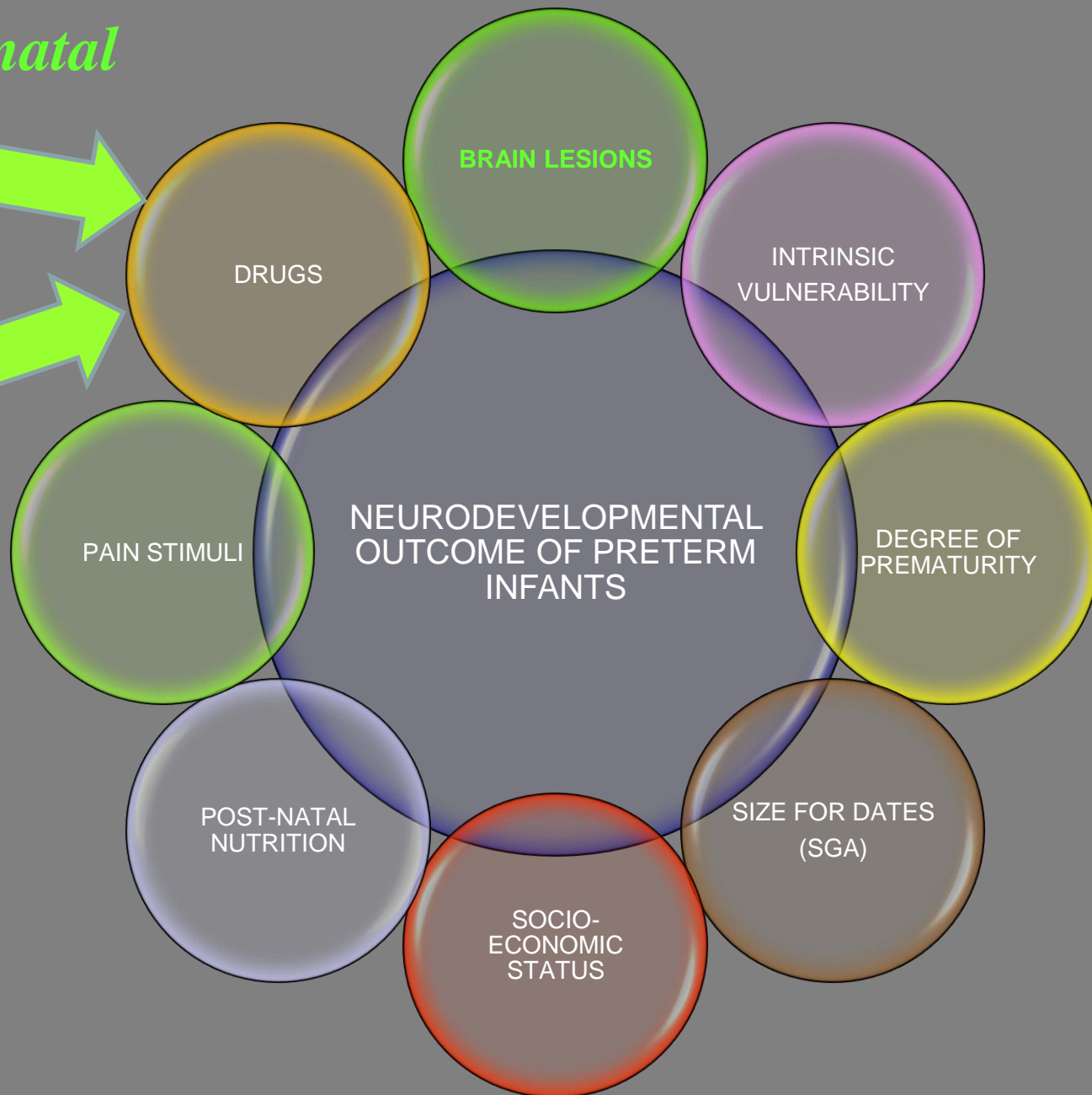
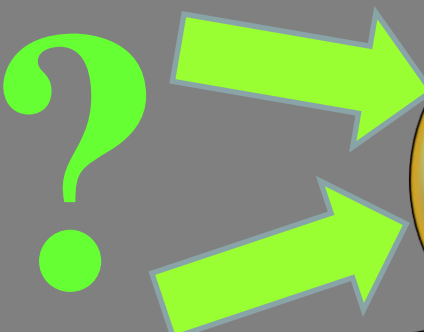


**Karolinska  
Institutet**

Figure 2. Disability-Adjusted Life-Year Ranks for the Top 30 Diseases and Injuries in 1990 and 2010 and Percentage Change Between 1990 and 2010



*perinatal*



BRAIN LESIONS

DRUGS

INTRINSIC  
VULNERABILITY

PAIN STIMULI

NEURODEVELOPMENTAL  
OUTCOME OF PRETERM  
INFANTS

DEGREE OF  
PREMATURITY

POST-NATAL  
NUTRITION

SIZE FOR DATES  
(SGA)

SOCIO-  
ECONOMIC  
STATUS

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# Impact of Common Treatments Given in the Perinatal Period on the Developing Brain

Géraldine Favrais<sup>a</sup> Pierre Tourneux<sup>b</sup> Emmanuel Lopez<sup>a</sup> Xavier Durrmeyer<sup>c</sup>  
Géraldine Gascoin<sup>d</sup> Duksha Ramful<sup>e</sup> Elodie Zana-Taieb<sup>f</sup> Olivier Baud<sup>g</sup>

<sup>a</sup>Neonatal Intensive Care Unit (ICU), CHRU de Tours, Tours, <sup>b</sup>Neonatal and Pediatric ICU, Pôle Femme – Couple – Enfant, Amiens, <sup>c</sup>Neonatal ICU and Clinical Research Centre, Centre Hospitalier Intercommunal de Créteil, Créteil, <sup>d</sup>Neonatal ICU, University Hospital of Angers, Angers, <sup>e</sup>Neonatal and Pediatric ICU, CHR Félix Guyon, Saint-Denis, La Réunion, <sup>f</sup>Neonatal ICU Port-Royal, Groupe Hospitalier Cochin-Broca-Hôtel Dieu, APHP, and <sup>g</sup>Neonatal ICU, Groupe Hospitalier Robert Debré, APHP, Paris, France



**Table 1.** Unexpected effects of perinatal drugs used in preterm infants: rationale in perinatal risk factors, pre-clinical and clinical evidences as well as long-term effects

Risk factors	Drugs	Preclinical evidence for neuroprotection	Beneficial effect on brain lesions	Long-term effect
Inflammation	antibiotics	0	0	0
	NSAIDs	+	+	0
	antenatal steroids	++	++	+/-
Hypoxia/haemodynamic disturbances	surfactant	?	++	+
	caffeine	++	+	++
	iNO	+	+/-	+/-
	inotropes	0	0	0
Stress (pain)	opioids	+/-	+/-	0
Growth factor deprivation	erythropoietin	+++	+	+
Excitotoxicity	magnesium sulphate	+++	+	+