XII INTERNATIONAL CONGRESS ON KMC /INK 2018
KANGAROO MOTHER CARE AND NEUROPROTECTION OF THE PREMATURE BRAIN

STUDYING THE PREMATURE INFANT BRAIN DEVELOPMENT: ROLE OF NEUROIMAGING

Cristina Borradori Tolsa, MD
Division of development & growth
Department of child & adolescent
University Hospital Geneva, Switzerland

14 – 17 November 2018

BOGOTA, COLOMBIA

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG Hôpitaux Universitaires Genève

Vulnerability of the developing brain associated with Very Preterm birth - functional deficits

- 5-10% major neurological deficits
  - Severe cognitive delay, cerebral palsy and/or neurosensory impairments

- 25-50% less severe neurodevelopmental
  - Clumsiness
  - Executive Functions deficits
  - Language problems, learning difficulties
  - Behavioral preterm phenotype : emotional, attention/hyperactivity, anxiety, peer relationship difficulties
  - Risk factor for psychiatric diseases
- 40–60% of VPT children will require support from special education services by school age

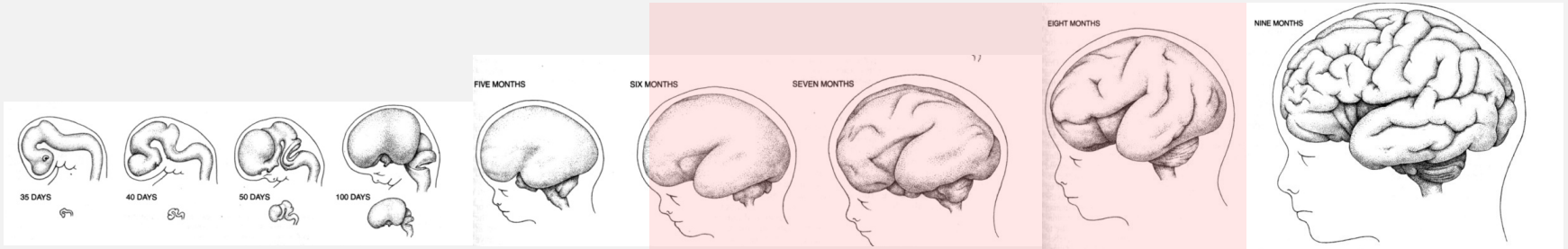
Aarnoudse-Moens, et al. 2009; Brydges, et al. 2018 ; Pritchard, et al. 2014; Bhutta, et al. 2002; Saigal and Doyle 2008, Johnson and Marlow 2011; Arpi and Ferrari 2013; MacKay, et al. 2010; Johnson and Marlow 2011

Why PT children are at risk for neurodevelopmental impairment?

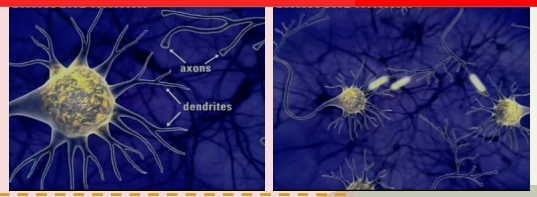
BY ALISON ABBOTT

NATURE | VOL 518 | 5 FEBRUARY 2015

Disruption in the typical progression of Brain development



Organisation: Orientation of neurons, interconnections, synaptogenesis

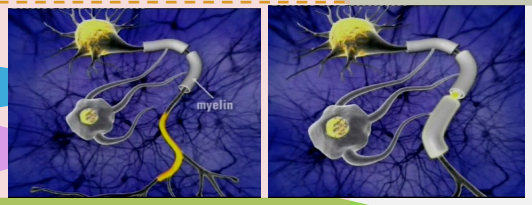


Migration

Proliferation

Glial differentiation

Myelinisation



Radial Glia

Subplate Neurons

Cortical folding

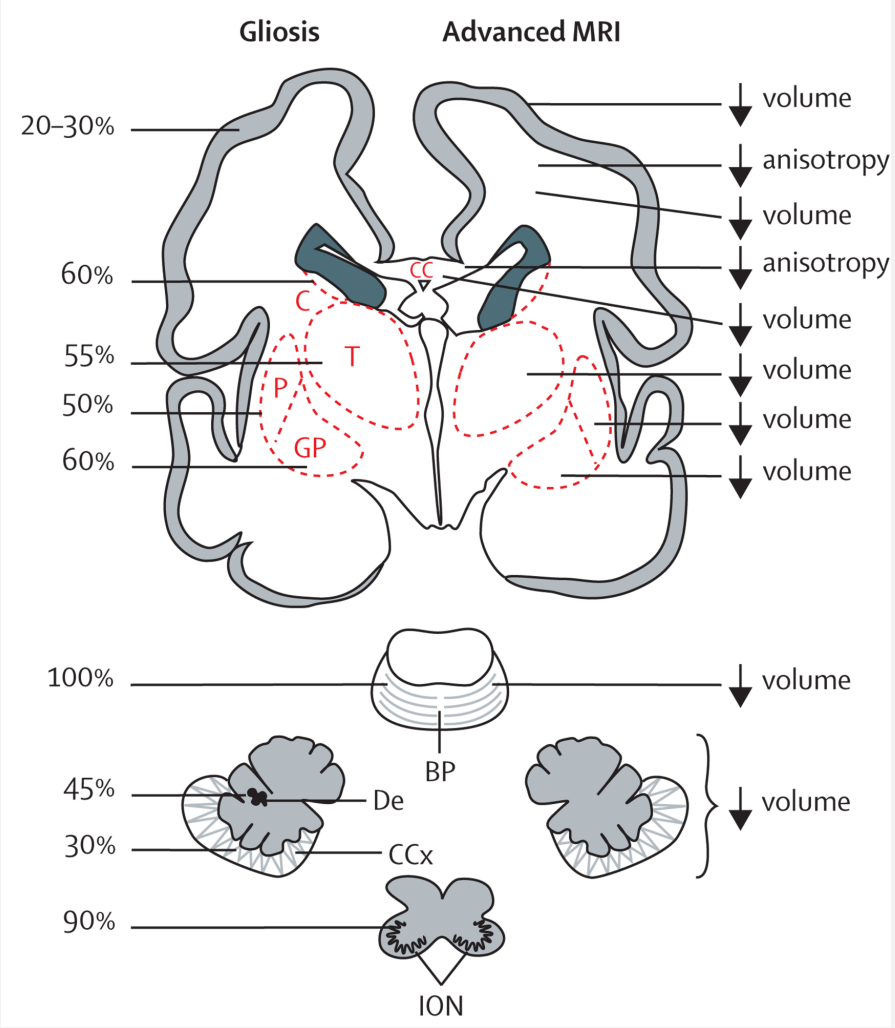
10 15 20 25 30 35 40

Weeks of pregnancy

Preterm birth

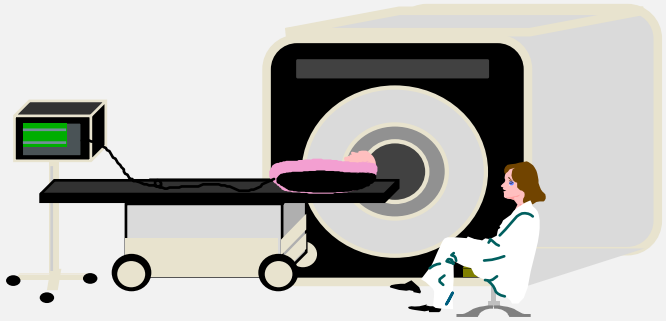
Injury in the developing brain
The "encephalopathy of prematurity"

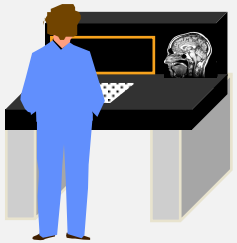
- **Diffuse injury of the white matter accompanied by neuronal and axonal disruption in up to 50% of VP neonates**
- Regions such, thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum are also involved
- MRI analyses:
  - Decrease volume of these structures at TEA, as well as in childhood and adolescence
  - Decreased connectivity

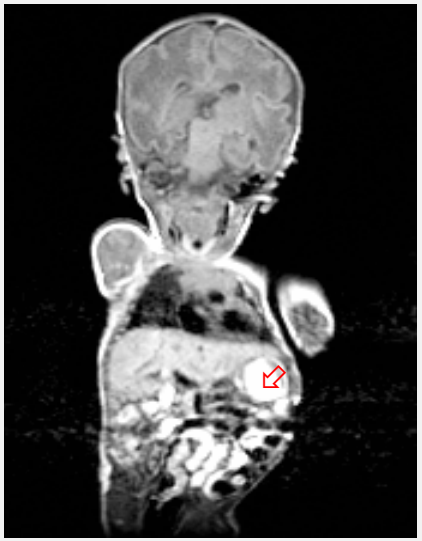


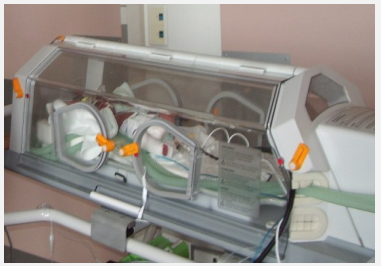
Volpe JJ Lancet Neurol 2009;8:110-24

Magnetic resonance techniques : non invasive method to study brain development and injury





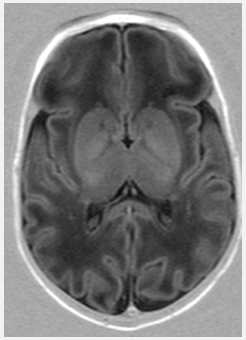


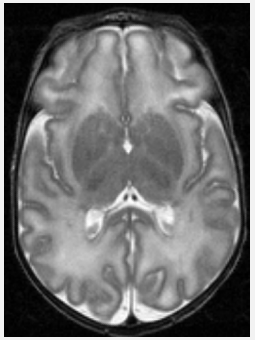


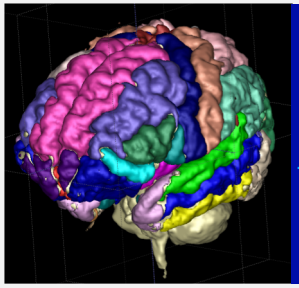
➢Visualization and Quantification of changes in the developing brain by new quantitative neuroimaging techniques

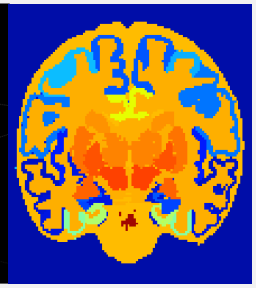
Advanced MRI: Multimodal tools to study brain development and injury

MACROSTRUCTURE



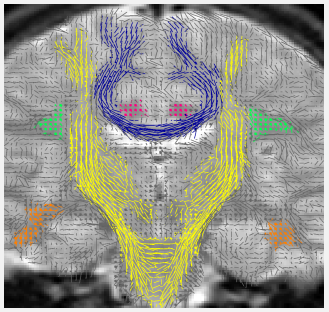


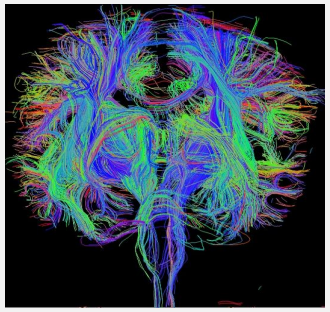


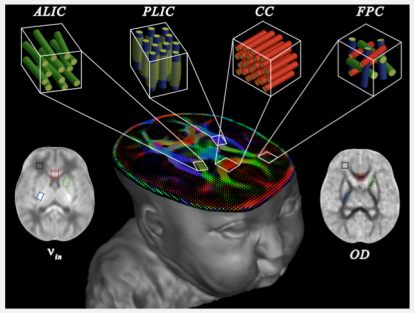


T1-T2; 3D MRI

MICROSTRUCTURE

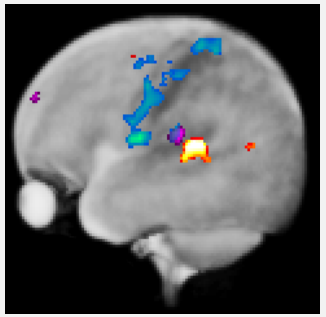


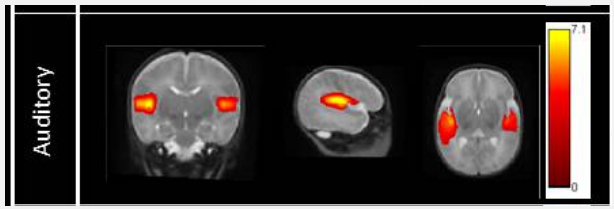




DWI-DTI

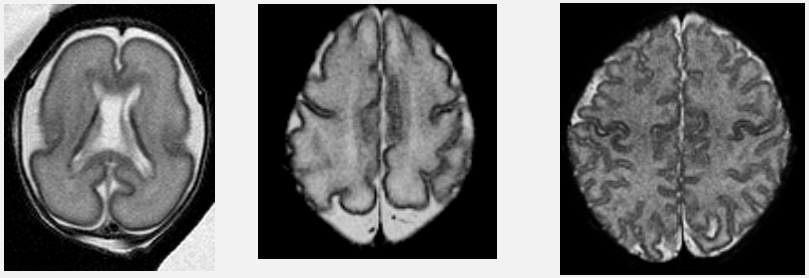
FUNCTION



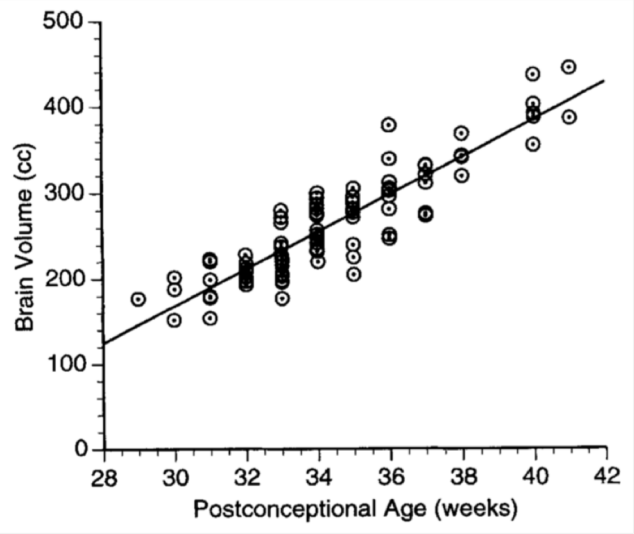


f-MRI

Brain growth & cortical development

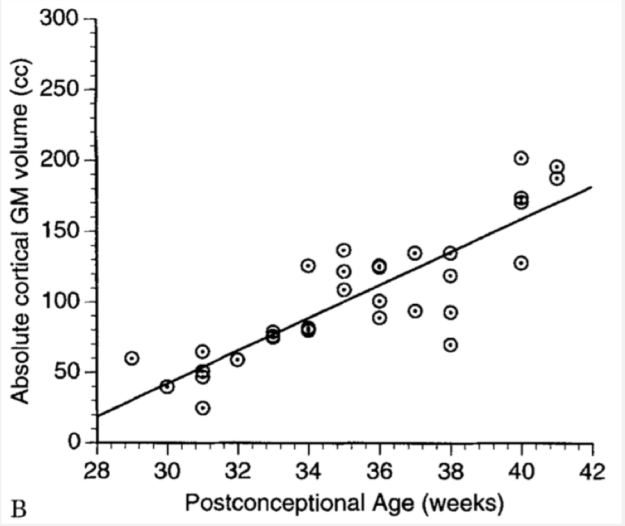


T2-weighted MR

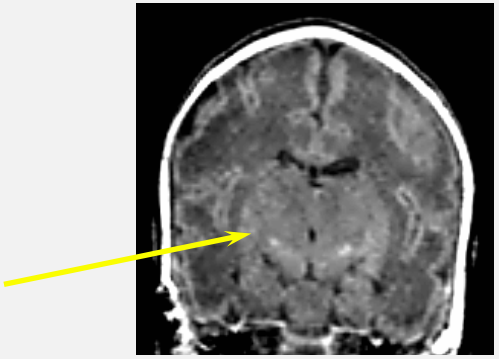


- Twofold increase in total brain volume
- Fourfold increase in absolute cortical gray matter volume

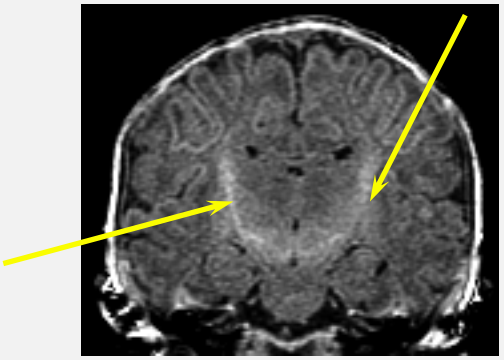
Hüppi, PS et al Ann Neurol 1998



Myelination
("birth" – years postnatal)

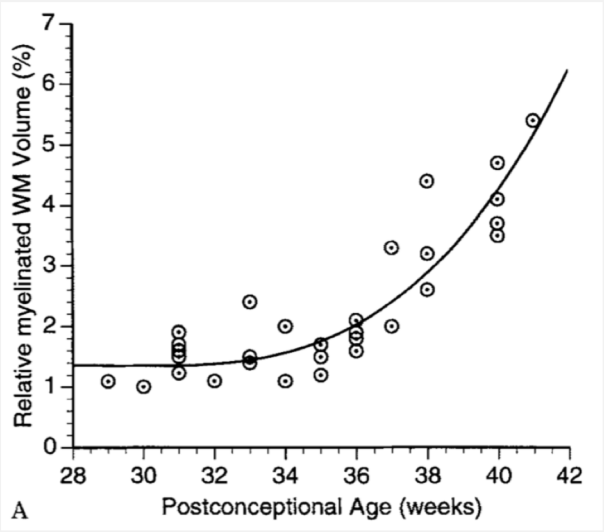


31 wks



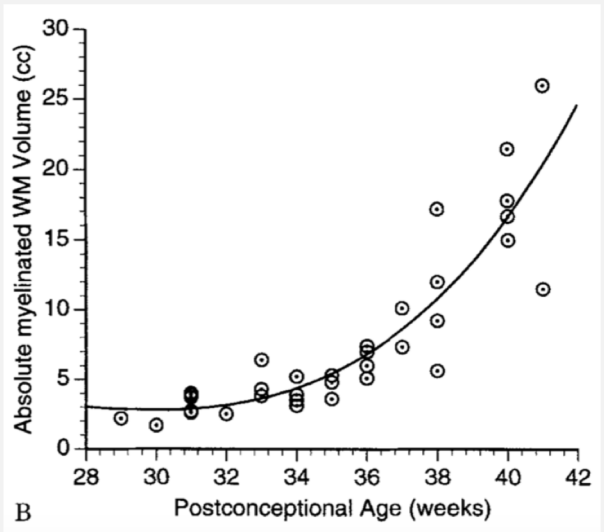
T1-weighted MR

40 wks



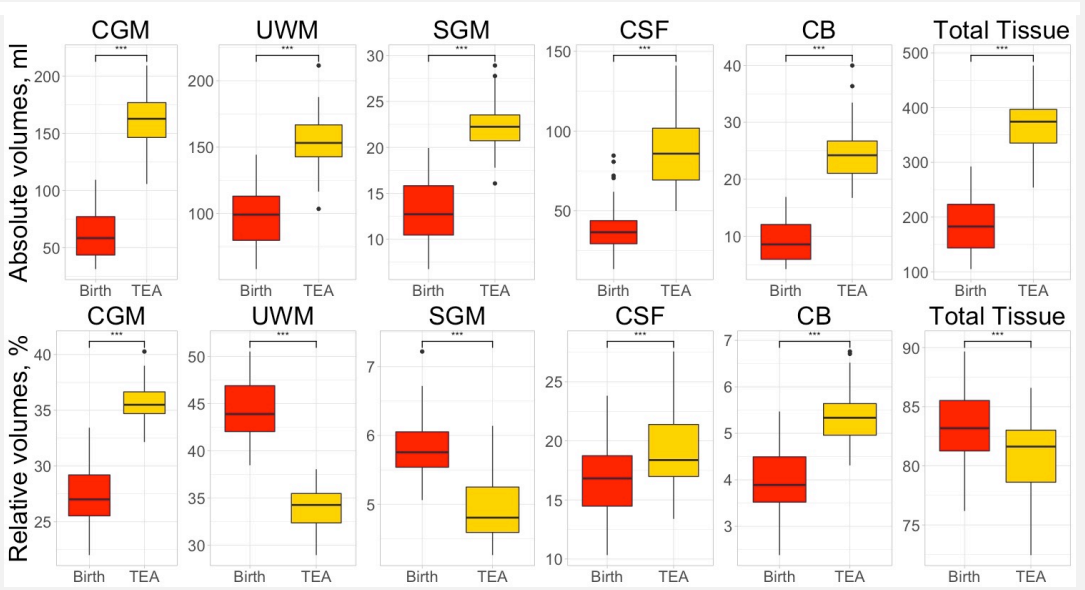
- Fivefold increase in absolute myelinated white matter volume

Hüppi, PS et al Ann Neurol 1998



Longitudinal study of neonatal brain tissue volumes in preterm infants
Brain development between birth and TEA

- Rapid increase of the relative volumes of CGM, CB and CSF with respect to total intracranial volume
- Decrease of relative volumes of UWM and SGM



Absolute and relative cerebral tissue volumes measured at birth and at TEA (expressed as medians with 25/75 centile box, 10th/90th centile error bars, and outliers)

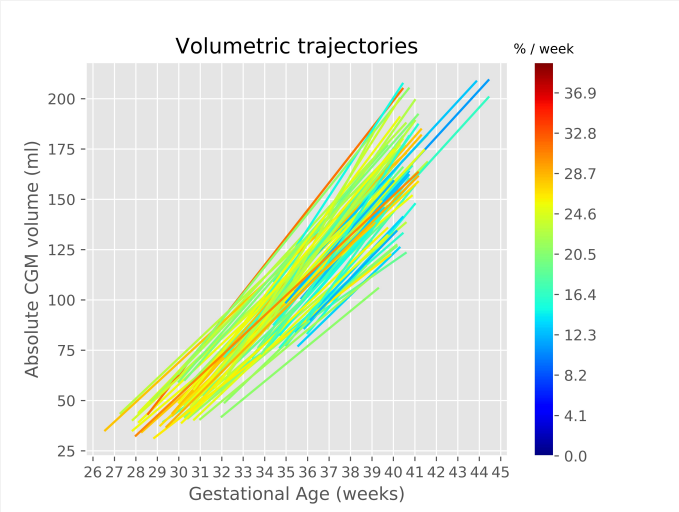
Gui L et al. Neuroimage 2018

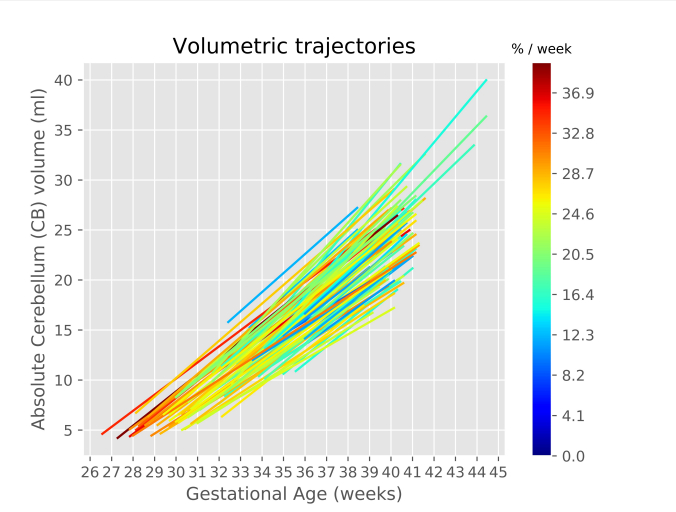
Longitudinal study of neonatal brain tissue volumes in preterm infants
Volumes growth rate between birth and TEA

- CGM and the CB were the fastest growing tissues between birth and TEA
- Lower GA at birth was associated with lower growth rates of CGM, CB and total tissue

Variable	Tissue type						
	CGM	**UWM**	**SGM**	**CB**	**CSF**	**Total tissue**	**IC**
Absolute GR*, mean (SD) in ml / week	11.94 (2.1)	6.51 (1.3)	1.05 (0.2)	1.76 (0.3)	5.77 (1.9)	21.44 (3)	27.22 (3.7)
Relative GR**, mean (SD) in % / week	21 (5)	7 (2)	9 (3)	22 (7)	17 (9)	12 (3)	13 (3)

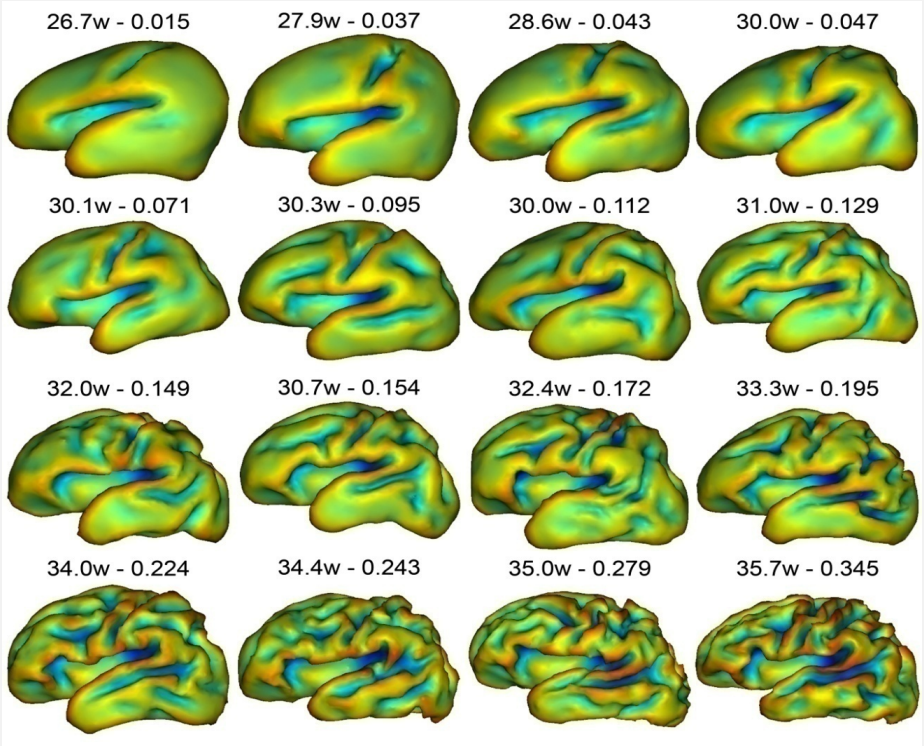
* Tissue absolute growth rates were computed as: (TEA volume – birth volume) / (GA TEA – GA birth)
** Tissue relative growth rates were computed as: absolute growth rates x 100 / birth volume.

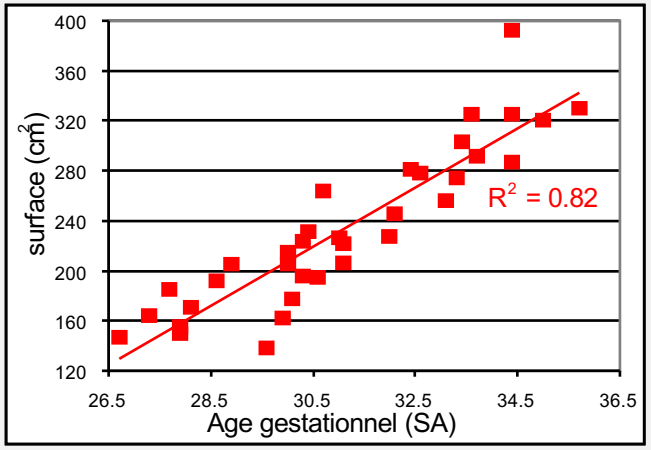




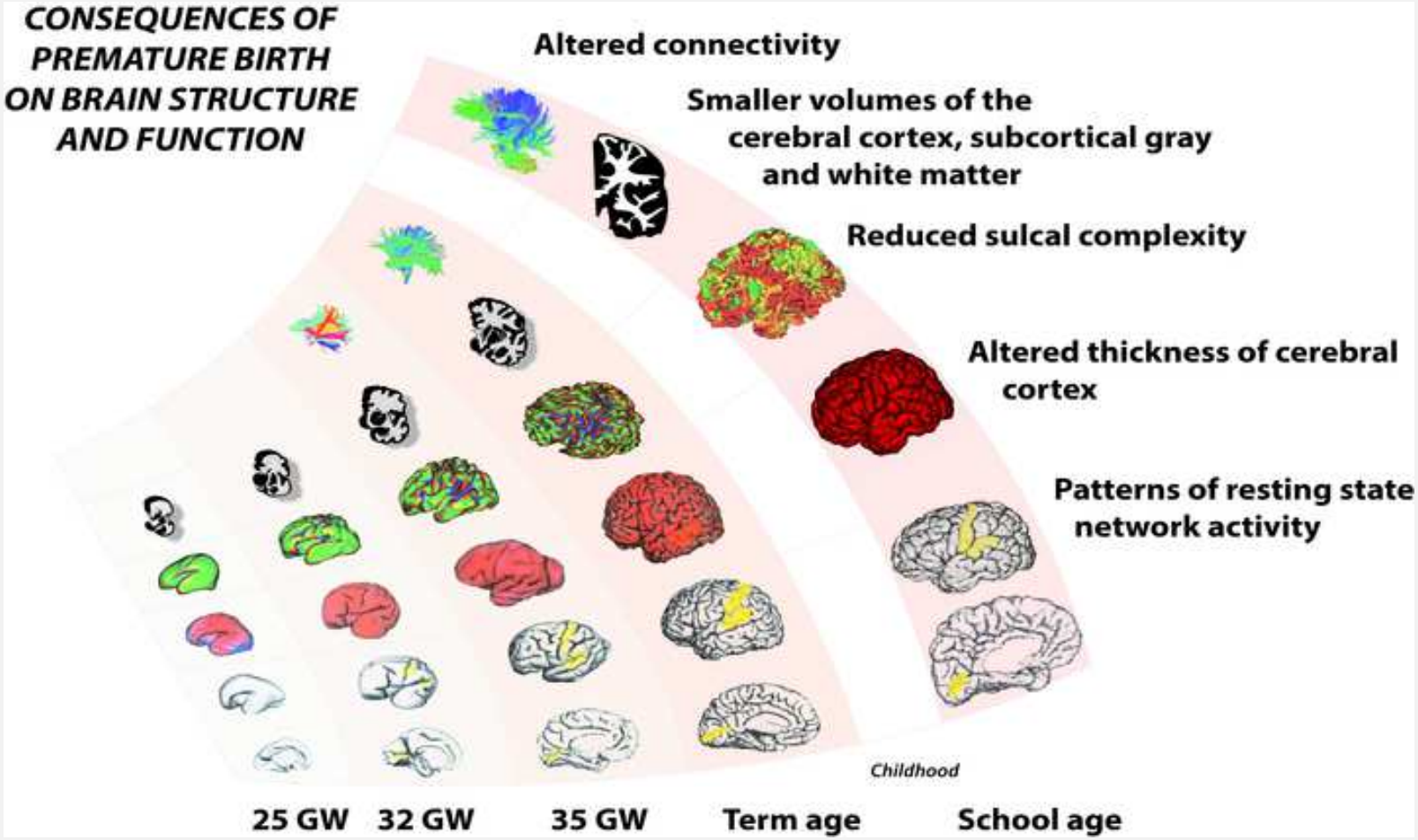
Individual volume growth trajectories from birth to TEA: (a) CGM volume; (b) CB volume; . Line colors indicate tissue growth rates relative to birth volumes (faster and slower growth are represented by red and blue colors, respectively)

Early cortical folding process in the preterm newborn brain





Dubois J et al. Cerebral cortex 2008; 18: 1444-54.


CONSEQUENCES OF PREMATURE BIRTH ON BRAIN STRUCTURE AND FUNCTION
Altered connectivity
Smaller volumes of the cerebral cortex, subcortical gray and white matter
Reduced sulcal complexity
Altered thickness of cerebral cortex
Patterns of resting state network activity
Childhood
25 GW
32 GW
35 GW
Term age
School age

Associations between neurodevelopmental outcomes and degree of white matter injury

Coronal T2-Weighted MRI

T1-weighted MRI

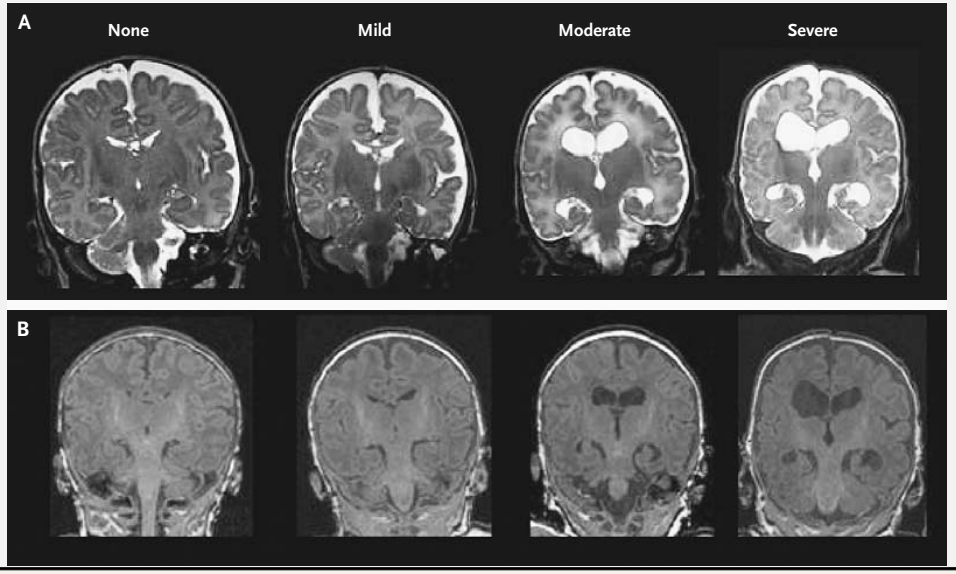


Table 2. Neurodevelopmental Outcomes at a Corrected Age of Two Years.*

Outcome Measure	White-Matter Abnormality				P Value
	None (N=47)	Mild (N=85)	Moderate (N=29)	Severe (N=6)	
MDI score†	92.50±15.63	85.32±15.46	77.93±19.16	69.67±25.30	<0.001
Severe cognitive delay (%)	7‡	15	30	50	0.008
PDI score†	94.63±13.45	90.73±12.75	80.11±18.18	56.17±23.50	<0.001
Severe motor delay (%)	4	5	26	67	<0.001
Cerebral palsy (%)	2§	6	24	67	<0.001
Neurosensory impairment (%)	4	9	21	50	0.003

Woodward LJ.
N engl j med 2006

MACROSTRUCTURE IN VIVO: 3D VOLUMETRIC MRI
Altered brain tissue volumes at Term-Equivalent Age

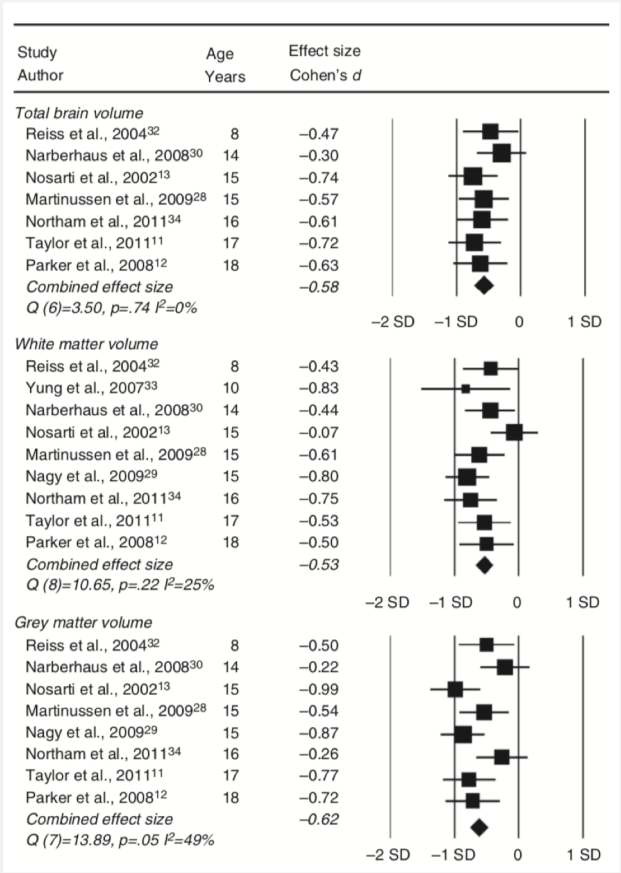
TABLE 2. Cerebral Tissue Volumes (Mean ± SD as absolute volume [mL] and relative to ICV) for All Premature (n = 119) and Term-Born (n = 21) Infants

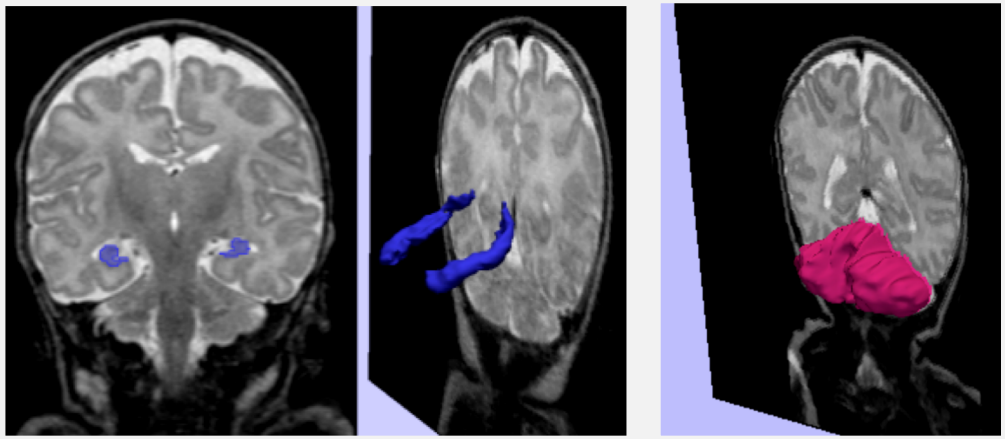
Tissue Class	Premature Infants (n = 119)	Term-Born Infants (n = 21)	P Value (t Test)
Cortical GM			
Absolute volume, mL	178 ± 41	227 ± 26	.001
% ICV	39.4 ± 7.6	48.2 ± 9.5	.01
Deep nuclear GM			
Absolute volume, mL	10.8 ± 4.2	13.8 ± 5.2	.02
% ICV	2.4 ± 1.0	2.9 ± 0.9	.09
Myelinated WM			
Absolute volume, mL	13.5 ± 5.8	20.8 ± 12	.02
% ICV	3.4 ± 1.1	4.2 ± 2.2	.05
Unmyelinated WM			
Absolute volume, mL	202 ± 41	206.5 ± 78	.9
% ICV	42.6 ± 5.9	41.4 ± 9.9	.9
Cerebral tissue, total			
Absolute volume, mL	406 ± 57	457 ± 67	.003
% ICV	89.9 ± 4.4	94.1 ± 3.1	.001
Cerebrospinal fluid			
Absolute volume, mL	45.6 ± 22.1	28.9 ± 16.8	.01
% ICV	10.1 ± 3.8	5.2 ± 3.0	.001

- White matter abnormalities can be detected by MRI in up to 50-70% of VPT infants
- Reduced cortical grey matter volumes
- Specific loss of volume in hippocampus, basal ganglia and cerebellum at TEA

Inder, et al. 2003; Miller, et al. 2005 ; Ment, et al 2009
Padilla, et al. 2014

MACROSTRUCTURE IN VIVO: 3D VOLUMETRIC MRI
ALTERED BRAIN TISSUE VOLUMES IN CHILDHOOD AND ADOLESCENCE





- Persistent reduction in white and grey matter volumes, as well as in volumes of thalamus, caudate nucleus, corpus callosum, cerebellum, hippocampus, amygdala, throughout childhood and adolescence

de Kieviet, Developmental Medicine & Child Neurology 2012
Nosarti, Early human development 2013

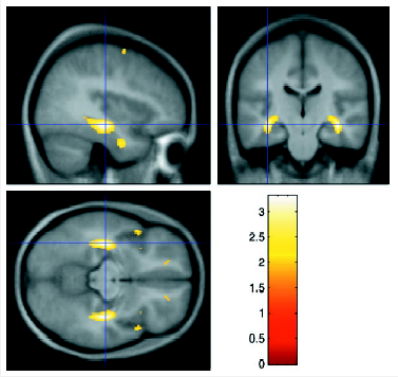
Associations between neurodevelopmental outcomes and reduced global and regional tissue volumes

Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: A systematic review

K. Keunen, K. J. Kersbergen, F. Groenendaal, I. Isgum, L. S. de Vries & M. J. N. L. Benders

To cite this article: K. Keunen, K. J. Kersbergen, F. Groenendaal, I. Isgum, L. S. de Vries & M. J. N. L. Benders (2012) Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: A systematic review, The Journal of Maternal-Fetal & Neonatal Medicine, 25:sup1, 89-100, DOI: 10.3109/14767058.2012.664343

To link to this article: https://doi.org/10.3109/14767058.2012.664343



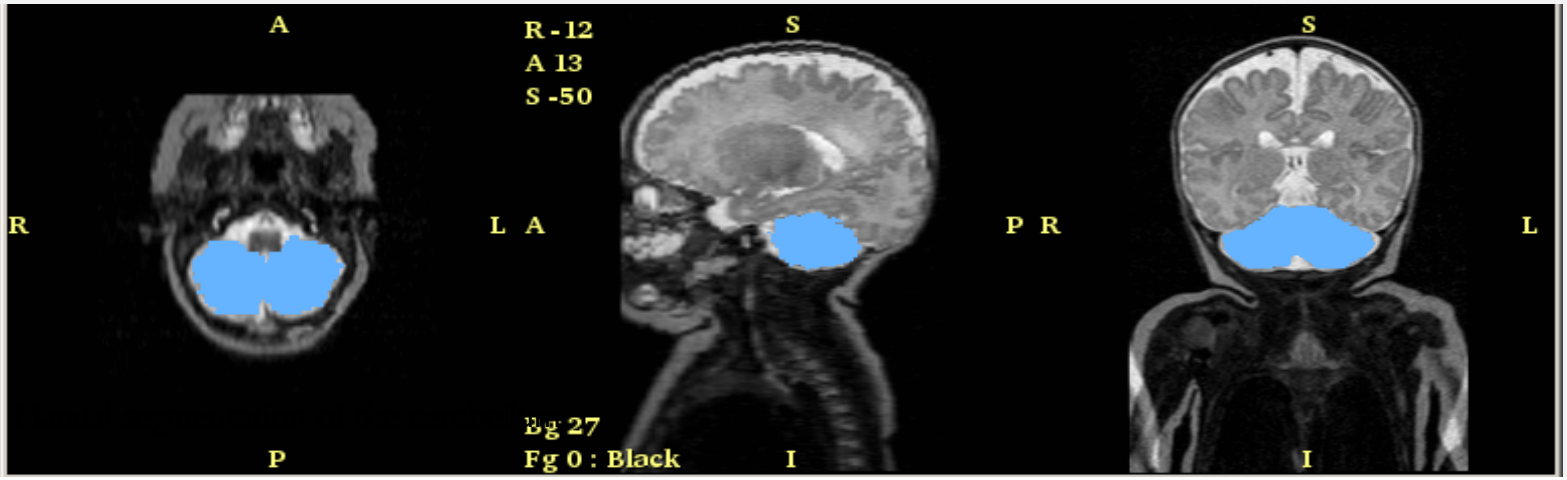
*

- Brain structure abnormalities associated with the full spectrum of behavior and neurodeveloppmental outcomes in the VPT population
- Brain tissue volume reductions was shown to explain up to 20-40% of the IQ and educational outcome differences between EPT and control adolescents
- Grey matter volume reduction in the dorsal prefrontal cortex specifically associated with attention/hyperactivity problems from age 4 to 9 years
- * Hippocampal volume reduction has been associated with lower IQ and everyday memory deficits in PT born children
- *Isaacs, et al 2004,Isaacs et al. 2000; Bora 2014; Limperopoulos 2014*

Vulnerability of the cerebellum

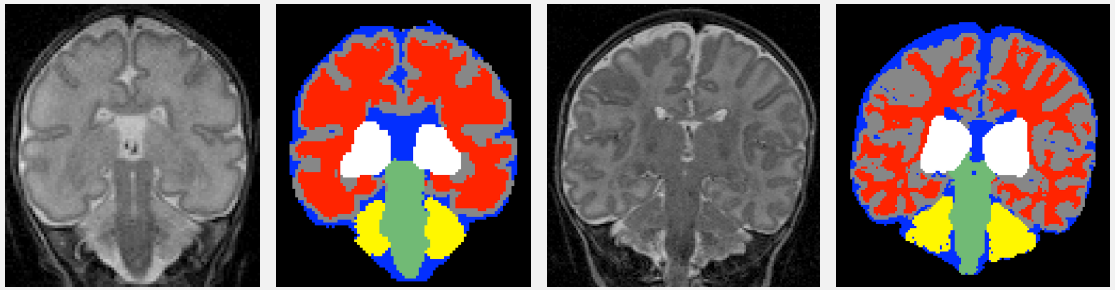
- Reduction in cerebellar volume in the newborn period in VPT compared with term-born controls (Limperopoulos, et al. 2005; Spittle, et al. 2010)
- Important role of the CB in the development of motor control, coordination of movements and posture, but also for cognitive, behavioral and social functions
- Persistent significant reduction of the cerebellum volume in VPT adolescents which was significantly associated with lower cognitive scores in several domains (Allin, et al. 2008; Peterson, et al. 2000)

[3] SK Warfield et al, Medical Image Analysis 2000; 4: 43-55



Longitudinal study of neonatal brain tissue volumes in preterm infants and their ability to predict neurodevelopmental outcome

- Volumetric MRI data of 84 PT infants born between 26 and 36 weeks GA (mean age 30.16 ± 2.56 wks) were acquired at birth and at TEA. Volume growth rate between birth and TEA was calculated.
- Neurodevelopmental outcome was assessed at 24 months by the BSID II (MDI and PDI scores) and at 5 years of age by K-ABC (CMP).

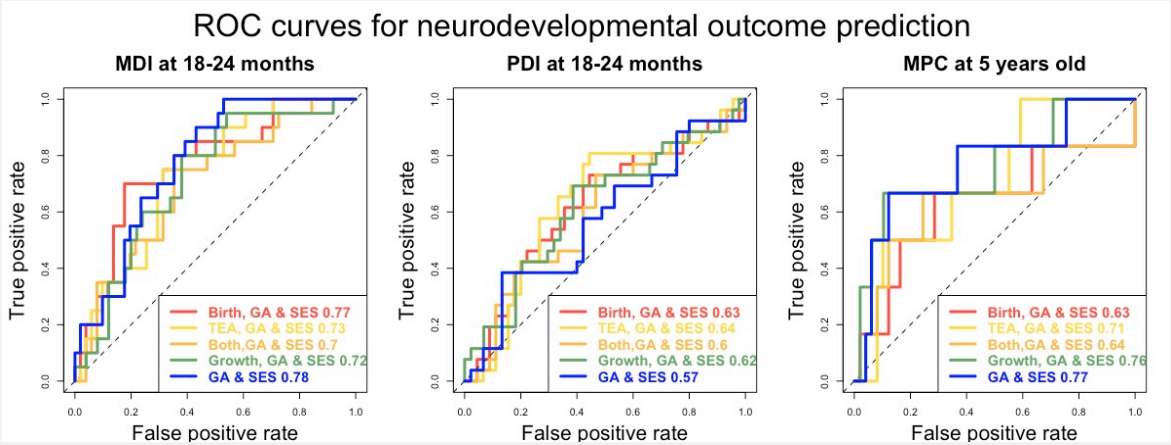


(a) (b) (c) (d)

Automatic segmentation of longitudinal T2-weighted images acquired **at birth** (a, b, 30 4/7 GW) and **TEA** (c, d, 41 3/7 GW) into CGM (gray), WM (red), SGM (white), CB (yellow), brainstem (green), and CSF (blue). *Gui L et al. 2012*

Gui L et al. Neuroimage 2018

Longitudinal study of neonatal brain tissue volumes in preterm infants and their ability to predict neurodevelopmental outcome



The figure presents the ROC curves of the LDA classification of the children into two classes: those with outcome scores < 85 and those with outcome scores ≥ 85 at 18-24 months and 5 years of age using the four sets of birth weight normalized features, as well as the GA at birth and the SES.

- **Cognitive outcomes** (MDI scores) at 18-24 months and at 5 years of age (MPC scores) were **predicted** with highest AUC by the LDA based on **GA and SES** (AUC = 0.78 for MDI and AUC = 0.77 for MPC).
- **Motor outcome** (PDI scores) at 18-24 months was **predicted** with the highest AUC obtained by combining **GA and SES with brain volumes at TEA**

Parental SES was found to be the major determinant of the prediction of cognitive outcome

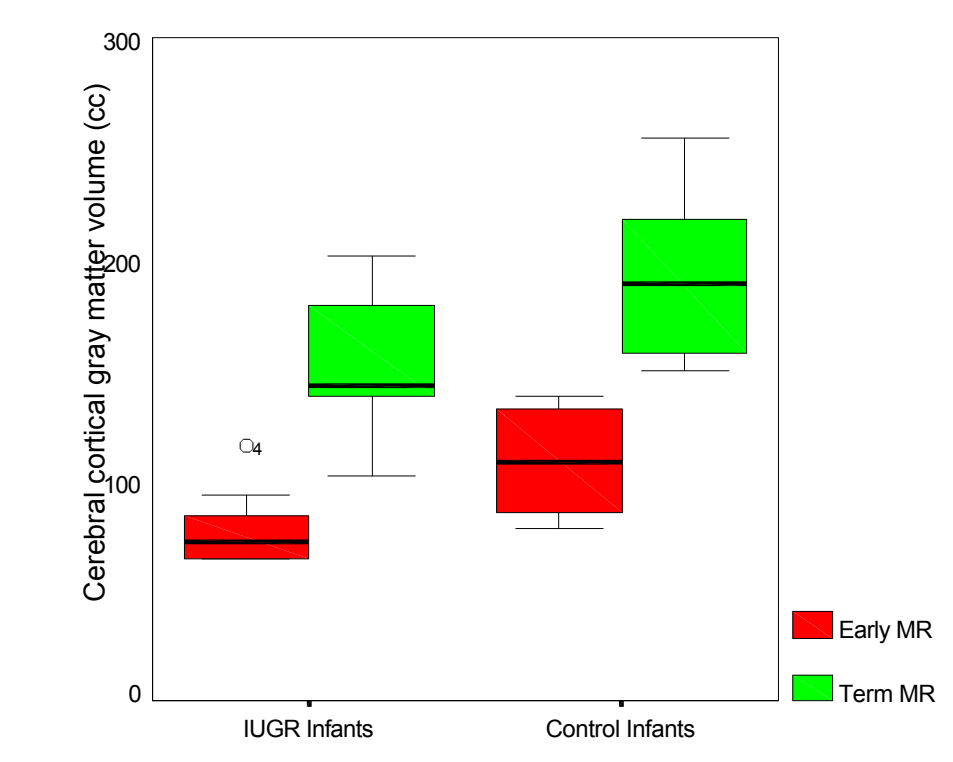
Gui L et al. Neuroimage 2018

Extreme prematurity vs moderate prematurity and IUGR

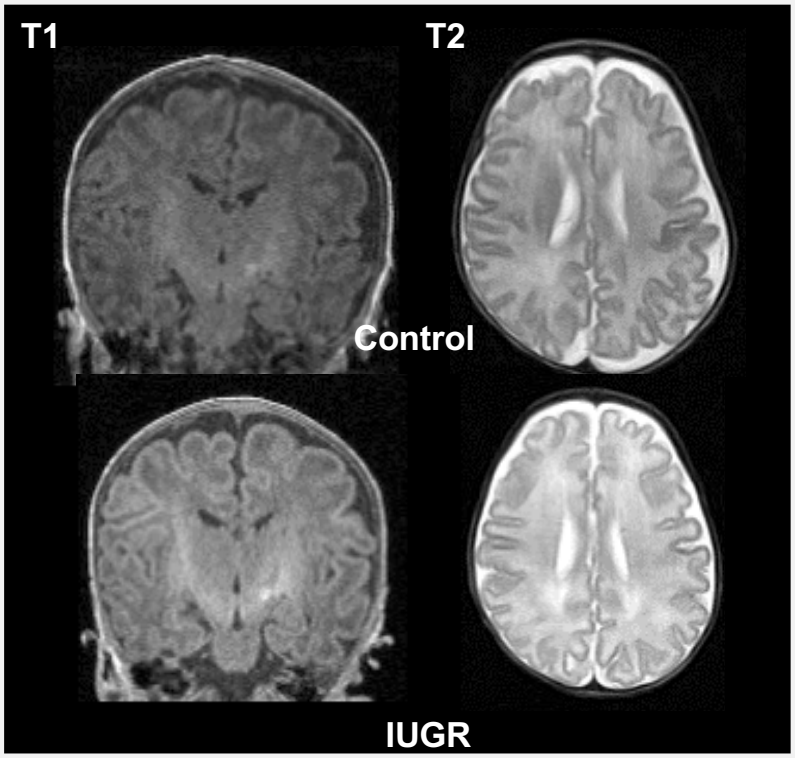
	AGA	M-SGA	S-SGA	P-value
24-28 weeks				
Cognitive deficiency	38.2 %	32.1 %	37.5 %	0.85
Inattention-Hyperactivity symptoms	21.7 %	21.2 %	19.1 %	0.96
School difficulties	33.2 %	44.8 %	35.3 %	.43
29-32 weeks				
Cognitive deficiency	28.7 %	41 %	40 %	< .01
Inattention-Hyperactivity symptoms	15 %	15.7 %	23.5 %	.07
School difficulties	18.4 %	23.1 %	28 %	.04

GUELLEC et al PEDIATRICS 2011

Reduced cortical development in preterm infants with IUGR at birth and at TEA



Borradori Tolsa C et al. Pediatr Res 2004

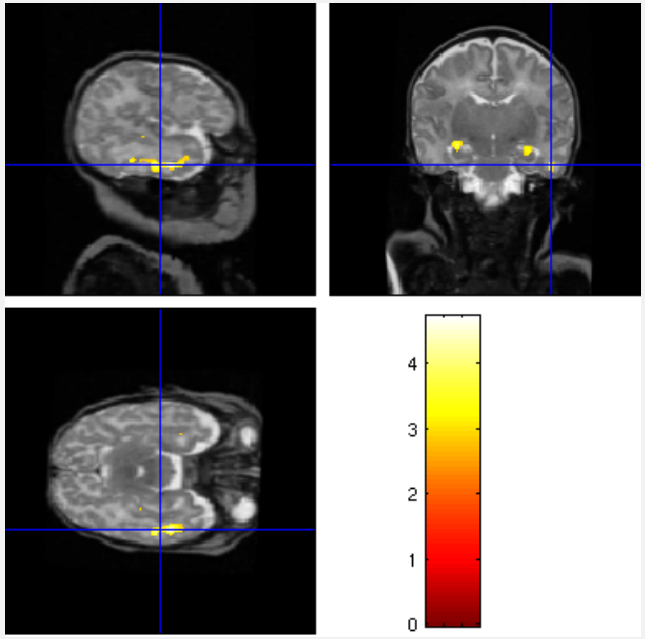


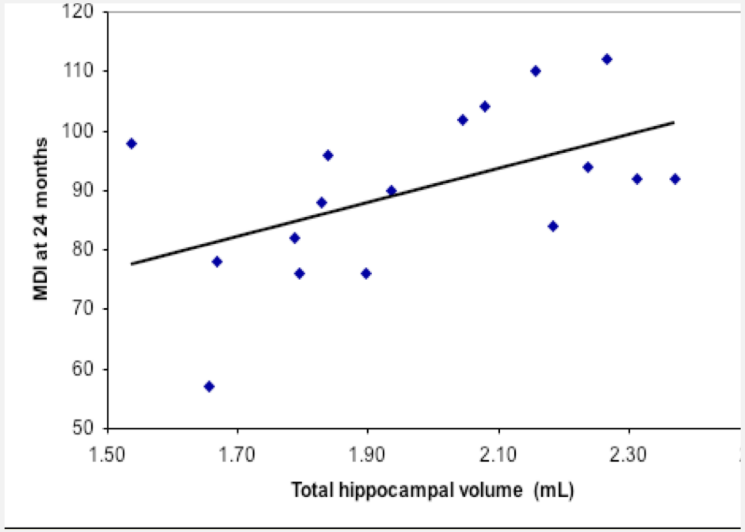
T1 and T2 MRI of the brain on coronal section

Intrauterine growth restriction affects the preterm infant's hippocampus

Advanced Image analysis
voxel-based-morphometry

Bilateral Hippocampus
Unilateral Temporal lobe

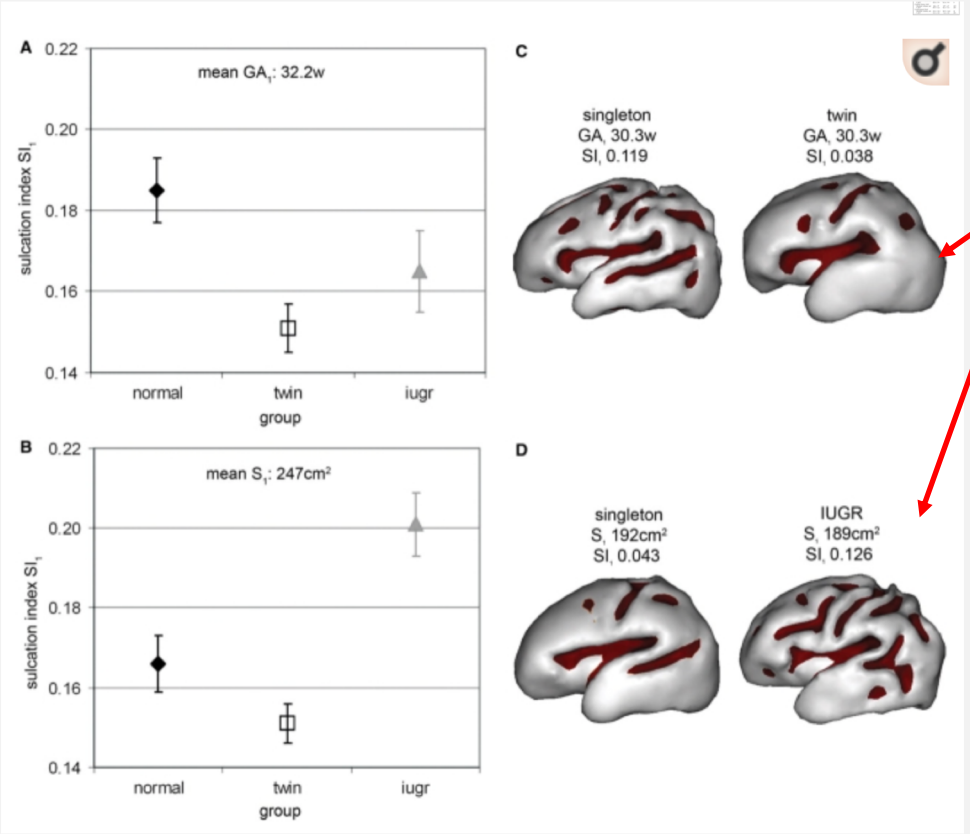




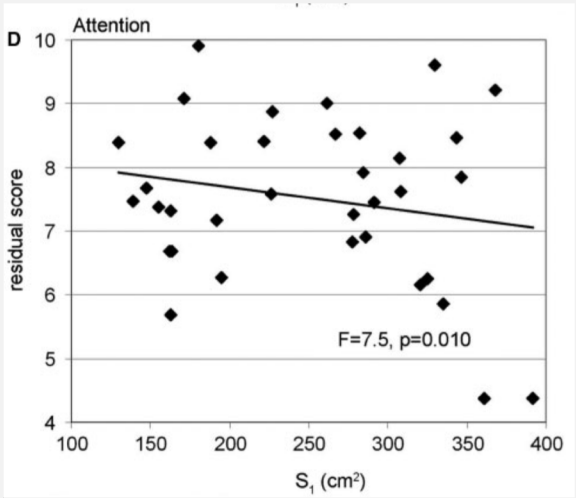
Scatterplot of the total hippocampal volume with the MDI at 24 mo corrected age with a best-fit regression line (MDI = 28.36 × hippocampal volume + 34.022; R^2 0.2665)

Lodygensky G et al. Pediatr Res 2008 ;63:438-443

Cortical maturation: effects of twinning and IUGR



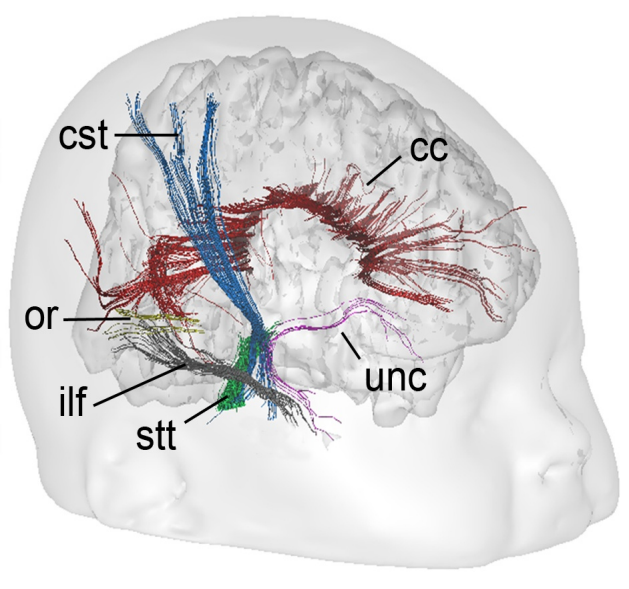
- Harmonious delay in twins
- Early impairment in IUGR
- newborn

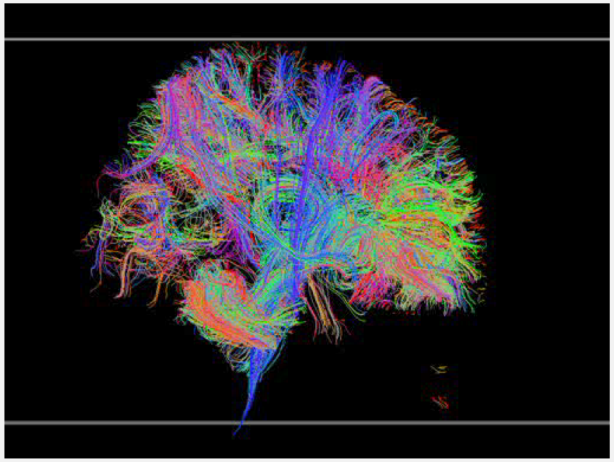


Sulcation index quantification among groups at birth

Dubois J et al. 2008

Diffusion tensor imaging : identification of major white matter fiber tracts in the newborn brain



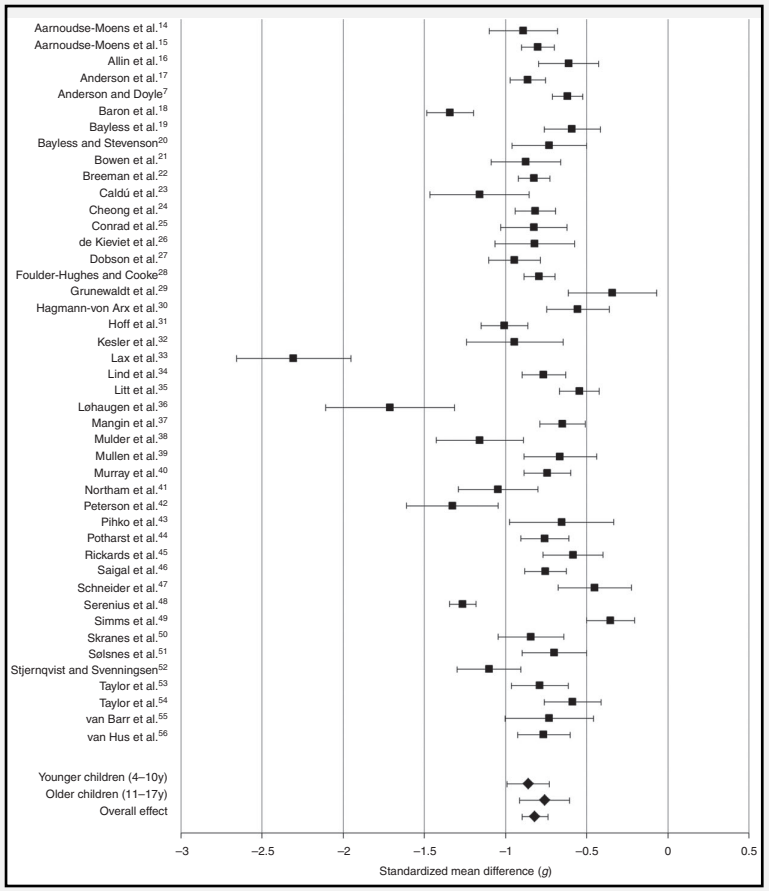


Hüppi PS & Dubois J. J Semin Fetal Neonatal Med 2006.

Cognitive outcomes in children and adolescents born VP
IQ

- 6163 children born VP and 5471 FT born control, from 60 studies
- VPT scored de 0,82 SD (95% [IC]: 0,74-0,90; p <0,001) lower on intelligence tests compared to their FT born peers

  corresponding to 12,3 IQ points
- No change in IQ scores for more recent cohorts
- Cognitive impairments in children born VP are deficits rather than delays



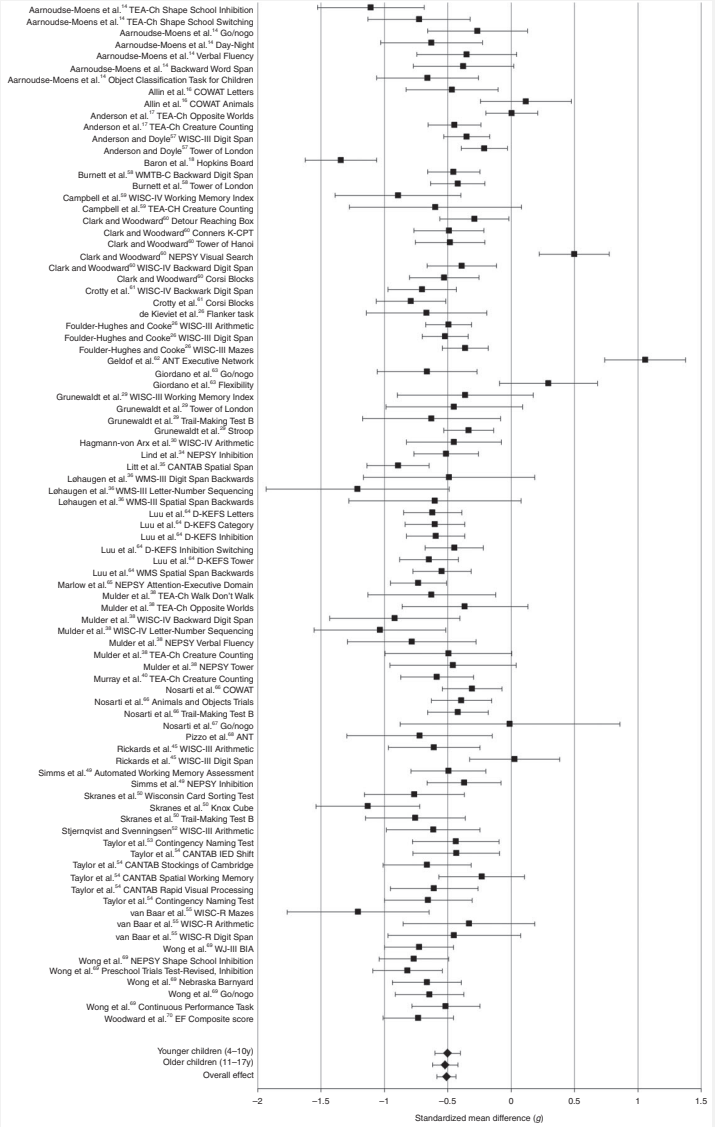
Brydges CR. *Dev Med Child Neurol* 2018

Cognitive outcomes in children and adolescents born VP
EF

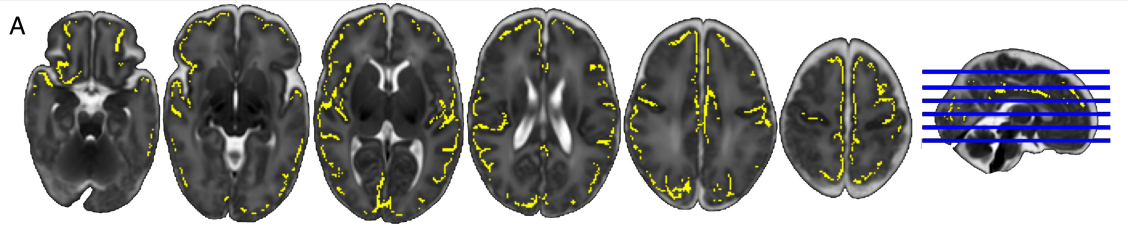
- VPT scored 0,51 SD (95% [IC]:0.74–0.90; p<0.001) lower on measures of EF compared to their FT born peers

- PT birth leads to widespread disruptions in the **frontoparietal network**, whose is associated with optimal cognitive development

Brydges CR. Cognitive outcomes in children and adolescents born very preterm: a meta-analysis. Dev Med Child Neurol 2018.



Thalamocortical connectivity at TEA predicts cognition in children born preterm



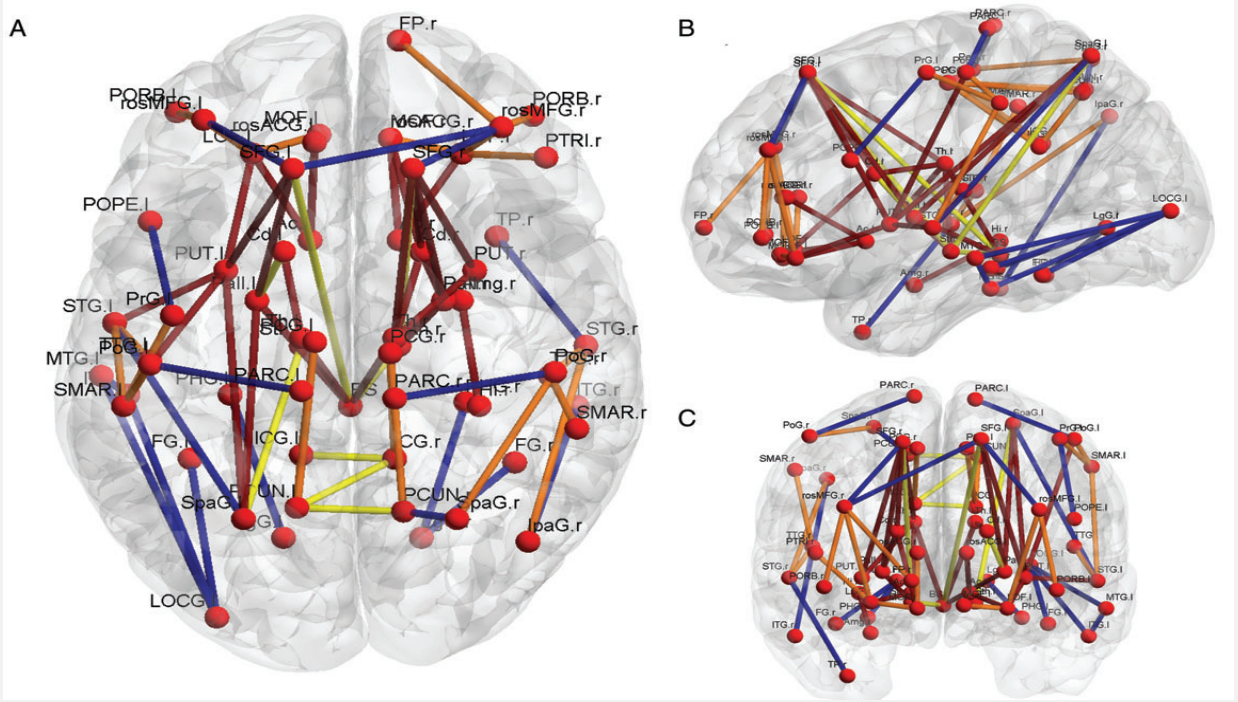
Thalamocortical connectivity and cognition. (A) Regions where thalamocortical connectivity at term equivalent age was correlated to cognition at 2 years, $P < 0.05$ adjusted for GA at birth, PMA at scan, and parental socioeconomic group, are shown in yellow.

- 57 PT infants <35 weeks GA with no evidence of focal abnormality underwent DTI-MRI at TEA and cognitive assessment (BSID III) at 2 years
- Cognitive scores at 2 years were correlated with structural connectivity between the thalamus and extensive cortical regions at TEA including,
  - inferior frontal lobe, frontal pole, supplementary motor cortex, operculum, anterior and dorsal cingulum, superior parietal cortex, supramarginal gyrus, somatosensory cortex, motor cortex, superior temporal lobe, medial temporal lobe, anterior temporal lobe, and insula
- **Mean thalamocortical connectivity across the whole cortex explained 11% of the variance in cognitive scores at 2 years**

Ball et al. Cerebral Cortex 2015

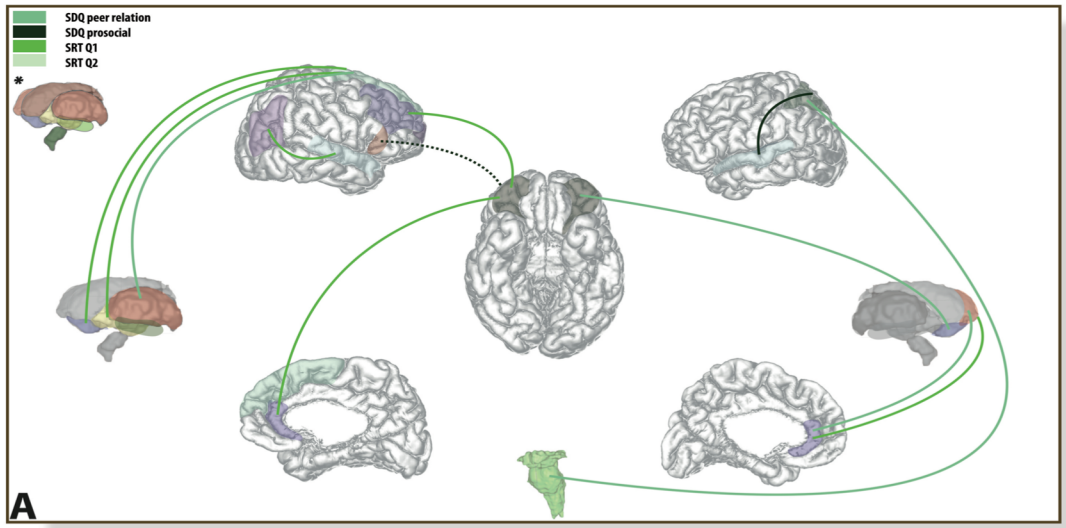
Brain connectivity in preterm children at 6y

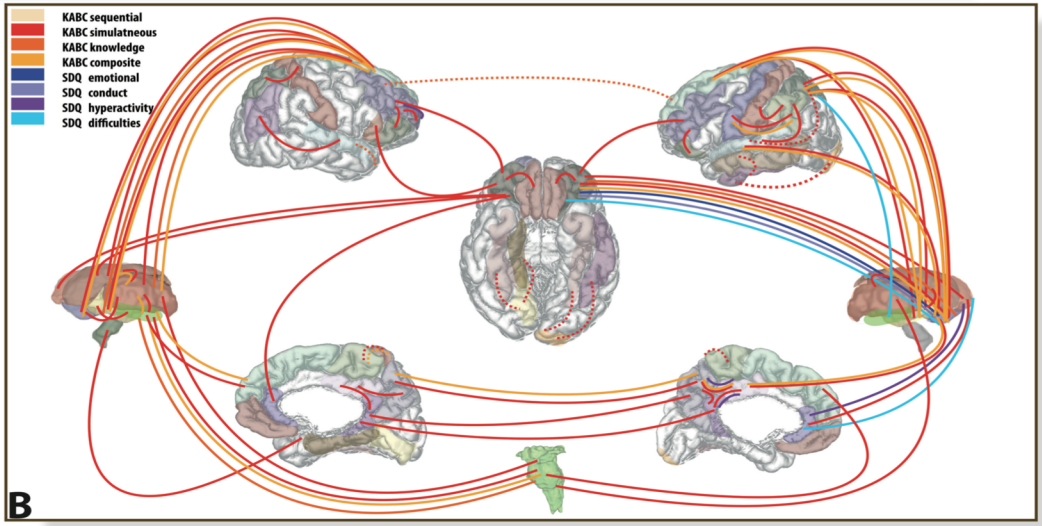
- the cortico-basal ganglia-thalamo-cortical loop connections
- intrahemispheric cortico-cortical connections
- brainstem, subthalamic, and callosal connections
- intrahemispheric cortico-cortical connections



Projection to axial (A), sagital(B) and coronal (C) plane of connections showing statistically significant FAw-SC decrease (EP < controls: red, orange, yellow) or increase (EP > controls: blue) when compared to controls.

E Fischi et al. Cerebral cortex 2015





✓ **Schematic drawing of altered connections in EP subjects and correlations with socio-cognitive outcome at 6y**

A. Social reasoning skills, behaviour and peer problems

B. Higher cognitive skills

✓ In EPT at 6 y: connectivity alterations in the **prefrontal cortico-basal ganglia-thalamo-cortical network** linked with the level of their socio-cognitive performances

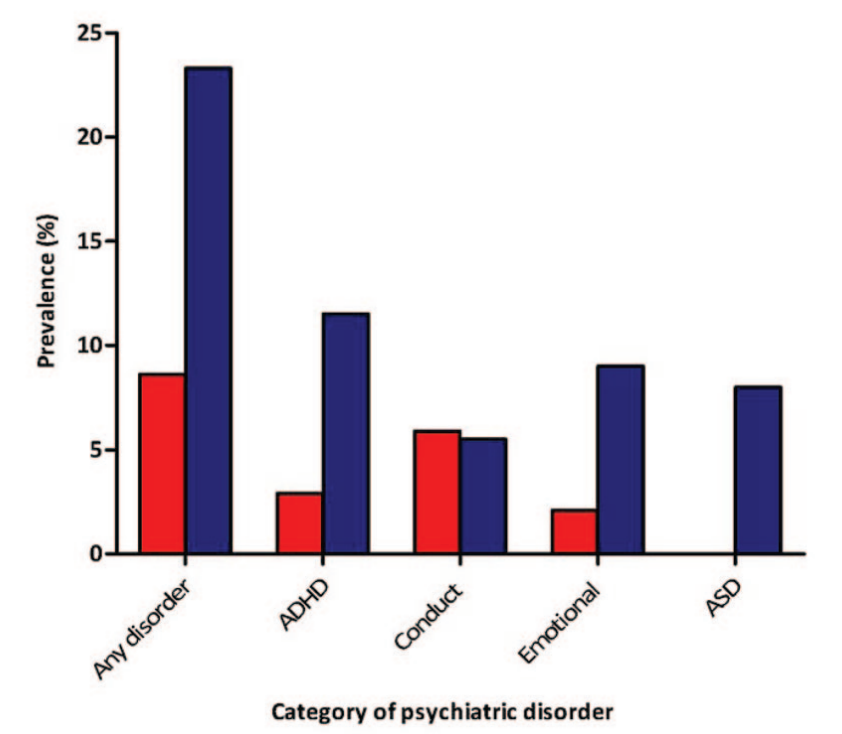
Elda Fischi et al. Cerebral cortex 2014

Behavioral and socio-emotional difficulties in VPT children

The preterm behavioral phenotype

- increased risk for symptoms and disorders associated with
  - Inattention
  - Anxiety
  - Social difficulties
- associated with altered brain development after preterm birth

Prevalence of psychiatric disorders in EPT at 11 y of age

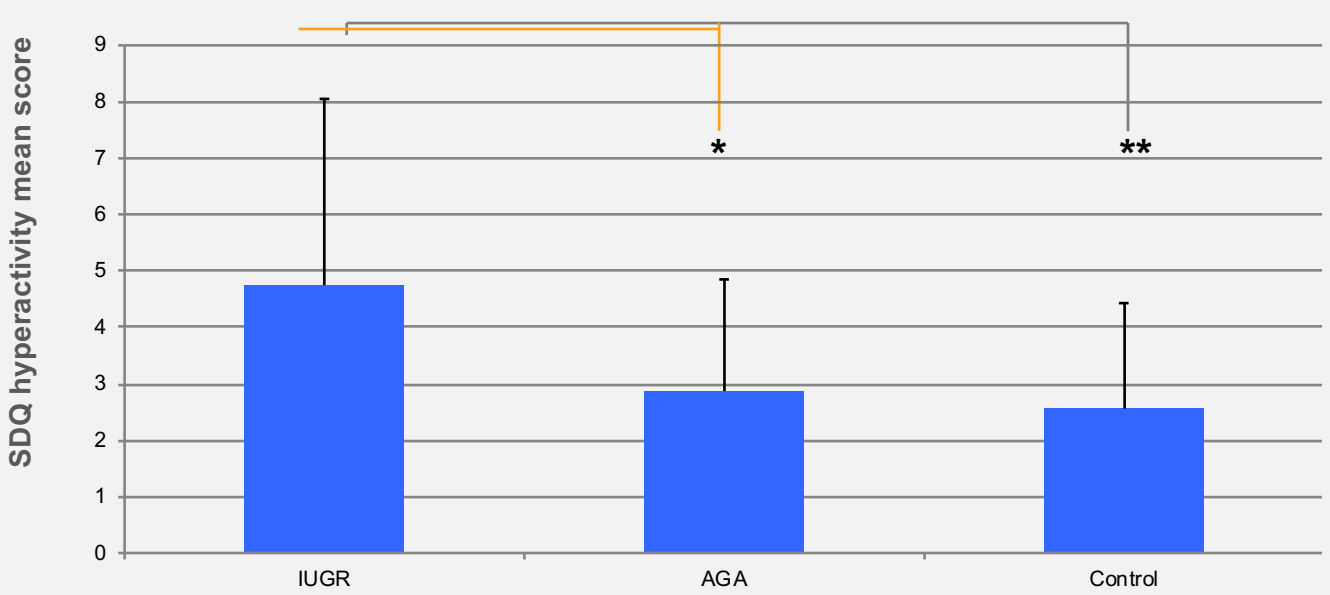


Johnson S & Marlow N Pediatr Res 2011

Neuroanatomical substrates of hyperactivity symptoms in IUGR preterm children at 6y of age : implications of the basal Ganglia

- ✓58 PT children (< 33 wks GA)
  - ✓22 were born with IUGR
  - ✓36 were born AGA
- ✓35 Term born control children

- ✓ PT with low BW had higher hyperactivity/inattention symptoms (SDQ)
  - ✓ Compared to term controls
  - ✓ Compared to AGA

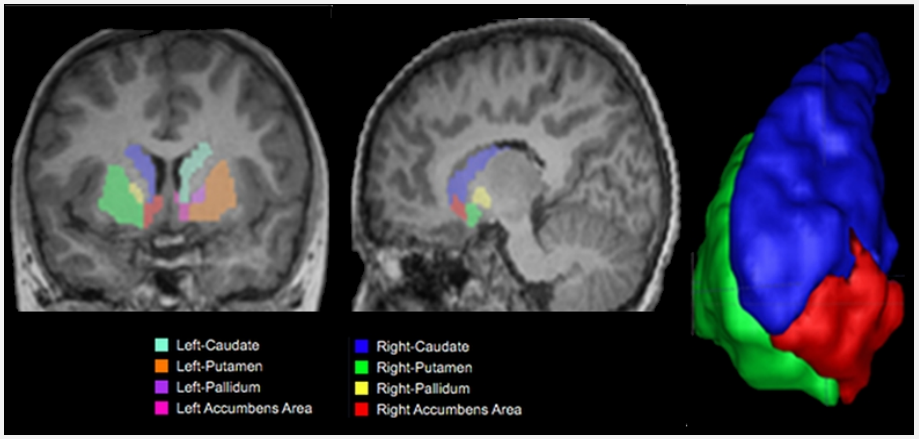


**p = 0.007/ ** p =0.003*

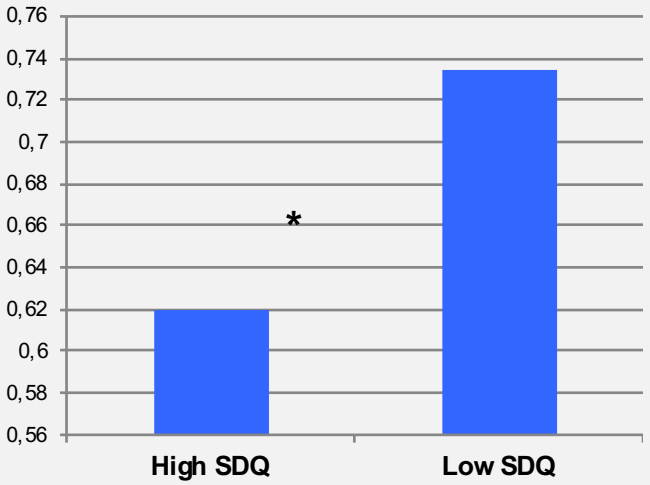
Hyperactivity/ inattention symptoms and nucleus Accumbens

PT born infants with high hyperactivity/inattention scores (>5) have lower right Nucleus Accumbens volume (*cm^3)* than those with low levels of hyperactivity /inattention scores (≤5)

(0.620 cm^3 ± 0.1, vs 0.735 cm^3 ± 0.1; *p = .015)*



MRI : post acquisition volumetric image analysis and automatic parcellation of P, GP, C, NA (freesurfer software)



Van Hanswijck De Jonge L et al. under revision

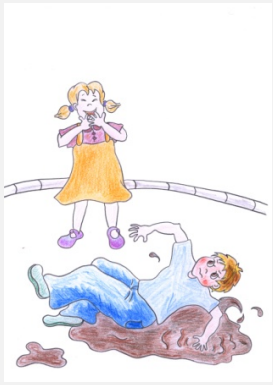
DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY SYSTEMATIC REVIEW

Social development of children born very preterm: a systematic review

KIRSTEN RITCHIE[1] | SAMUDRAGUPTA BORA[2] | LIANNE J WOODWARD[2]

1 Department of Psychology, University of Canterbury, Christchurch, New Zealand. **2** Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Correspondence to Kirsten Ritchie at Department of Psychology, University of Canterbury, Christchurch 8140, New Zealand. E-mail: kirsten.ritchie@pg.canterbury.ac.nz



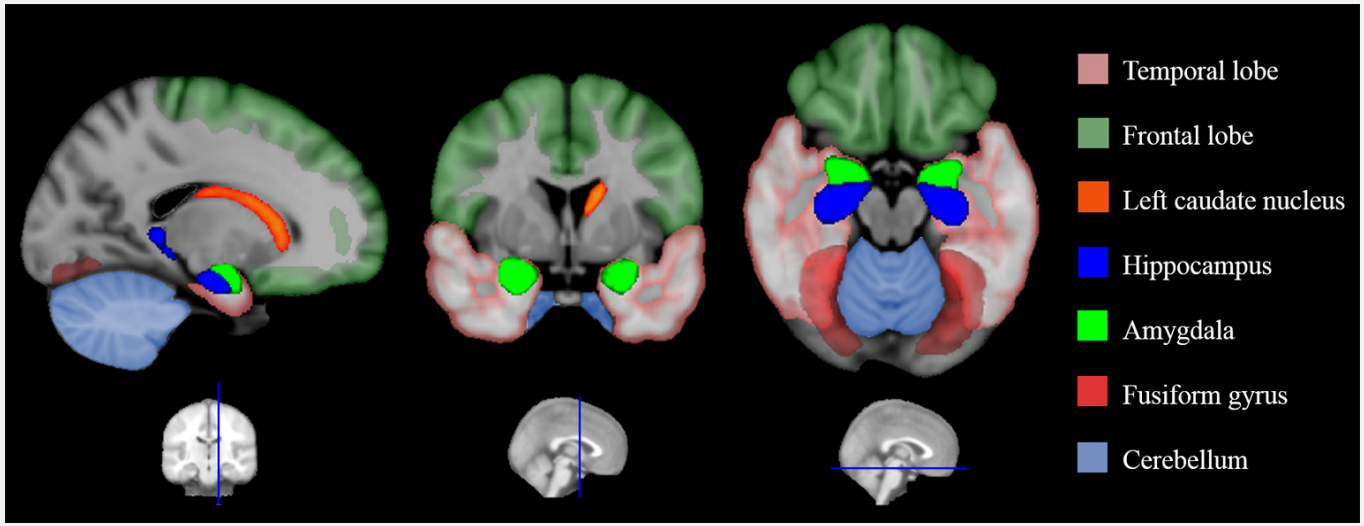
PUBLICATION DATA
Accepted for publication 16th March 2015.
Published online

ABBREVIATIONS

EPT	Extremely preterm
SDQ	Strengths and Difficulties Questionnaire
VPT	Very preterm

AIM To review systematically studies examining the development of social competence in children born very preterm (VPT) (gestation <33wks) and identify neonatal and family predictors.
METHOD Peer-reviewed original articles were extracted from PubMed and PsycINFO following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Selection criteria included children born VPT and comparison children born at term, sample born after 1990, and children assessed between 0 and 17 years on at least one measure of social competence spanning social adjustment, performance, and/or social skills.
RESULTS Twenty-three studies were included. Seven focused on social competence and another 16 examined social competence within a range of outcomes. Study quality was low. Limitations included reliance on single informant data, cross-sectional measurement, use of brief screening tools, absence of child or peer report, and no conceptual model. In terms of social adjustment, 16 out of 21 studies found children born VPT had more peer problems and social withdrawal. Findings of social performance were mixed, with some studies suggesting differences in prosocial behavior (4/14) and others not. Social skills were assessed in four studies and showed children born VPT had poorer skills than children born at term. Predictors of social competence included gestational age, neonatal brain abnormalities, and family socio-economic status.
INTERPRETATION Children born VPT have poorer social competence. These difficulties emerge early and persist throughout childhood.

Structural alterations in the social brain found in PT individuals



Montagna and Nosarti, Frontiers in Psychology 2016

Reduced volumes

- ✓ In the orbitofrontal cortex(Gimenez et al., 2006)
- ✓ of the fusiform gyrus (Nosarti et al., 2008)
- ✓ of the amygdala (Peterson et al., 2000)
- ✓ of the insula (Nosarti et al., 2008, 2014)
- ✓ of the hippocampus (Nosarti et al., 2002)

Altered amygdala development and fear processing in prematurely born infants

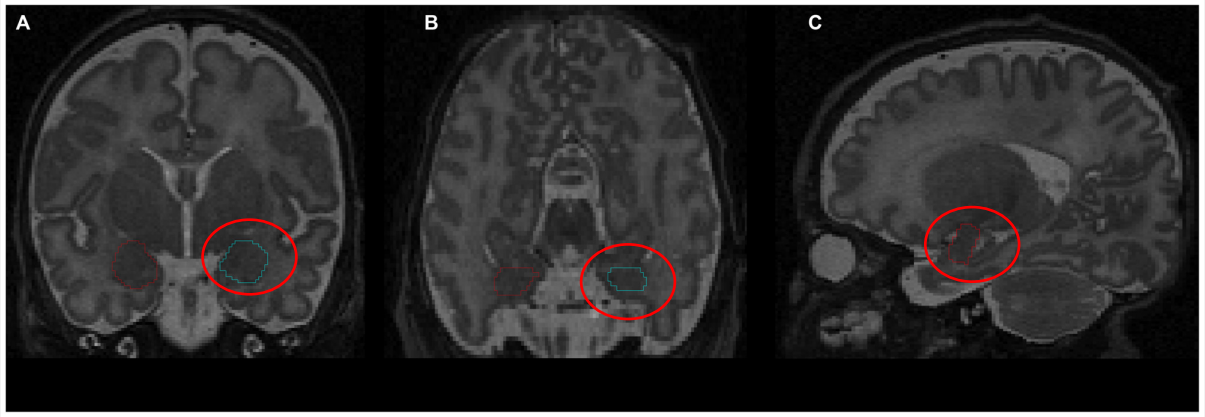
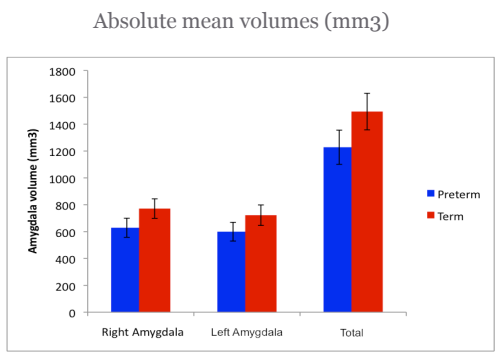


FIGURE 1 | Delineation of amygdala on T2-weighted magnetic resonance imaging (MRI) using the Amira software: (A) coronal view; (B) axial view; (C) sagittal view. Red contour—right amygdala, blue contour—left amygdala.



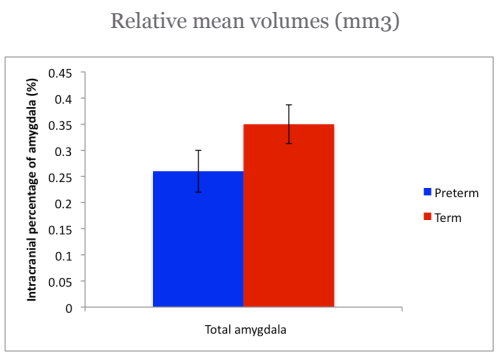


TABLE 4 | Whole brain segmentation volumes.

Volume (cm^3)	Preterm born infants ($n = 39$)	Term born infants ($n = 27$)	p-value[a]
CGM, mean (SD)	165.35 (18.13)	153.52 (17.58)	0.87
SGM, mean (SD)	21.09 (1.68)	19.68 (2.05)	0.53
WM, mean (SD)	143.26 (14.48)	149.97 (16.64)	<0.001
CSF, mean (SD)	98.68 (23.00)	69.44 (19.98)	<0.001

Cismaru et al. Frontiers in neuroanatomy 2016

Altered amygdala development and fear processing in prematurely born infants

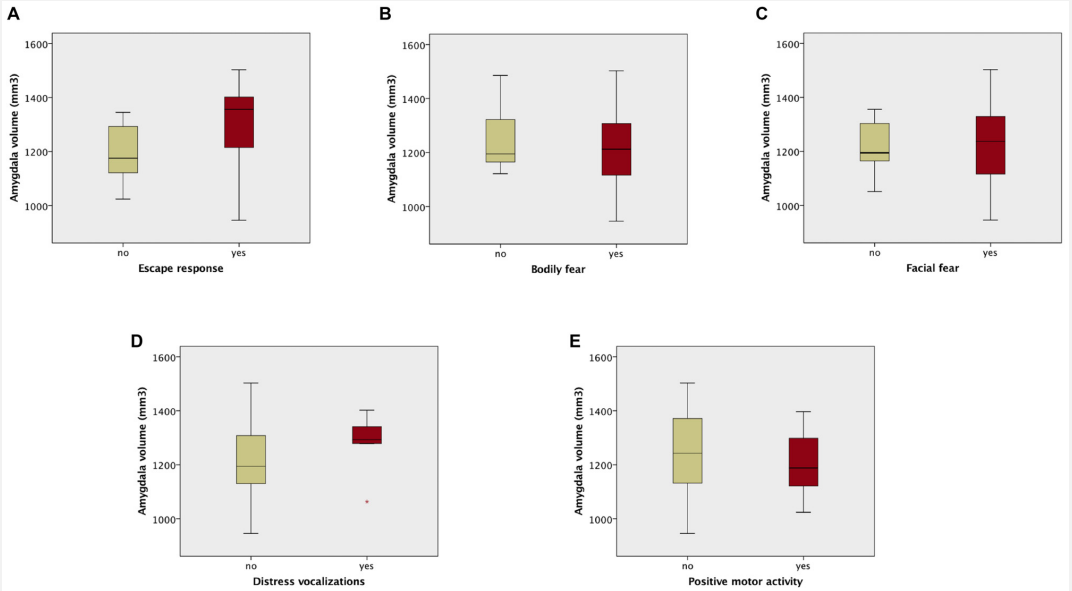


FIGURE 2 | Box plots of amygdala volumes dichotomized between infants who showed no fear reaction (composite score of corresponding variable = 0), and infants who showed any fear reaction (composite score of corresponding variable > 0) to the fearsome mechanical dog episode. Reaction/no reaction infants groups were created based on the following composite scores: **(A)** escape response; **(B)** bodily fear; **(C)** facial fear; **(D)** distress vocalizations; **(E)** positive motor activity.

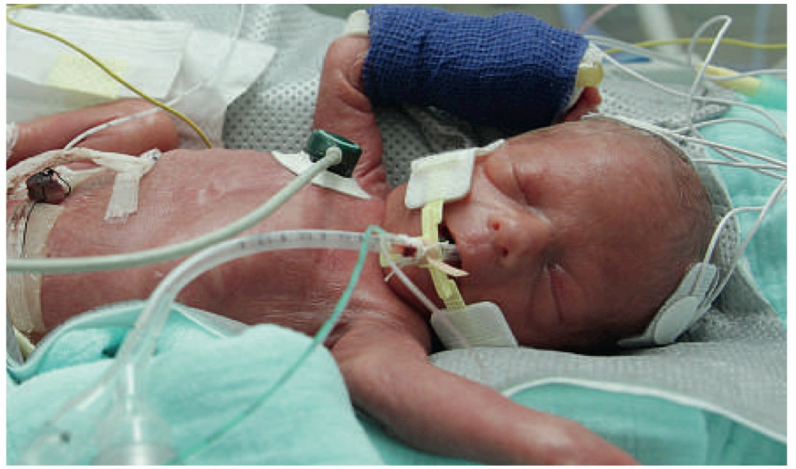
	Mean amygdala volume difference, mm^3 (95% CI)	*t*	df	*p*-value
Facial fear	−1.87 (−87.75–84.01)	−0.044	40	0.965
Distress vocalizations	58.12 (−67.59–183.84)	0.934	40	0.356
Bodily fear	−36.30 (−129.18–56.58)	−0.790	40	0.434
Escape response	120.97 (38.48–203.45)	2.964	40	**0.005**
Positive motor activity	−43.55 (−127.14–40.05)	−1.053	40	0.299

Amygdala volumes showed significant positive correlation with the **intensity of the escape response to a fearsome toy.**

Cismaru et al. Frontiers in Neuroanatomy 2016

The Neonatal Intensive Care Unit environment

- Preterm birth exposes newborn infants for weeks to months to various stressors, causing excessive stimulation affecting their growth and development
- NICU environment is noisy, chaotic
  - painful events
  - medical and nursing procedures
  - inappropriate auditory and visual stimuli
- In VPT/EPT infants, stressors can alter brain structure and function by influencing sensitive periods of brain development such as synaptogenesis and synapse elimination, and crucial cortical folding



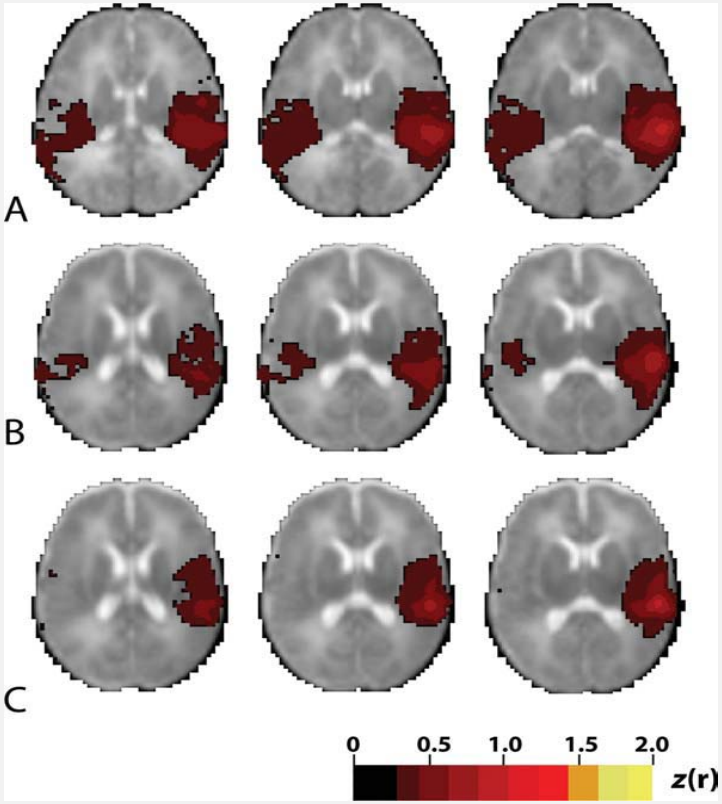
Neonatal Intensive Care Unit Stress Is Associated with Brain Development in Preterm Infants

Gillian C. Smith, BA,[1] Jordan Gutovich, BA,[1] Christopher Smyser, MD,[1,2]
Roberta Pineda, PhD, OTR/L,[1,3] Carol Newnham, BBsc, PhD,[4]
Tiong H. Tjoeng, MD, MPH,[1] Claudine Vavasseur, MD,[1] Michael Wallendorf, PhD,[5]
Jeffrey Neil, MD, PhD,[1,2,6] and Terrie Inder, MD, PhD[1,2,6]

Compared to term control infants (A) and low-stress infants (B)

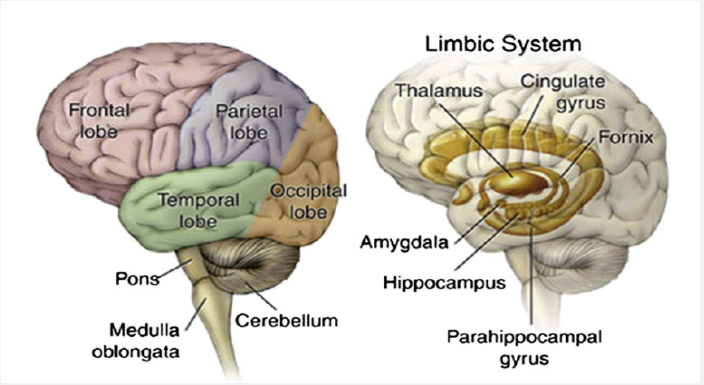
exposure to a greater number of stressors during the NICU hospitalisation (C)

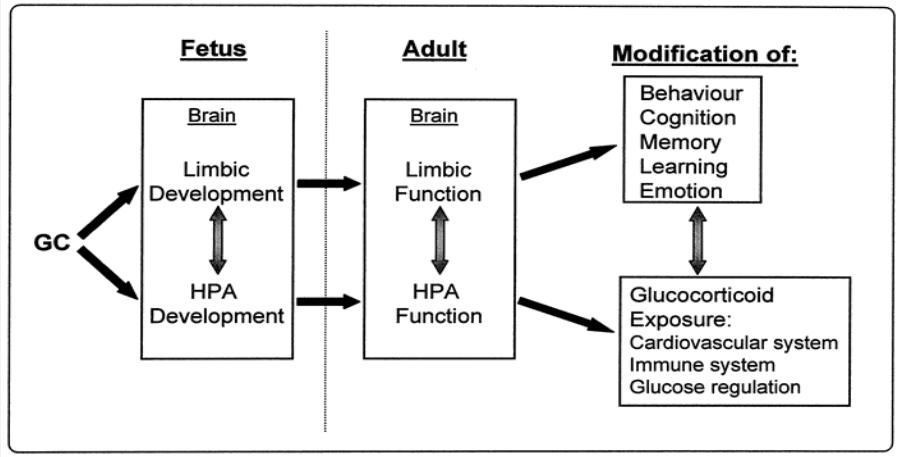
- was associated with
  - decreased frontal and parietal brain width,
  - altered functional connectivity in the temporal lobes,
- was correlated with abnormalities in motor behavior at TEA



Smith G et al. Ann neurol 2011

Developmental consequences of perinatal stress



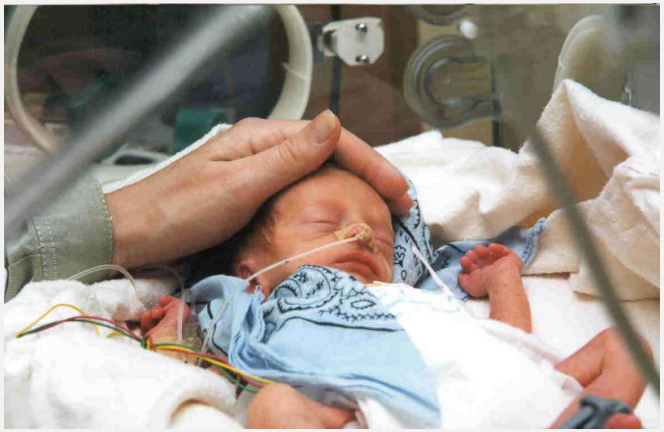


Regions of the limbic system, such as the hippocampus, amygdala, nucleus accumbens, PFC and OFC, and cingulate gyrus, play distinct roles in cognitive and emotional development and are affected by early stress/separation

Matthews SG Pediatr Res 2000

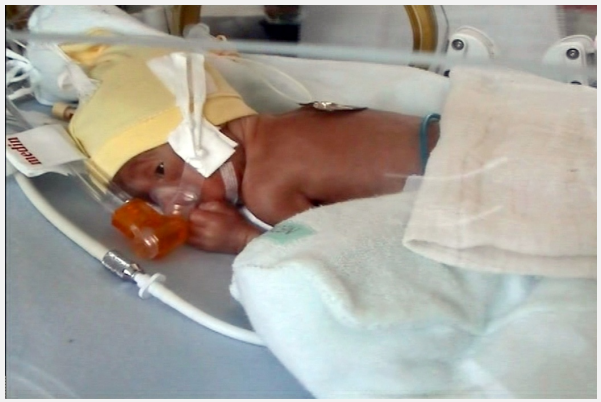
Stressors in the NICU

- Disruption of the biological and emotional caregiving bonding which generally occurs after birth
- The maturation of prefronto-limbic neuronal pathways that mediate essential affective and social regulatory functions is “experience dependent”
- After birth the infant’s affective experiences trigger the reorganization of synaptic circuits, which involves the pruning of rarely activated synapses within prefronto-limbic circuits in favour of those that are frequently activated during child–parent interactions
- Long periods of separations from parents during the stay in the NICU, may leave ‘scars’ in prefronto-limbic function



Developmental Care

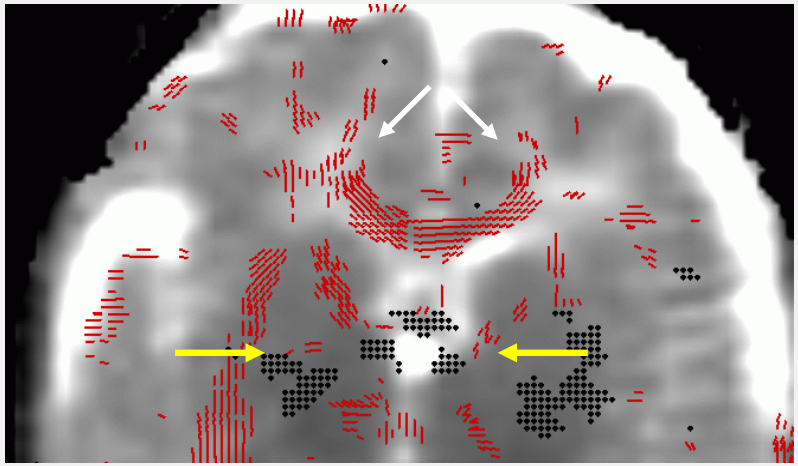
- Early preventive interventions are important
- Eight « principles of care » for newborns in the NICU include
  - 24-hours a day parents access
  - Pain management
  - Postural support
  - Skin-to-skin contact
  - Breast feeding
  - Sleep protection
  - Control of the noise levels of alarms and the intensity of light



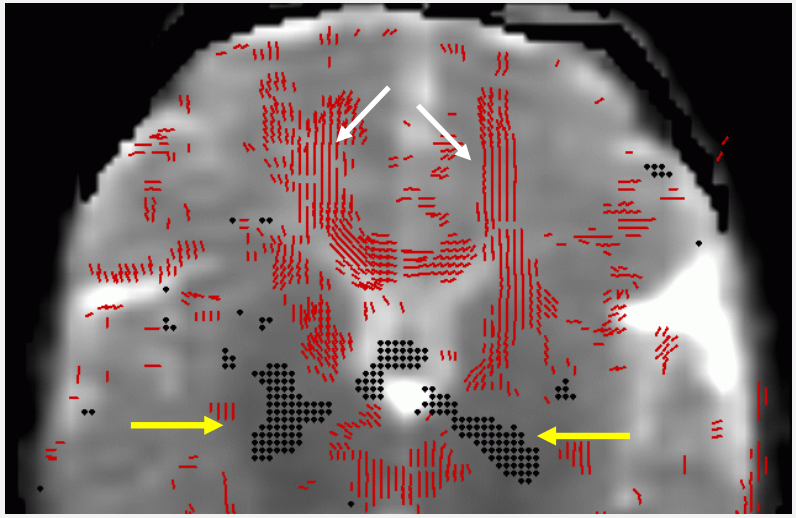
NIDCAP program guide, Als 1986. rev 2011 ; Roue, et al. 2017; Charpak et al 2017:; Cattaneo et al.2018

Developmental care and brain connectivity at TEA

Standard care



NIDCAP



Als et al. Pediatrics 2004

School-age effects of the newborn individualized developmental care and assessment program for preterm infants with intrauterine growth restriction: preliminary findings

Gloria McAnulty[1*†], Frank H Duffy[2†], Sandra Kosta[1†], Neil I Weisenfeld[3†], Simon K Warfield[3†], Samantha C Butler[1†], Moona Alidoost[1†], Jane Holmes Bernstein[1†], Richard Robertson[4†], David Zurakowski[5†] and Heidelise Als[1†]

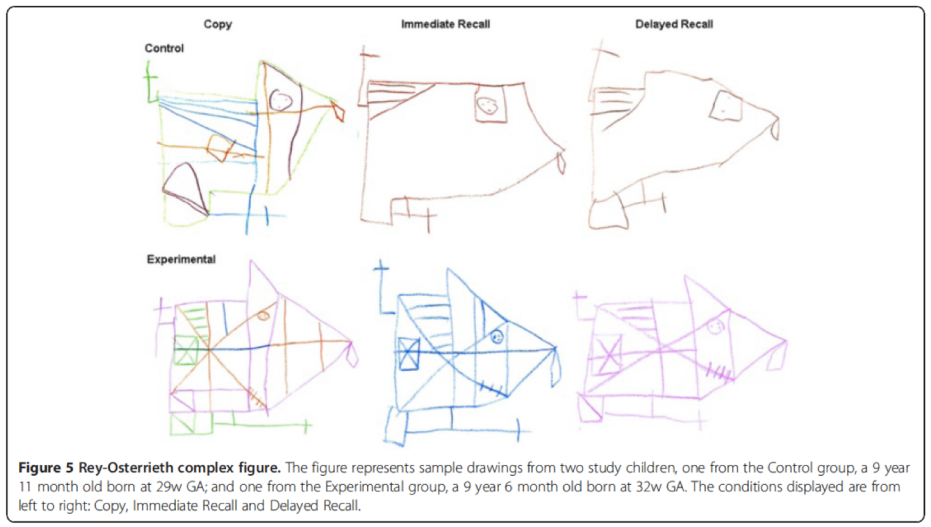


Figure 5 Rey-Osterrieth complex figure. The figure represents sample drawings from two study children, one from the Control group, a 9 year 11 month old born at 29w GA; and one from the Experimental group, a 9 year 6 month old born at 32w GA. The conditions displayed are from left to right: Copy, Immediate Recall and Delayed Recall.

Table 6 MRI tissue volumes

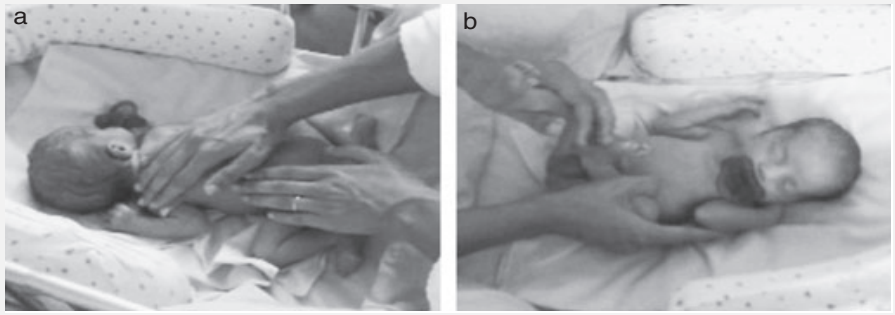
Variable	Control	Experimental	*p*
	(n = 11)	(n = 7)	
Right Cerebellum	4.91 (0.56)	5.31 (0.18)	0.05
Left Cerebellum	4.97 (0.36)	5.24 (0.18)	0.04
Total Cerebellum	9.88 (0.88)	10.55 (0.34)	0.04
Cerebellum + Vermis	10.65 (0.93)	11.38 (0.38)	0.04

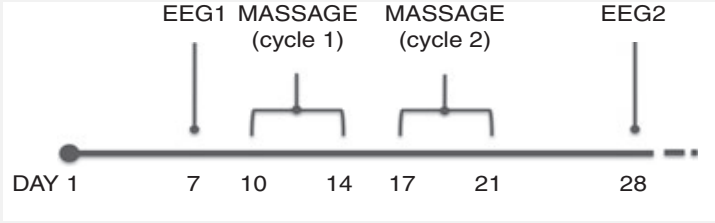
Results are means (SD). Statistical analysis used is Brown-Forsythe Univariate Analysis of Variance F*, two-tailed. MRI tissue volumes were measured in cubic millimeters, per structure. To control for ventricular size, all measures were expressed as a percentage of total parenchyma which is total brain tissue adjusted for the ventricles.

The results support the hypothesis that **NIDCAP in the NICU enhances aspects of executive function underlying visual-motor and memory functions**

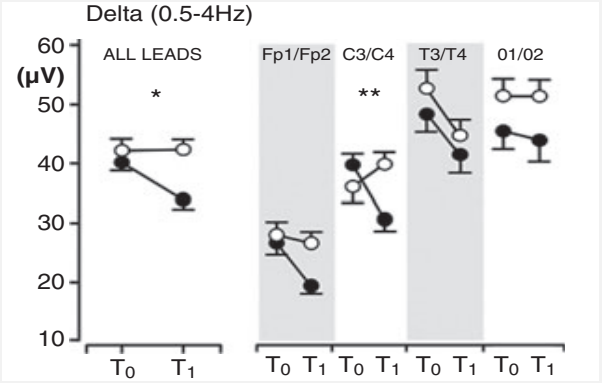
McAnulty et al. BMC Pediatrics 2013, 13:25

The effects of preterm infant massage on brain electrical activity





Massage intervention affects the maturation of brain electrical activity and **favours a process more similar to that observed in utero in term infants**



GUZZETTA et al. 2011

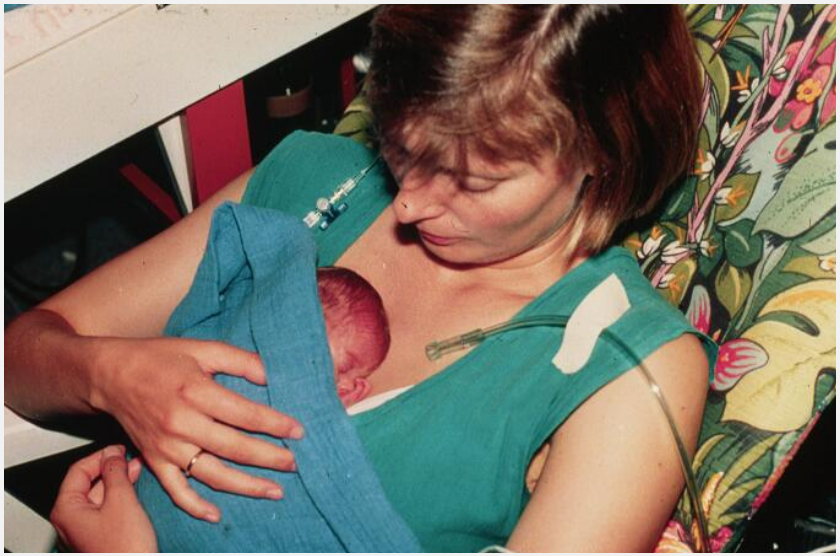
Skin to skin contact improves EEG maturation

An analysis of the kangaroo care intervention using neonatal EEG complexity: A preliminary study

F. Kaffashi [a,*], M.S. Scher [b], S.M. Ludington-Hoe [c], K.A. Loparo [a]

Clinical Neurophysiology 124 (2013) 238–246

[a] Department of Electrical Engineering and Computer Science, Case Western Reserve University, Cleveland, OH 44106, United States
[b] Department of Pediatrics, Case Western Reserve University, Cleveland, OH 44106, United States
[c] School of Nursing, Case Western Reserve University, Cleveland, OH 44106, United States



- KMC group neonates had increased complexity in EEG and are closer to the FT neonates than to the PT non-KMC group at the same age
- **KMC intervention accelerates neurophysiological maturation of PT neonates**

Twenty-year Follow-up of Kangaroo Mother Care Versus Traditional Care

Nathalie Charpak, MD,[a] Rejean Tessier, PhD,[b] Juan G. Ruiz, MD, MSc,[c,d] Jose Tiberio Hernandez, PhD,[e] Felipe Uriza, MD, MSc,[c,d] Julieta Villegas, MD, MSc,[a] Line Nadeau, PhD,[b] Catherine Mercier, PhD,[b] Francoise Maheu, PhD,[f] Jorge Marin, MD,[g] Darwin Cortes, PhD,[h] Juan Miguel Gallego, PhD,[h] Dario Maldonado, PhD[e]

WHAT'S KNOWN ON THIS SUBJECT: Kangaroo mother care (KMC) is an intervention for preterm and low birth weight infants. Short- and mid-term benefits of KMC on survival, neurodevelopment, and the quality of mother–infant bonding were documented in a randomized controlled trial in 1993–1996.

WHAT THIS STUDY ADDS: This study indicates that KMC had significant, long-lasting social and behavioral protective effects 20 years after the intervention in adolescence and young adulthood. Coverage with this efficient, scientifically based health care intervention should be extended.

Stress versus developmental care: impact on brain development

↗ Stressors:

- Decreased frontal and parietal brain width
- Altered diffusion
- Altered functional connectivity in temporal lobe

VERSUS

Developmental care:

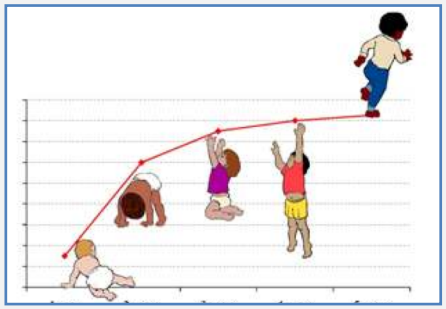
- Better neurobehavioral functioning
- Higher relative anisotropy
- Increased coherence (EEG) between frontal and a broad spectrum of mainly occipital brain regions

G. C. Smith et al., 2011.
H. Als et al. 2004.

SUMMARY

- 30-50% of infants born VPT will experience impairments in cognitive and motor performances, as well as behavior problems
- Despite being mild in degree individually, in combination such deficits often seriously limit their educational, social, and other life course opportunities
- Brain development is resulting in very complex processes that all interact in a programmed manner
- Any intrinsic or extrinsic event that will alter one process will disrupt the overall program and alter brain development
- Developmental care is about supporting the normal program for brain development in an altered environment

AKNOWLEDGEMENTS



- *Petra S. Hüppi*
- *Russia Ha-Vinh Leuchter*
- *Stephane Sizonenko*
- *Lucie Schoenhals*
- *Ana Sancho-Rossignol*
- *Silvia Roncoli*
- *Charlène Fournier*

- *Koviljka Barisnikov*
- *Fleur Lejeune*
- *François Lazeyras*
- *Laura Gui*
- *Lara Lordier*
- *Manuela Filippa*
- *Joana Alves Sa De Almeida*

Thank you for your attention!