

# Impact of IUGR on the premature brain and consequences at middle and long term

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# 1.500.000/y neonates are born preterm and small



1.304.000/y at risk  
neurodevelopmental disorders

195.900/y deaths

Lee et al., 2017; Kurjac et al., 2010

# The perfect storm

## Prematurity-IUGR: brain double jeopardized



Johnson and Marlow, 2014, Erdei and Dammann 2014

# The healthy brain

Prematurity

IUGR



Centers for Disease Control and Prevention





Vision

Sensory

perception

Audition

Motor

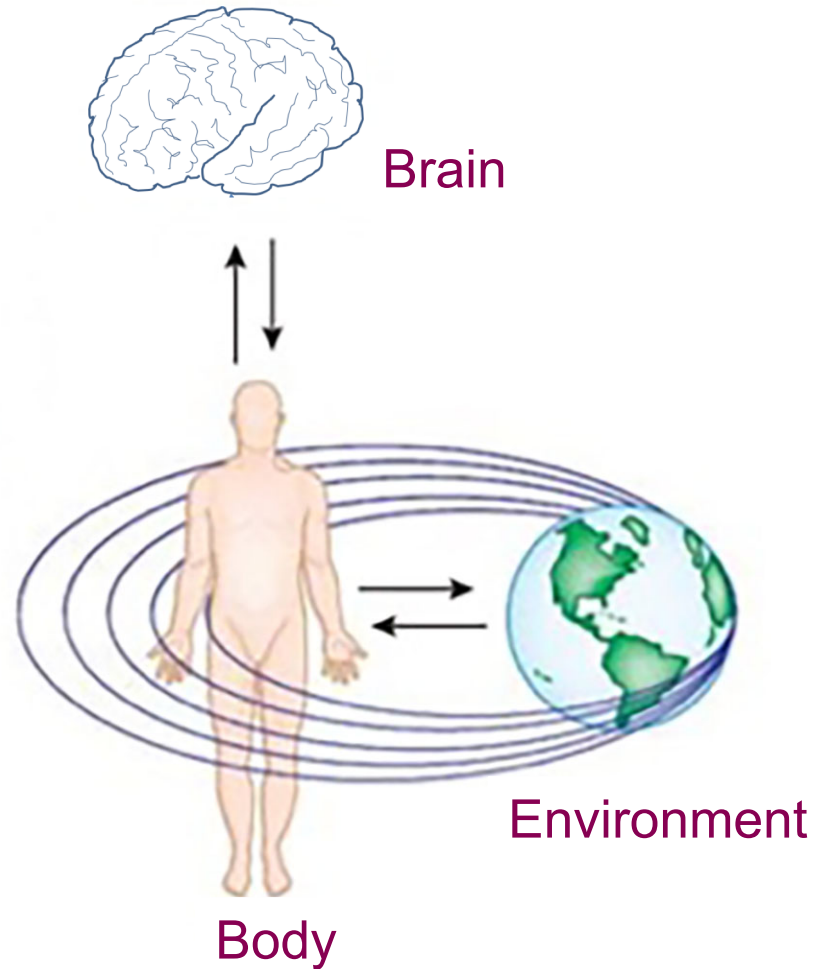


Movements

Emotions

Behaviours

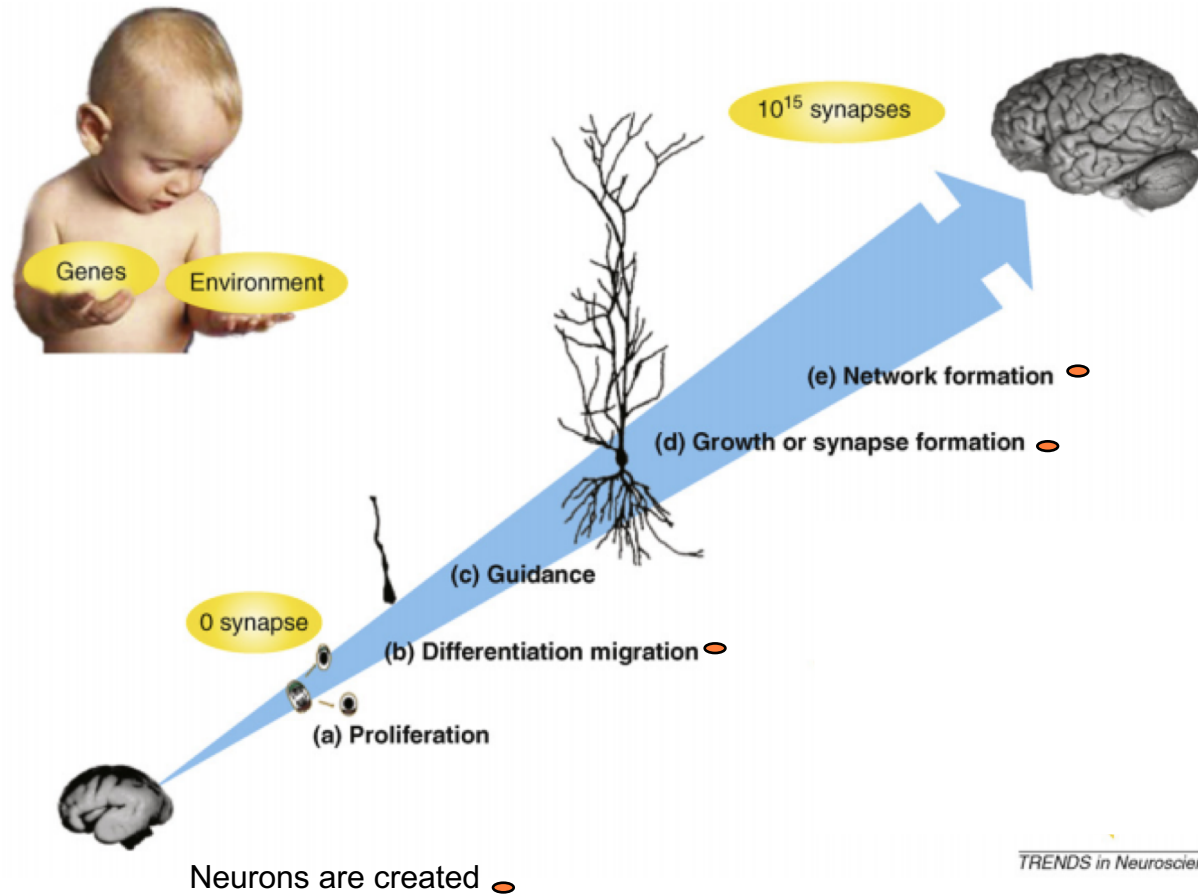
# Brain – Body - Environment



Oliveira and Oliveira 2014; Craig 2009; Chiel and Beer, 1997

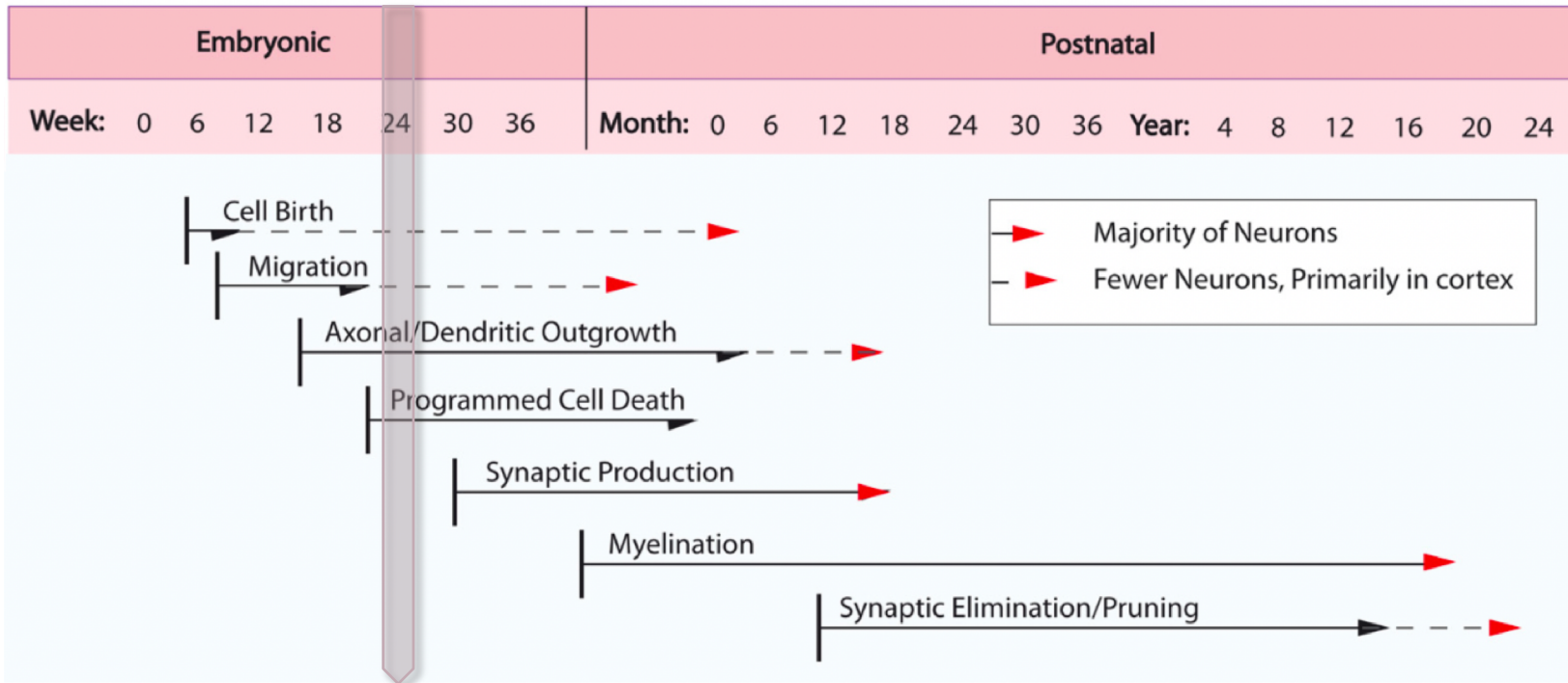
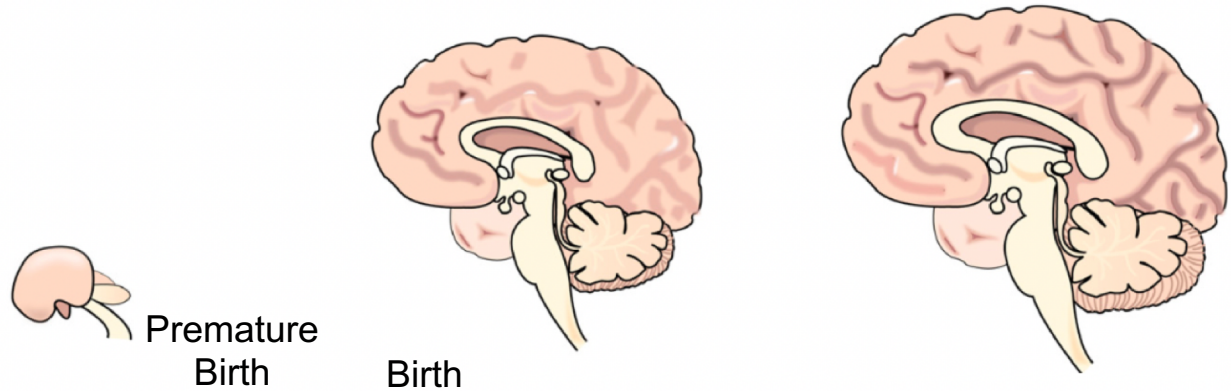


# Making human brains



Brain-Body-Environment

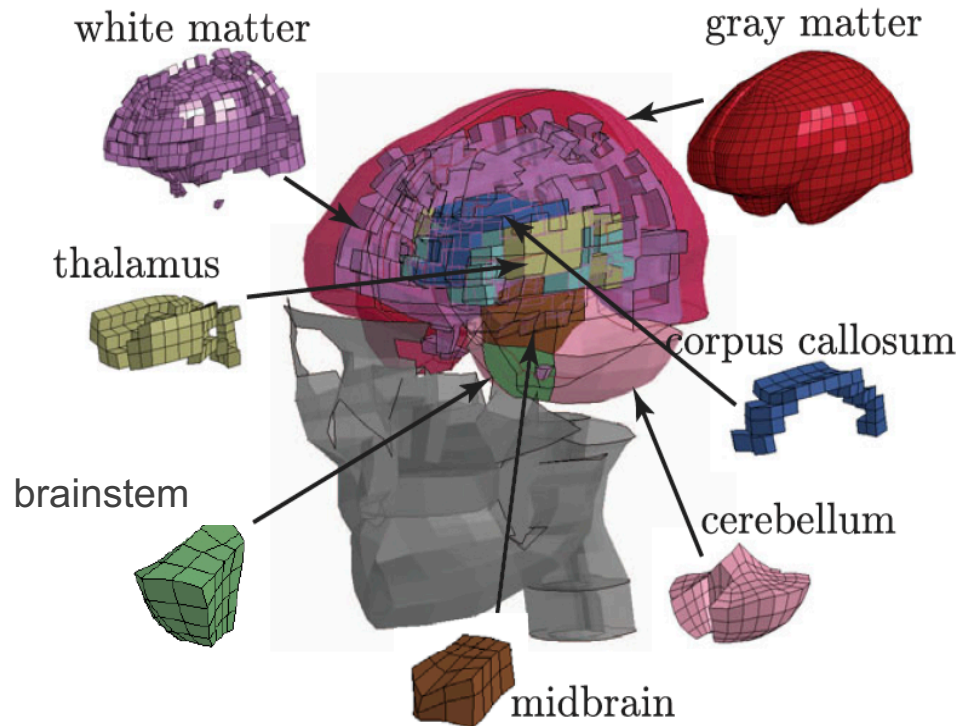
Ben-Ary I, 2008



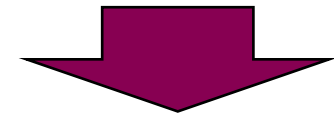
Brain-Body-Environment ➔

Kaplan et al., 2016

# How can the brain be reorganized?



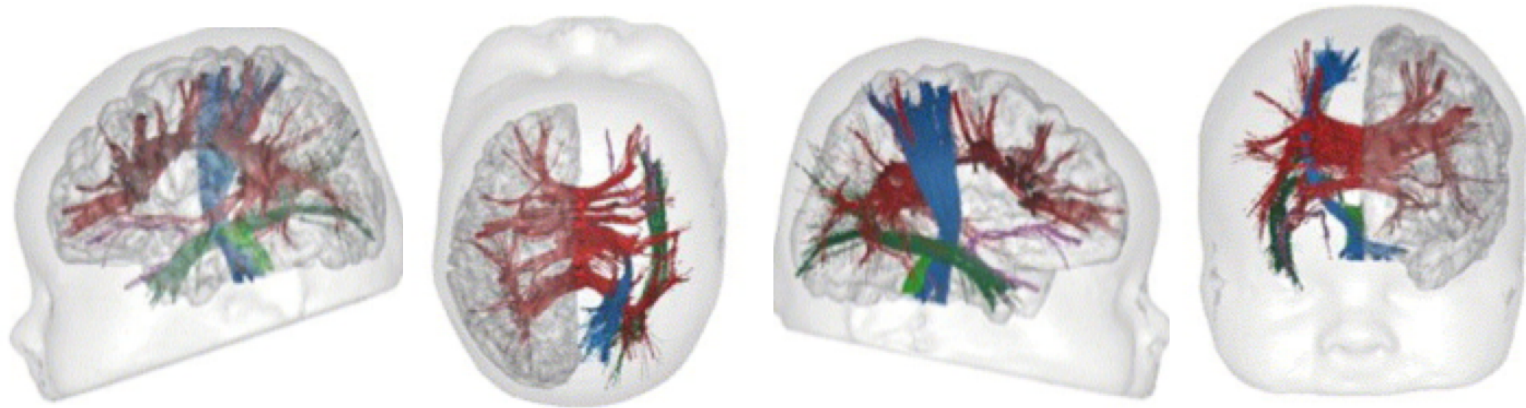
Assembled modules  
interactions



Mental states and  
behaviours

Laksari et al., 2018

# Connections: created and refined



## Genes and experiences

Brain-Body-Environment

Dubois and Dehane-Lambertz – Brain mapping; Dubois et al., 2006

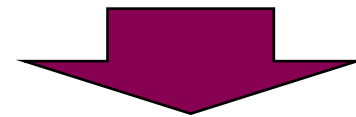
# Reorganization of the brain

Prematurity

IUGR

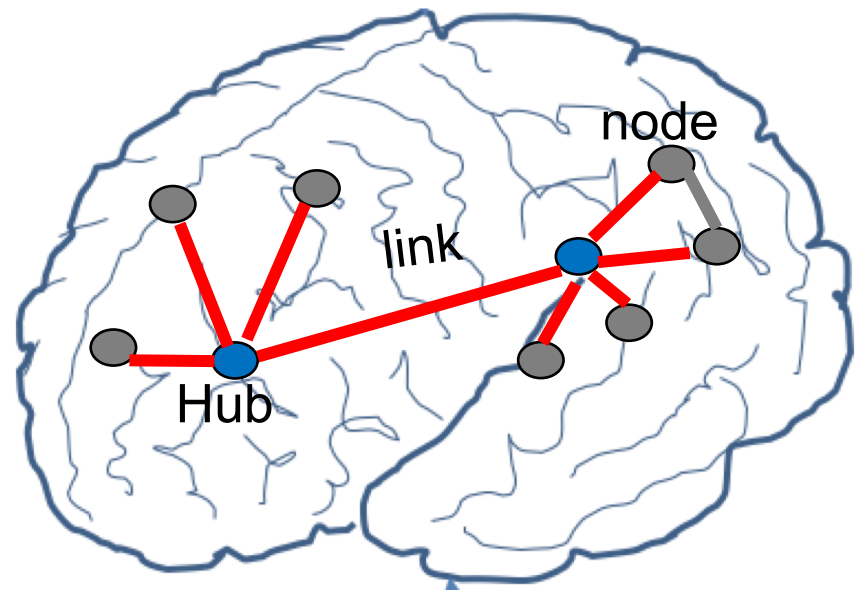
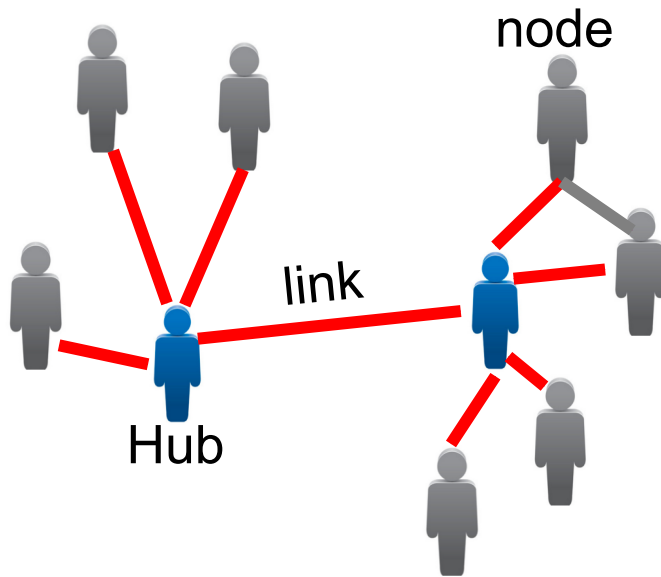


Adverse experiences



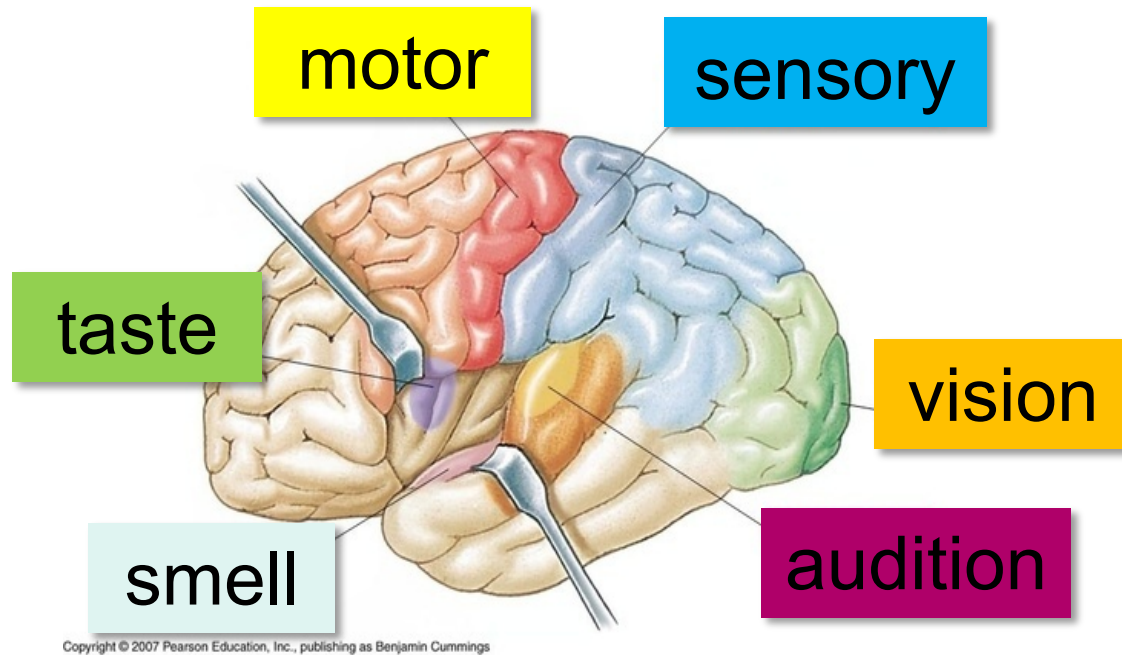
Reorganized connections

# Brain regions interact as friends in facebook



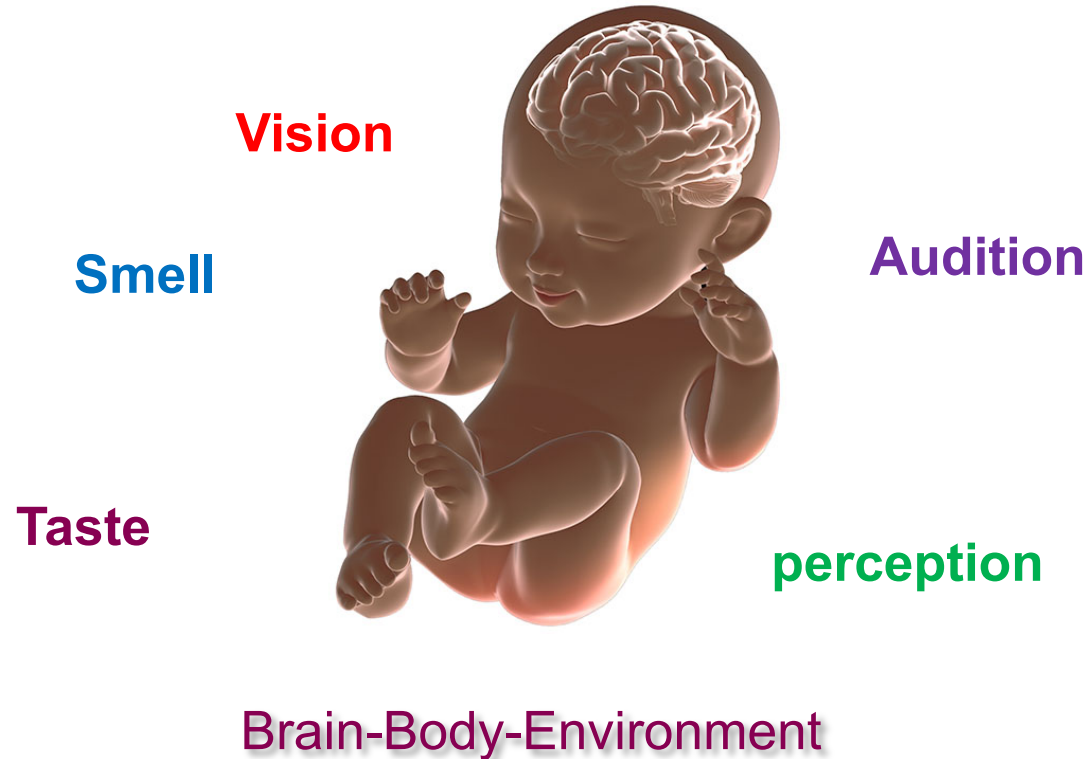
Crossley and Bullmore., 2016

# First areas to develop: sensorimotor functions



Porges et al., 2011

# Sensorimotor functions develop first



Friedrichs-Maeder et al., 2017; Gao et al., 2014, 2015; Porges et al., 2011



# First functions to develop first functions to be affected

Prematurity



Vision

Smell

Taste



Audition

IUGR

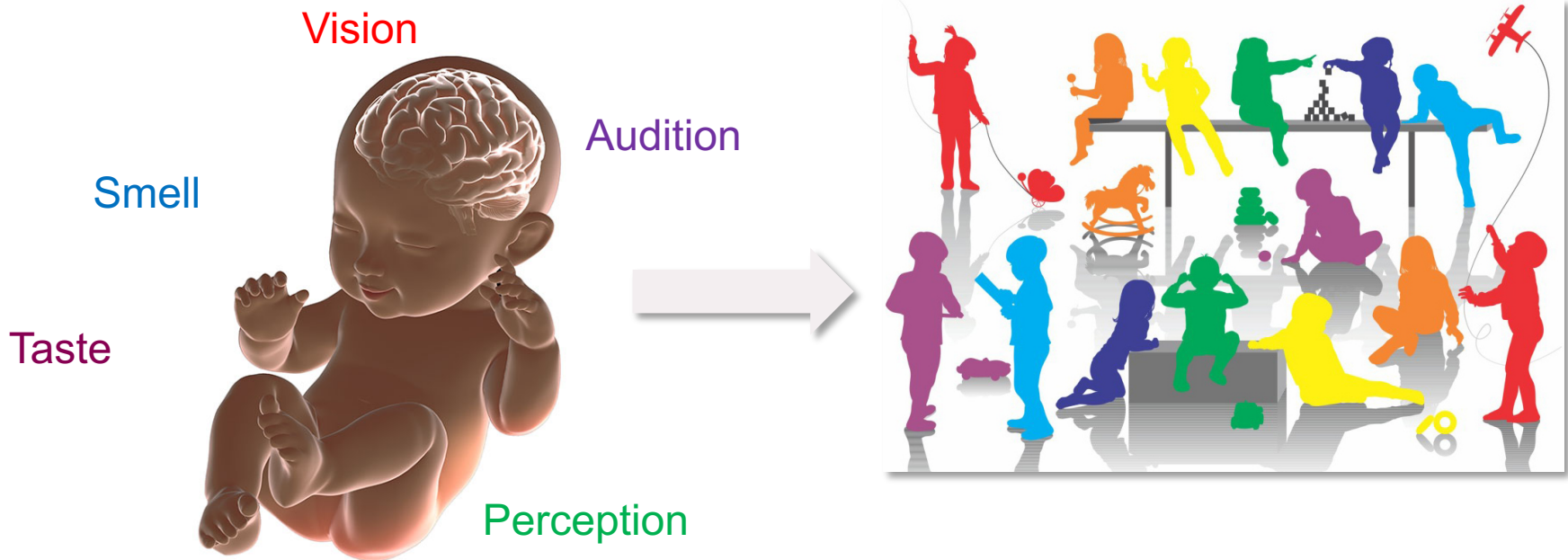


perception

Brain-Body-Environment

Friedrichs-Maeder et al., 2017; Gao et al., 2014, 2015; Porges et al., 2011

# Sensorimotor functions build the basis for complex mental functions

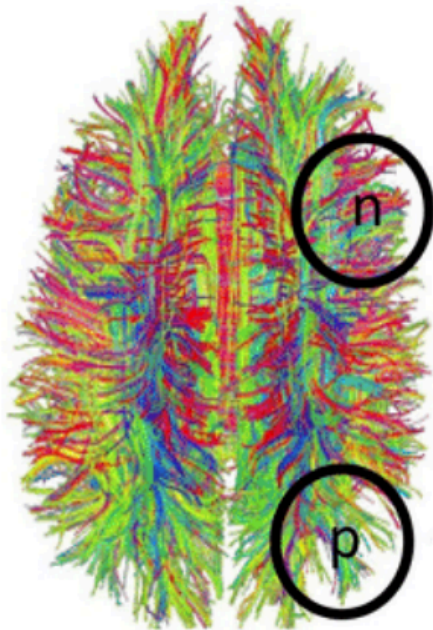


- Memory
- Language
- Attention
- Learning
- Cognition

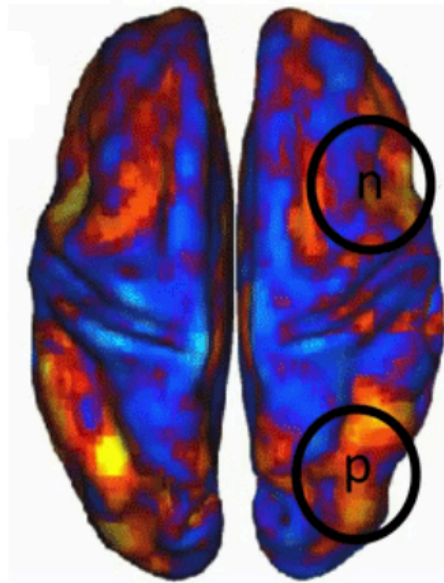
Stevenson et al., 2014

# Reorganization of the brain

Preterm birth and IUGR



structure



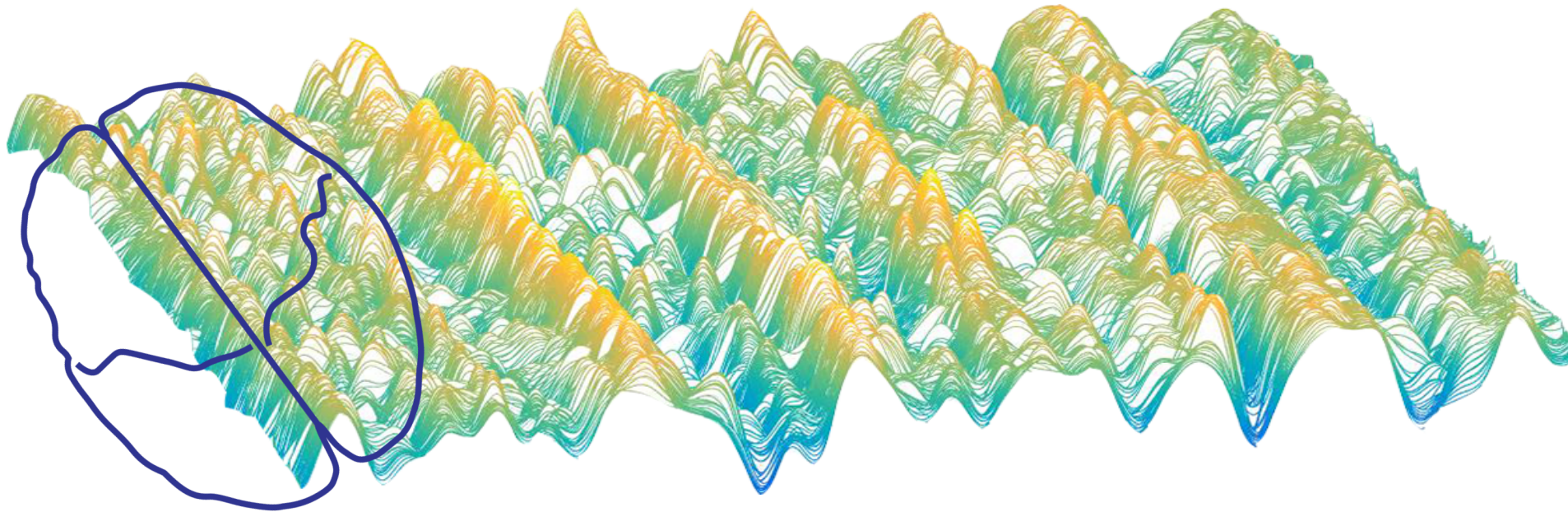
function

Structural and functional  
reorganization



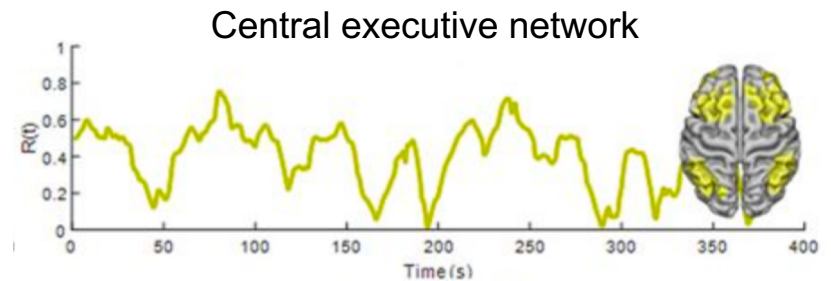
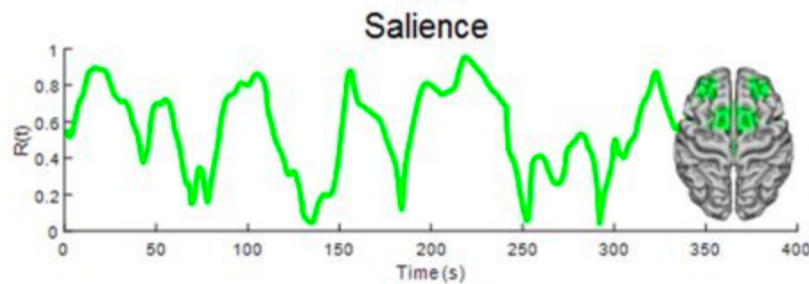
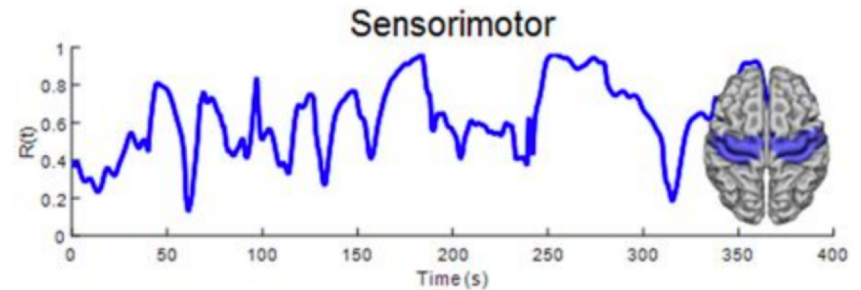
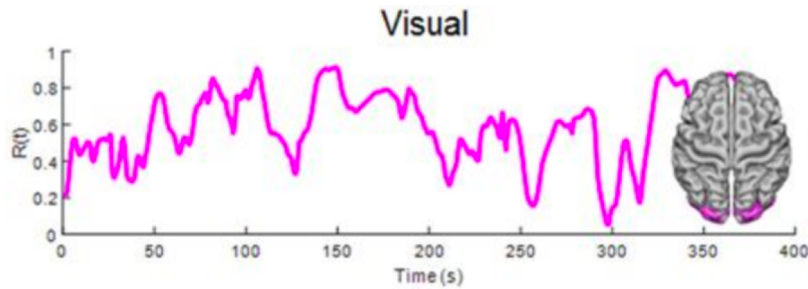
New patterns of interaction  
among regions and neural  
communication

# Resting state activity: Functional MRI



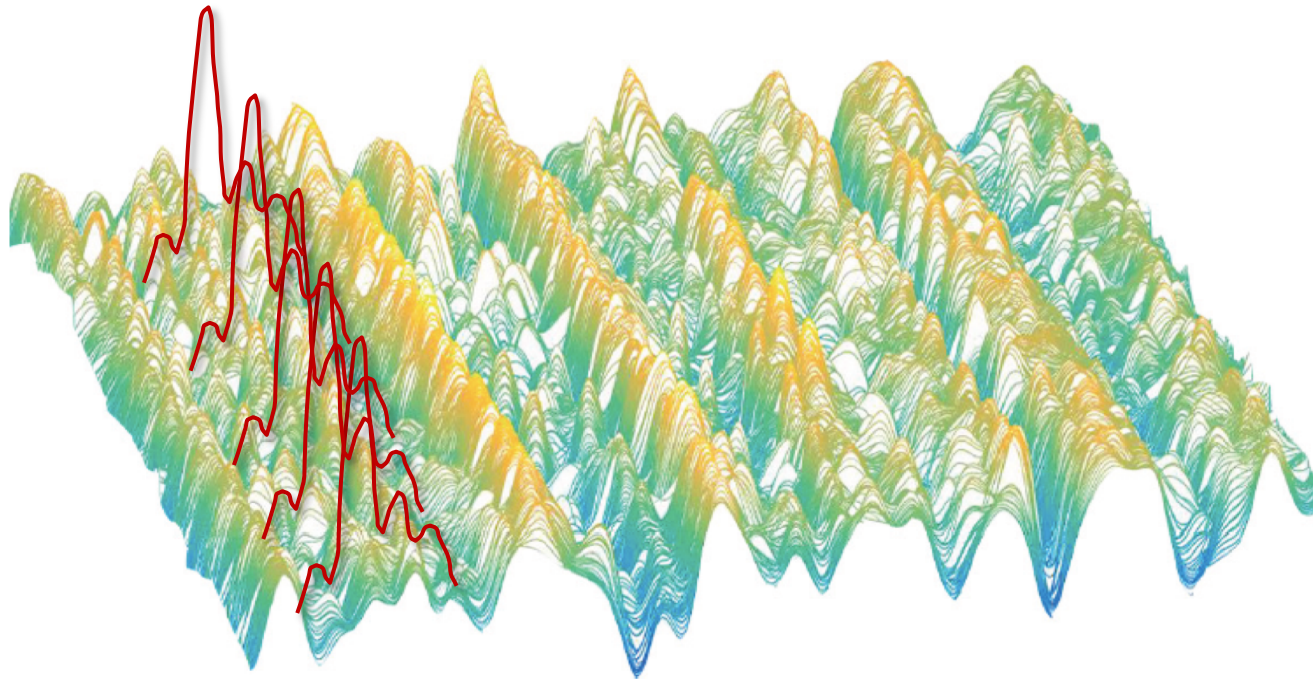
Spontaneous fluctuations of neural activity

# Resting state networks functional connectivity



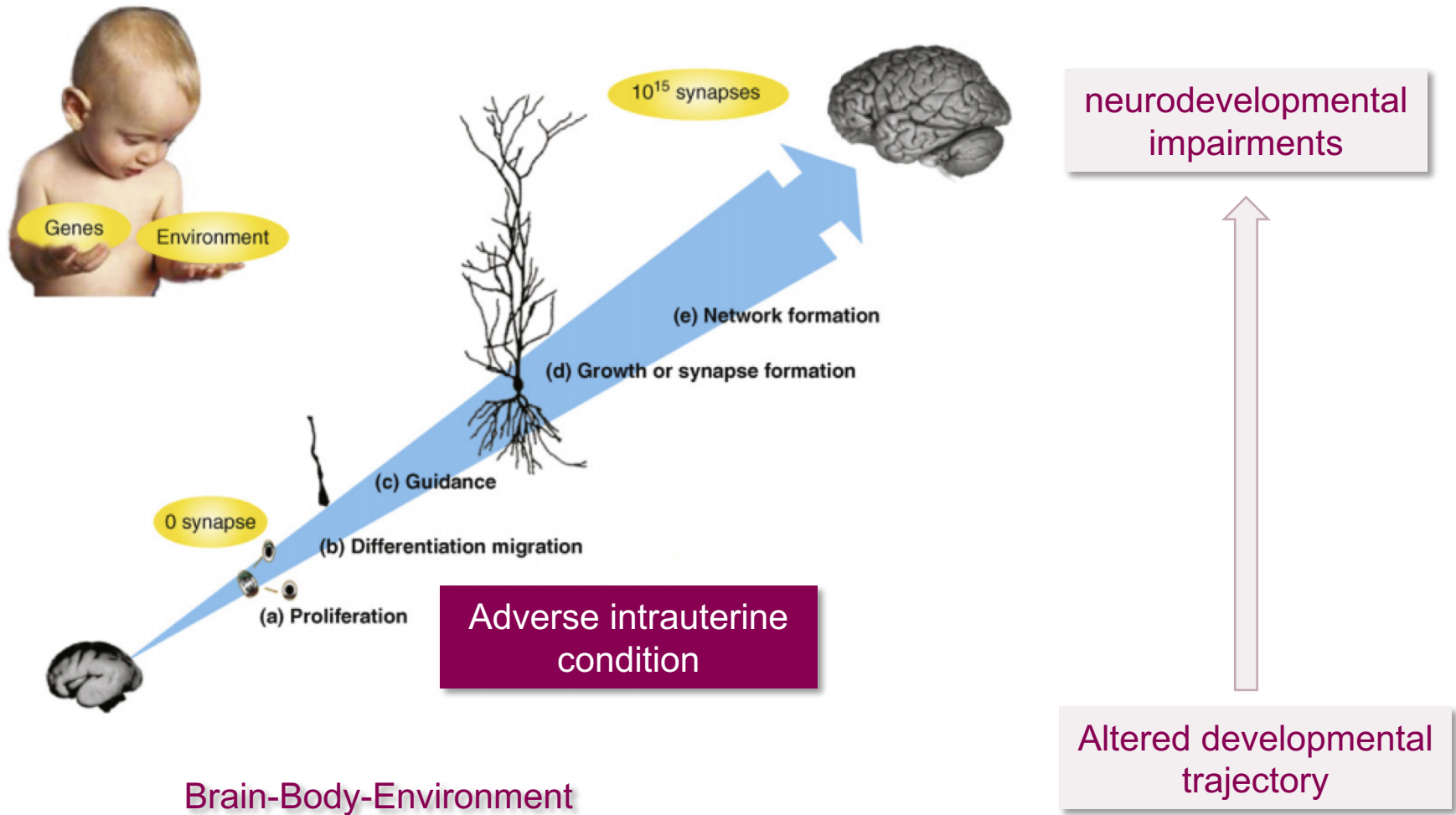
Organized spontaneous fluctuations into RSN

# intrinsic ignition activity



brain areas ignite and propagate neural activity  
to other regions in the brain

# Early insult affecting the brain

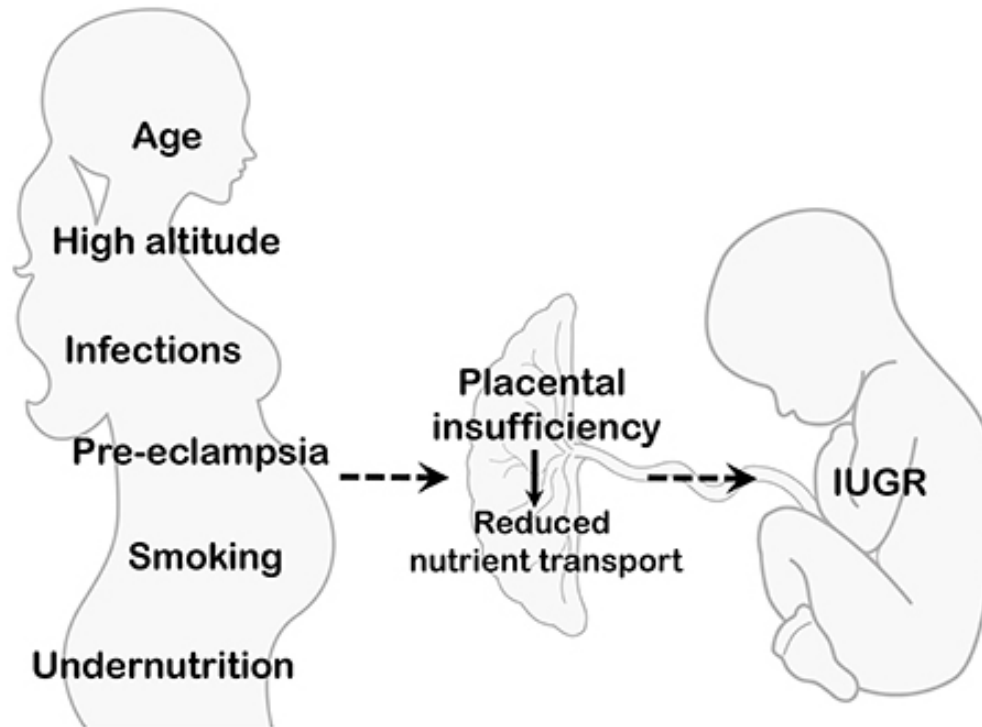


Johnson et al., 2015; Ben-Ary I, 2008



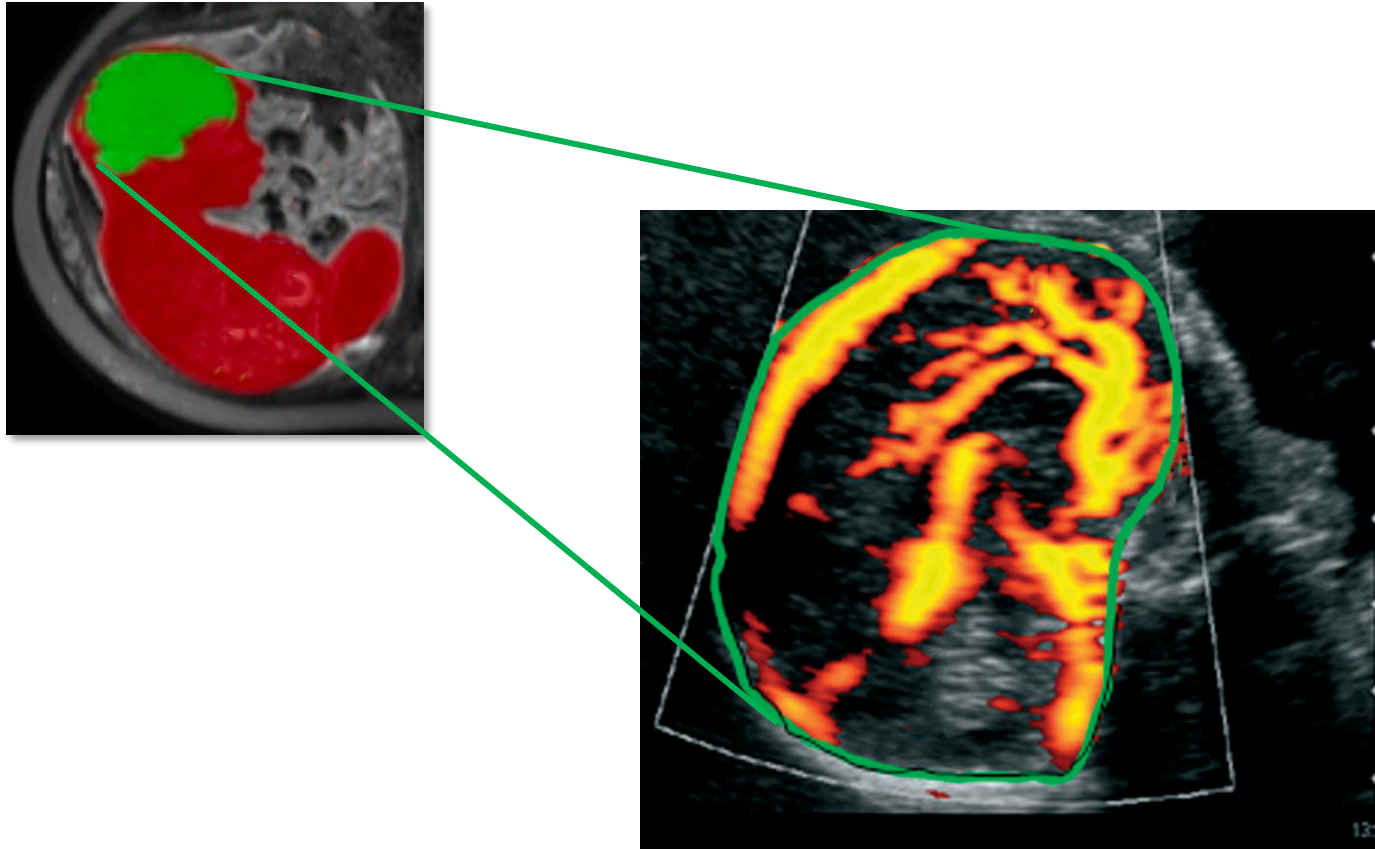


# Intrauterine Growth Restriction (IUGR)



Increased fetal and neonatal mortality, morbidity, and adverse neurodevelopmental outcome

# Brain sparing: redistribution of the blood flow to the brain

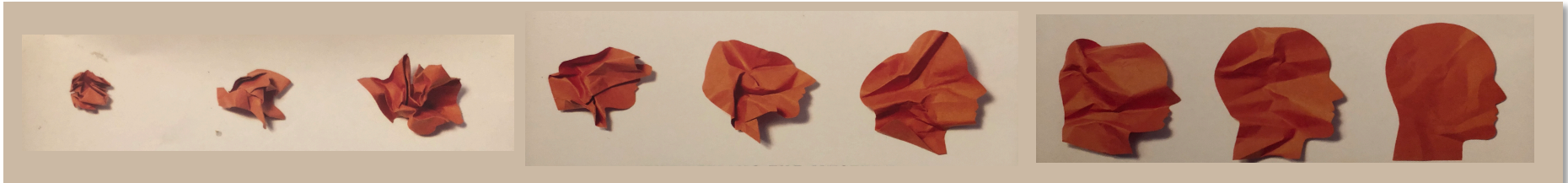


Brain sparing is associated to abnormal neurodevelopment

Padilla et al., 2014 ; Figueras and Gratacós 2014; Damodaram et al., 2012, Hernandez-Andrade et al., 2008; Tolsa et al, 2004

# IUGR: exposure to cumulative risks

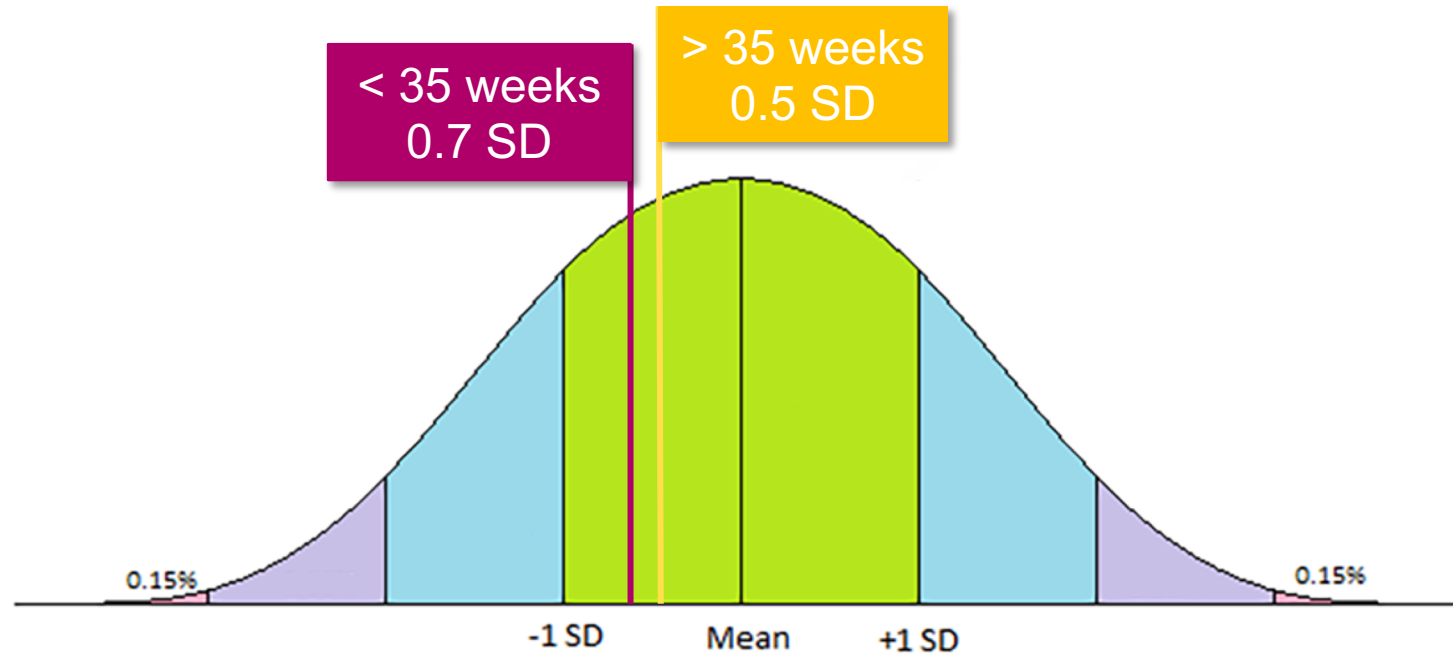
Infection  
Respiratory  
distress  
Haemorrhages  
Prematurity  
Brain sparing  
IUGR



Neurodevelopmental impairment 

Barnett et al., 2018; Gazzaniga M, 2018; Van Steenwinckel et al., 2014; Gullec et al., 2015

# IUGR, prematurity, and neurodevelopment

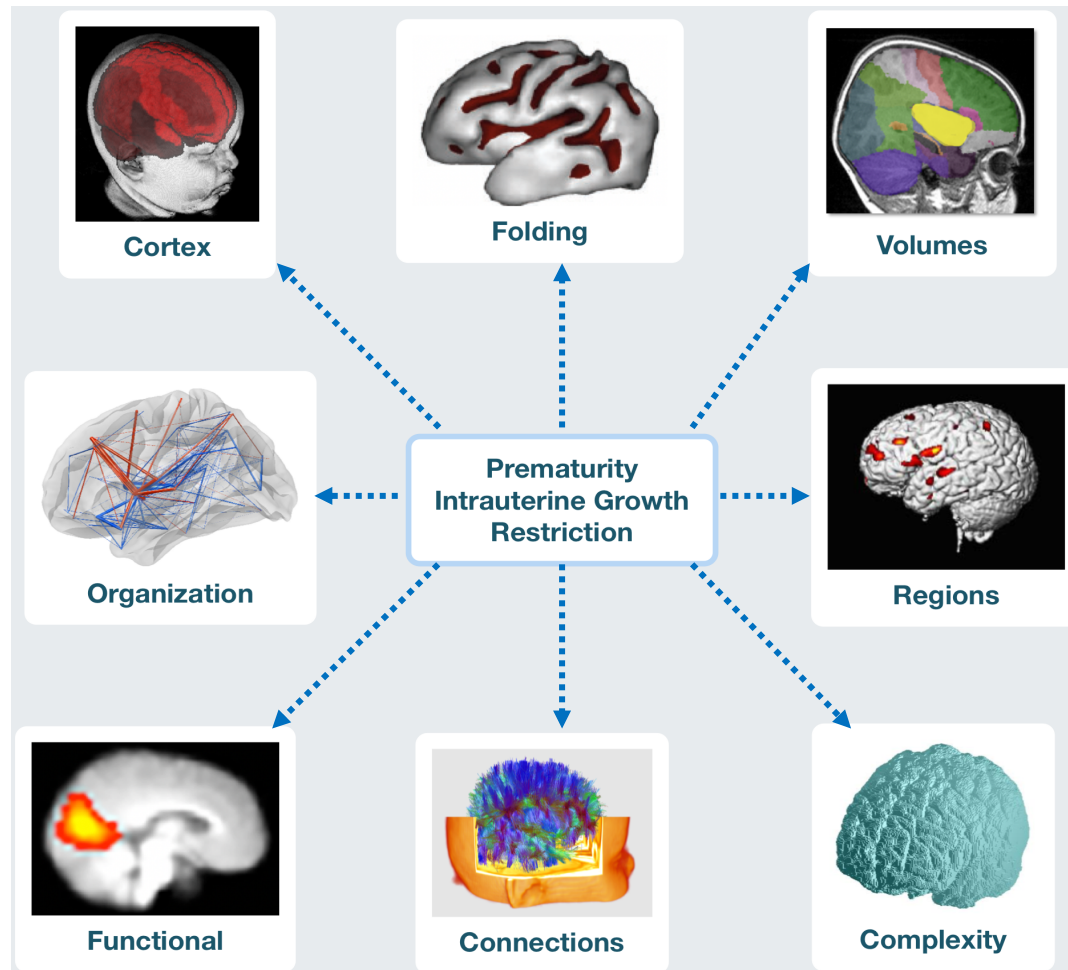


- Cognition
- Behaviour
- **Hearing**

- Cognition
- Behaviour
- **Vision**

Murray et al., 2015

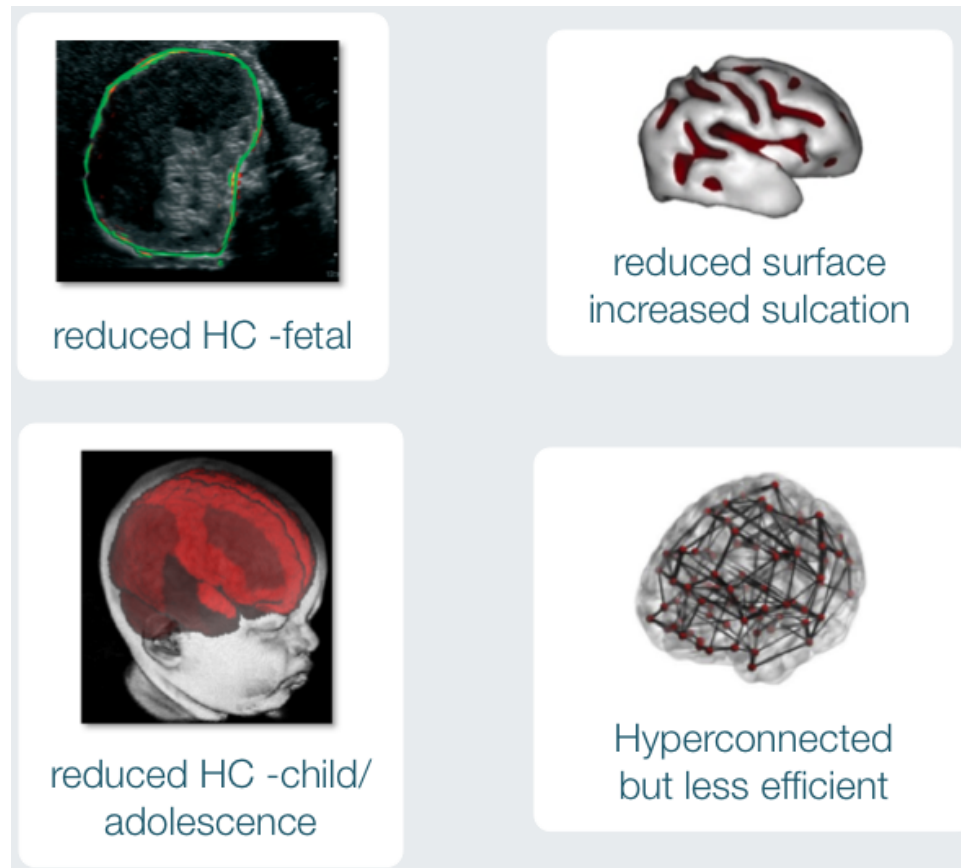
# Prematurity, IUGR and brain organization



Brain-Body-Environment

Padilla et al., 2017; Padilla et al., 2014; Padilla et al., 2011; Dubois et al., 2008; Esteban, Padilla et al., 2010, Tolsa et al., 2004

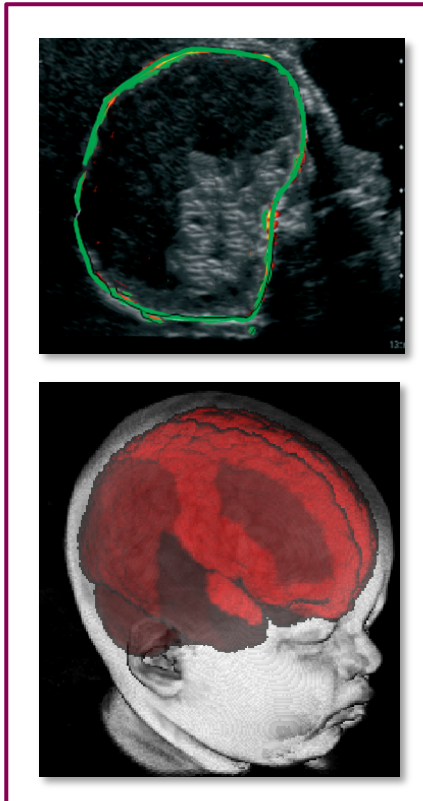
# IUGR and reduced head circumference



↓ HC risk marker of future adverse neurodevelopmental outcome

Guellec et al., 2015; Padilla et al., 2014; 2010; Figueras, Padilla et al., 2009; Tolsa et al., 2004

## Attention and self-organization



## Reduced social interaction

Guellec et al., 2015; Padilla et al., 2014; 2010; Figueras, Padilla et al., 2009; Dubois et al., 2008; Tolsa et al., 2004

# From self-organization to social interaction

- Breathing
- Muscle tone
- Posture
- Temperature
- Feeding

- Motor organization

- State regulation

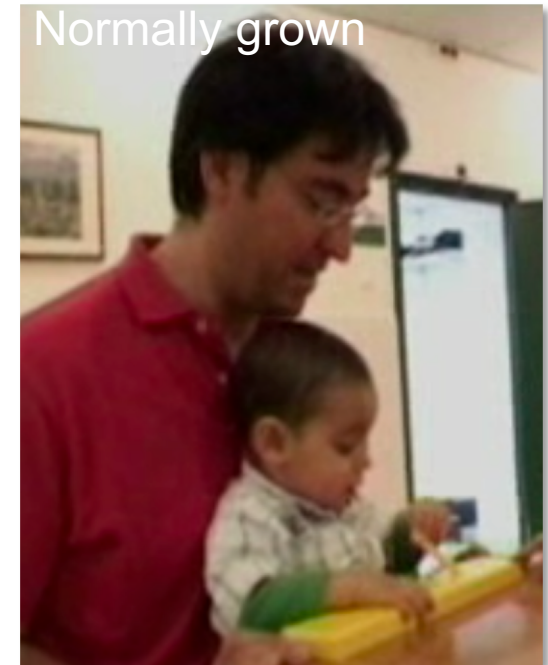
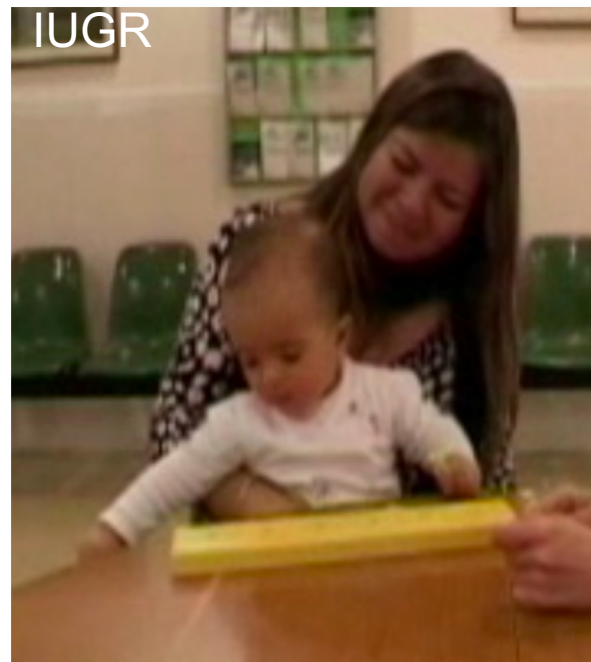
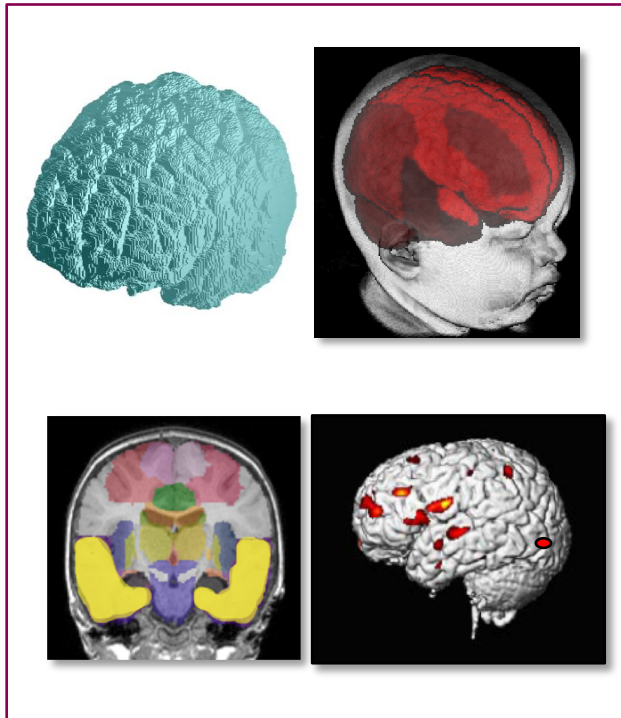


- Social interaction



# IUGR and brain development at 1 year

Reduced complexity of the brain, reduced global, and local brain volumes

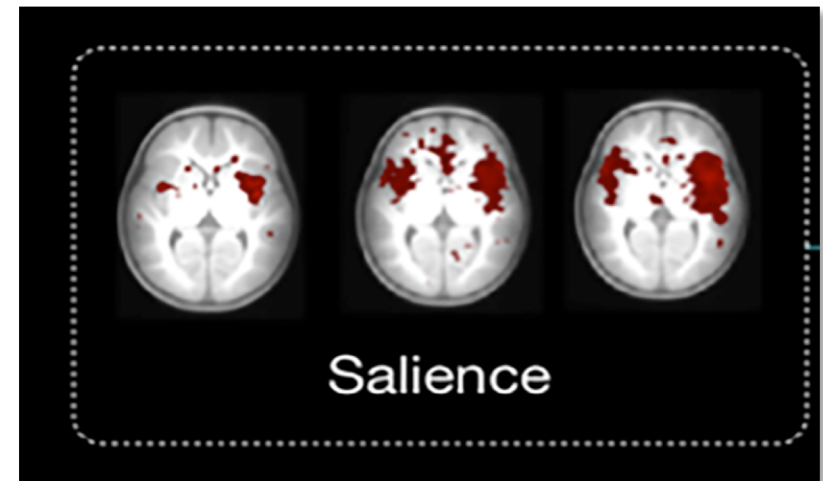


Difficulties in motor, language, behavioural functions

Busineely et al., 2015 ; Padilla et al., 2014; Esteban, Pdilla et al., 2009

# IUGR and autism at 1 year

Preterm IUGR: 31.6 % positive screening for ASD



Detection of relevant stimuli

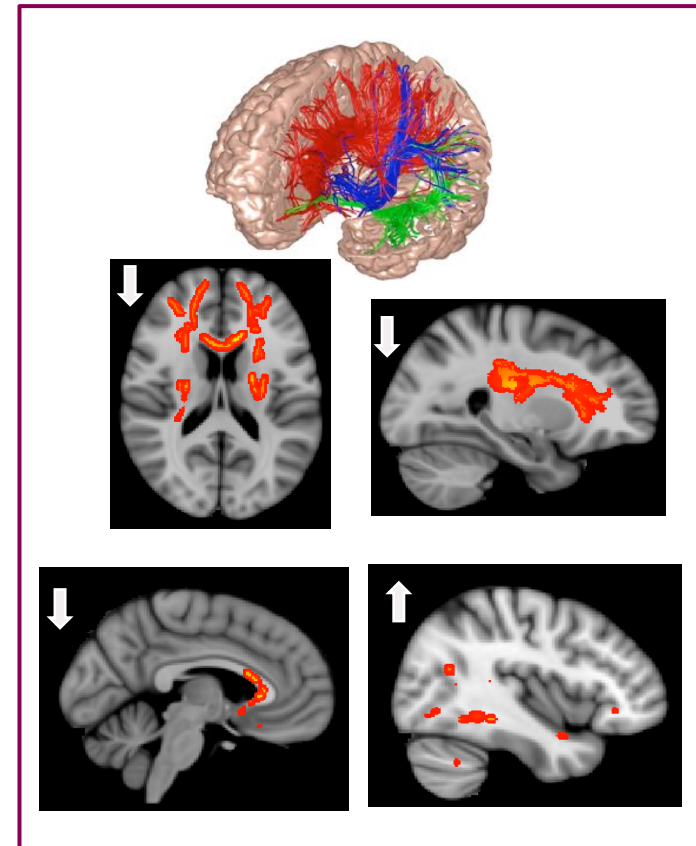
Abnormal brain response to basic sensory information

# IUGR and brain connections first 2 years

Motor and language  
impairments



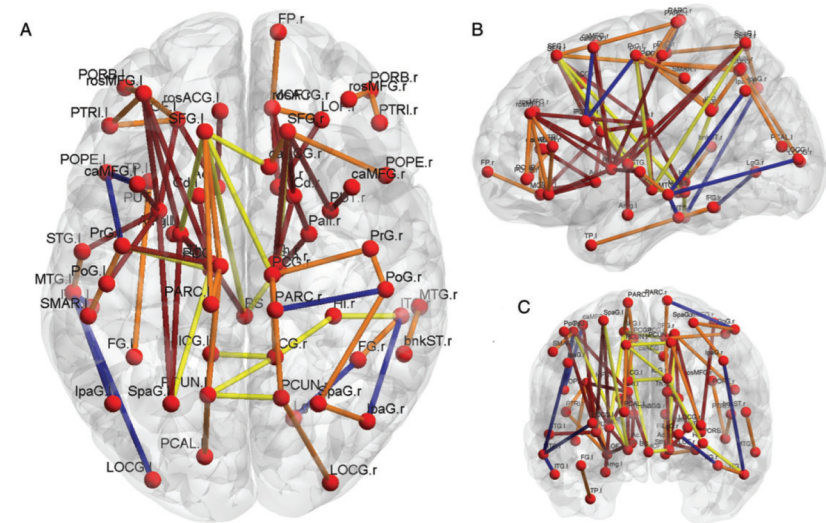
Different organization  
of connections



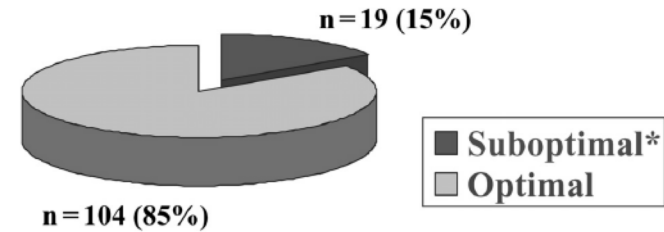
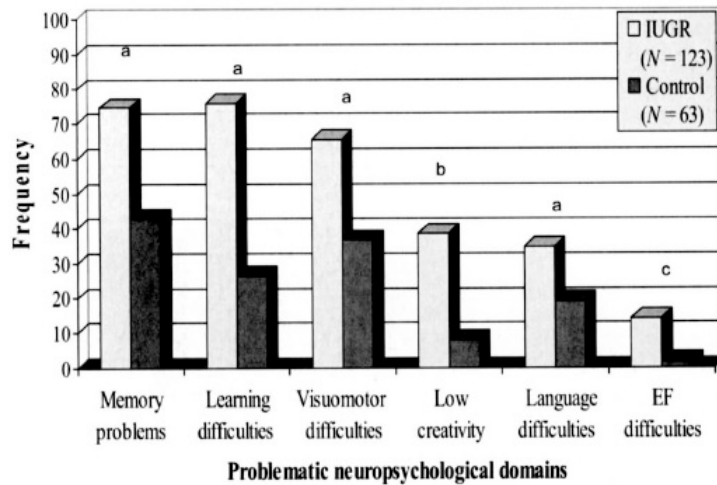
Padilla et al., 2014; Batalle et al., 2013, 2012

# Altered connectivity and less efficiency at school age

- Cognitive impairments
- Neurobehavioural difficulties



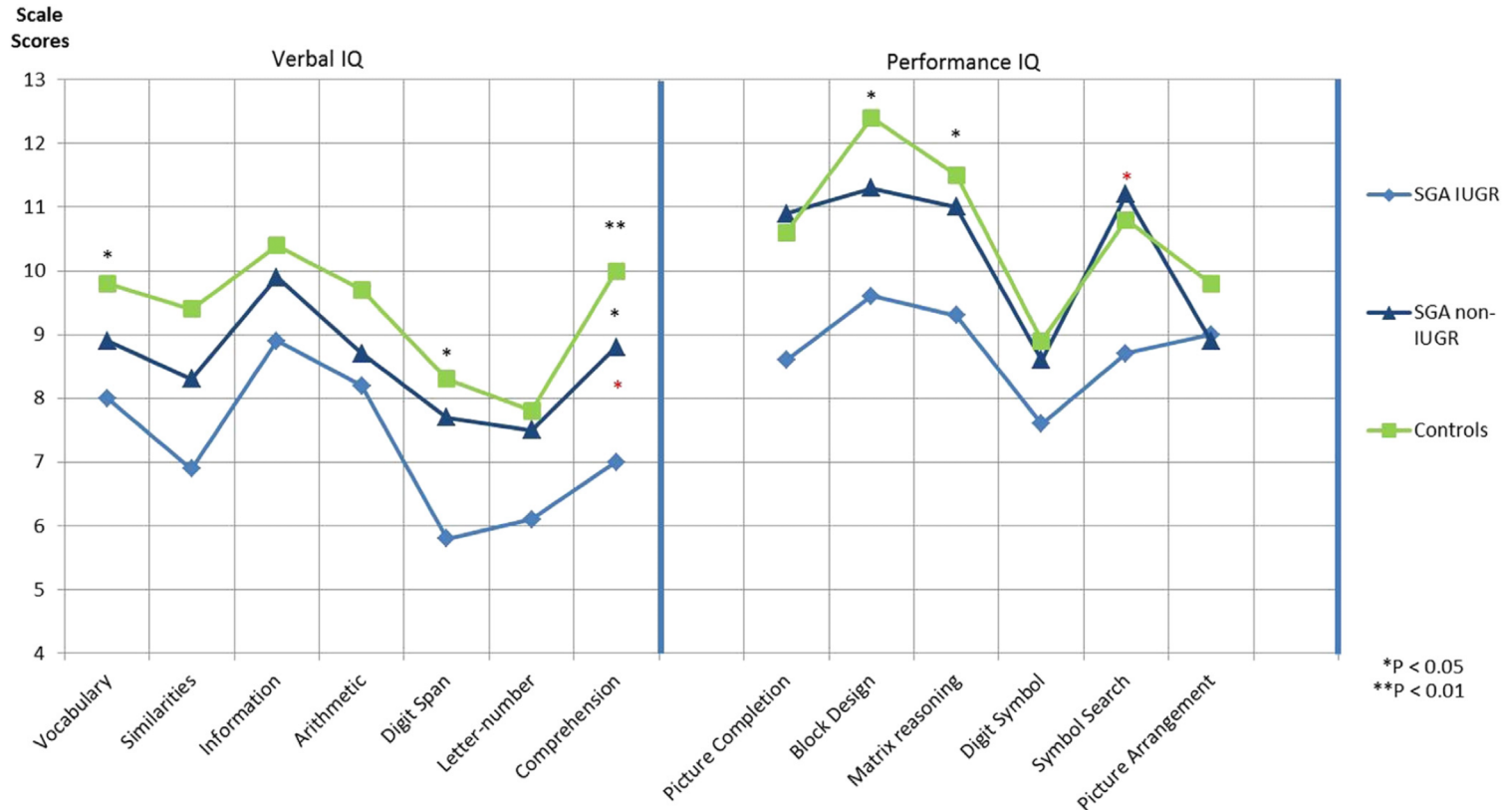
# IUGR and organization of the brain at 10 years of age



\*Suboptimal = IQ ≤ 85

Saunavaara et al., 2017; Leitner et al., 2007; ;Geva et al., 2006

# Impaired executive functions in adults



Martinussen et al., 2013; Tideman et al., 2007

# IUGR+prematurity → disadvantage

## Developmental deficits

- Reduced motor skills
- Reduced visuomotor skills
- Altered audition/language skills
- Altered behavior
- Altered organization

## First years of life

## Developmental deficits

- Reduced cognitive skills
- Reduced memory functions
- Learning difficulties
- Language difficulties
- Social and behavioural difficulties

## Adolescence and adulthood



## Structural and functional deficits

- Reduced head circumference
- Reduced volumes
- Reduced total number of cells
- Reduced connectivity
- Reduced processing

**IUGR, prematurity, neonatal complications  
early experiences (brain-body-environment)**

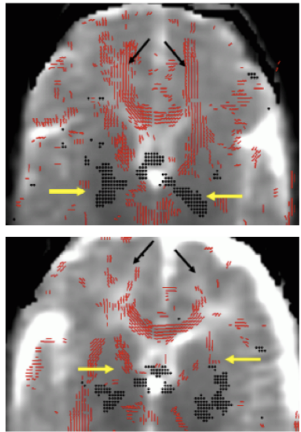
# What can we do?



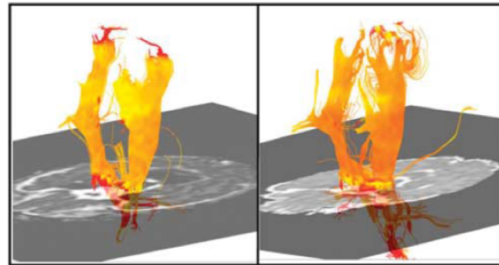


Greatest potential for optimal outcomes

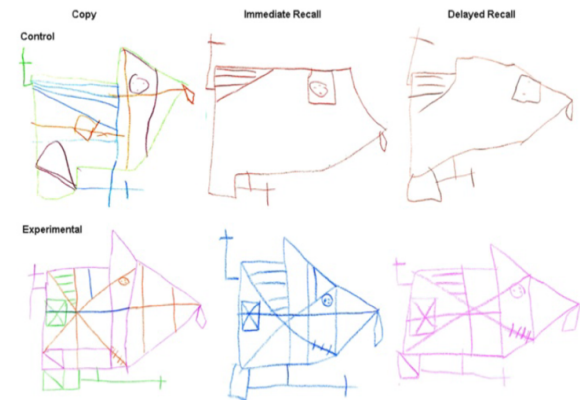
# Individualized interventions



**Improved structure**



**Improved connectivity**



**Improved executive functions**

↓ sensory impact of the NICU environment

↓ neurodevelopmental impairments

McAnulty et al., 2013; Als et al., 2012; Als et al., 2004

Optimal neural, family, and social connections

Kangaroo care: brain development, attachment, self-regulation

# Protecting the brain, the body, avoiding negative experiences.

- Stress and pain
- Positioning and handling
- Optimizing nutrition
- Protecting sleep
- Healing touch
- Controlling light

# Our aim

Observe

Interpret

Support

Promote self-regulation and stability

Promote Social interaction



Karolinska  
Institutet

# THANK YOU

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