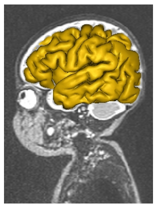
Human brain development



Jessica Dubois

INSERM, Cognitive Neuroimaging Unit,
CEA, NeuroSpin Center, Gif-sur-Yvette, France

Centre for Brain and Cognitive Development, Bootcamp
September 20th 2017

Learning objectives

- Basic principles of human brain development, at the anatomical and functional levels (*post-mortem* and neuroimaging findings): from genetically-determined to activity-dependent mechanisms

- Early architecture but plasticity of brain networks
  Influence of genetic, epigenetic and environmental factors

- Asynchrony in the networks maturation
  Early cerebral responses in neonates and infants for the somatosensory, visual and auditory systems, with insights on early lateralization

Open questions

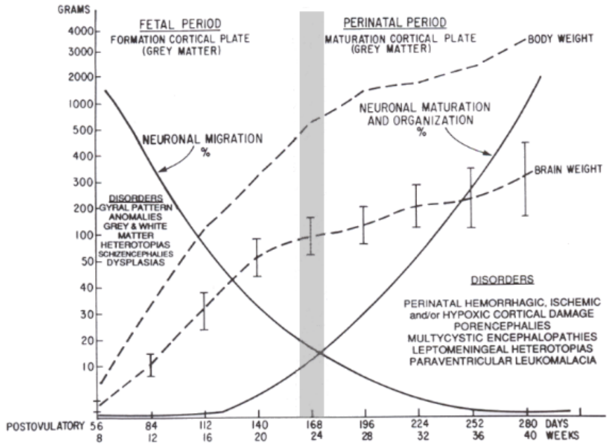
- The developing brain at birth: how is it already organized and functional?
- The "nature vs nurture" debate in the development of cognitive functions: does it still mean anything?
- The differential maturation and refinement of networks in the infant brain: how might infants process multi-sensory information and perform cross-modal integration?

Outline of the course

1. Basic principles on early brain growth
2. Brain development after birth
3. Studying brain development *in vivo*
4. MRI of the brain structural development
5. Neuroimaging of early functional activity
6. Examples of neuroimaging studies on the developing sensori-motor sytem
7. … on the developing visual sytem
8. … on the developing auditory system and language network

Disorders originating during early/late pregnancy

- Gestational age (GA) = counted from amenorrhea (~post-conception PC + 2 weeks)
- Post-menstrual age (PMA) = GA at birth + post-natal age
- Term birth: ~40w GA [France: 37-41w GA]
- Fetal period < 24w GA / pre-term period > 24w GA



Marin-Padilla, 1990

1. Basic principles on early brain growth

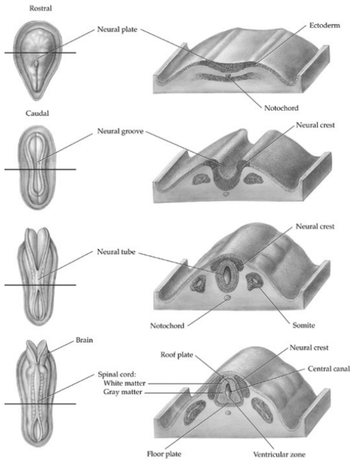
- The brain is composed of 86 billion neurons and much more synapses, dendrites, axons and glia cells connecting and supporting them. These cells are mostly formed during prenatal development.
- Between the third and fifth month of gestation, neuronal migration peaks with the first neurons appearing in the cortical plate by 15 post-conceptional weeks (PCW).
- By mid-gestation neurogenesis is largely complete. Once neurons have reached their destination in the cortical plate, they start extending axons and dendrites.
- Early development results from dynamic processes that are highly constrained genetically.

Morphogenesis (1)

- Formation of the neural plate:

Gastrulation stage (E14-E18) →differentiation of 3 layers (ectoderm, mesoderm, endoderm), specification of 3 major spatial axes.
Neural induction: neural progenitors are induced in the ectoderm.

- Formation of the neural tube:
  Neurulation stage (E18-E28)
- The brain originates from the anterior portion of the neural tube.



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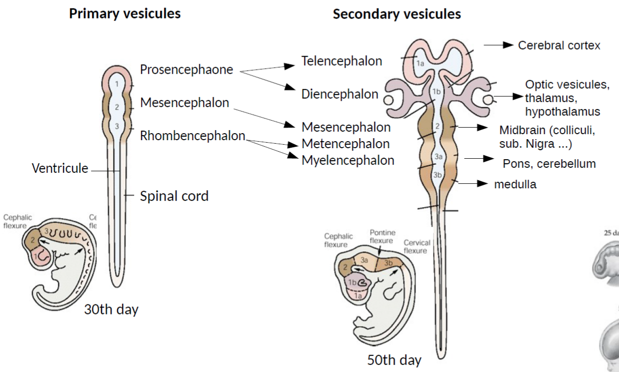
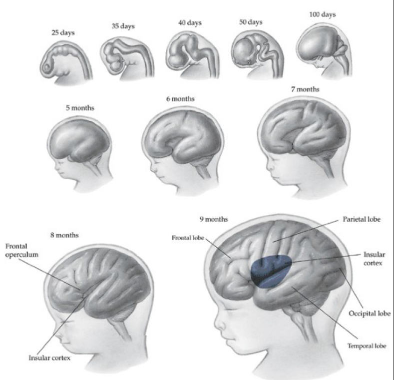
Morphogenesis (2)

- Differentiation of cephalic vesicles (E30-E50)

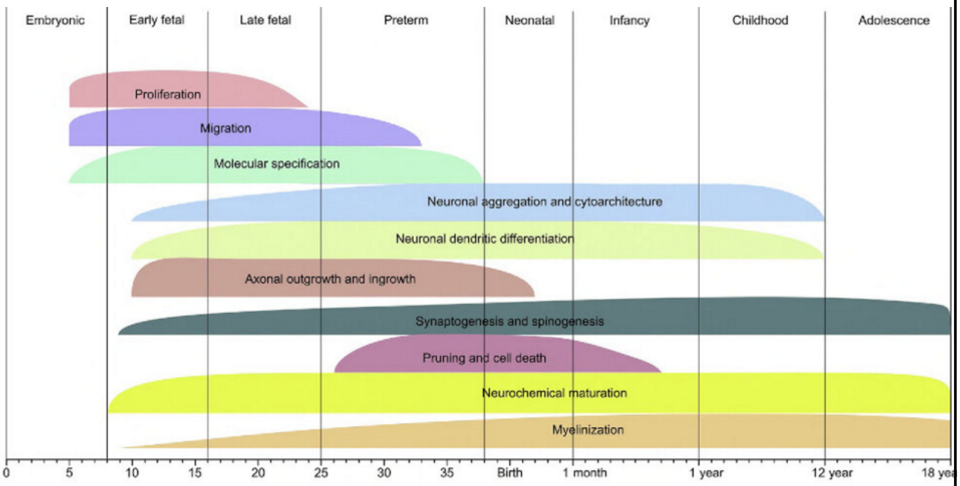




- Expansion of the telencephalon and diencephalon

Mechanisms of brain development

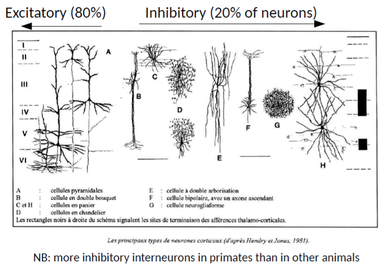
In the human species: several intertwined and protracted mechanisms

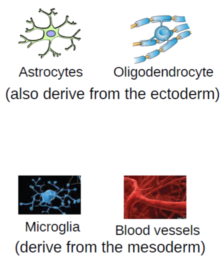


Kostovic and Judas.
Brain Mapping: An Encyclopedic Reference 2015

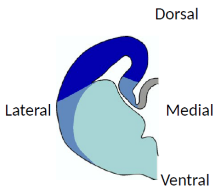
Expansion of the telencephalon

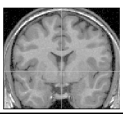
- Various cell types in the brain

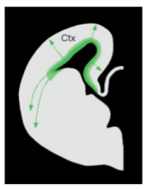




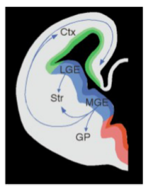
- Migration of projection neurons and inter-neurons from distinct origins







Excitatory projection neurons originates from the ventricular zone and migrate radially (max 2 cm)



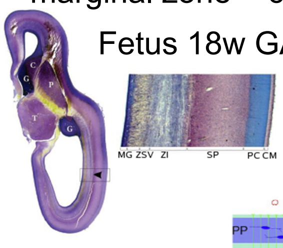
Inhibitory inter-neurons originates from the ganglionic eminence and migrate tangiatially (max 15 cm)

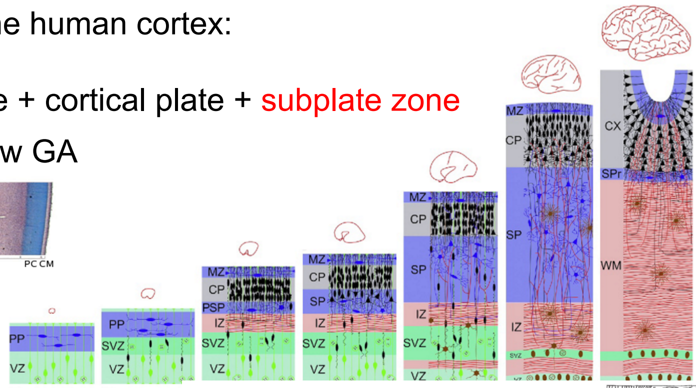
Adapted from slides by
Florent Meyniel, NeuroSpin

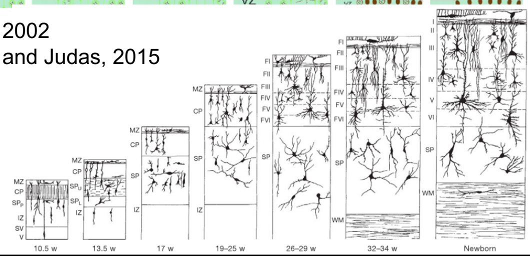
Transient laminar compartments

Formation of the human cortex:
- preplate
- marginal zone + cortical plate + subplate zone

Fetus 18w GA





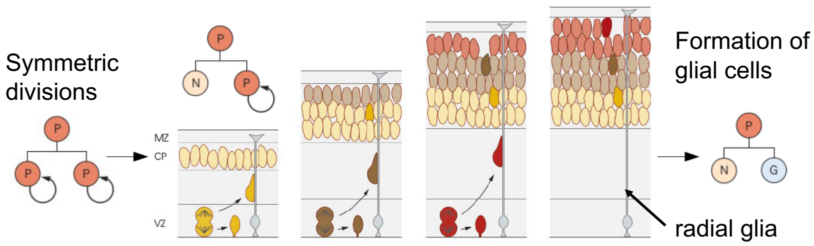


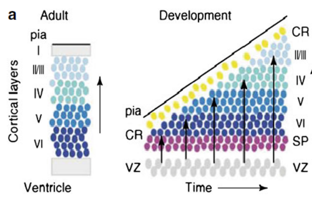
- MG germinal matrix
VZ ventricular zone
SVZ subventricular zone
- IZ intermediate zone
WM white matter
- PP preplate
(P)SP (pre-)subplate zone
CP cortical plate
MZ marginal zone
CX cortex

Kostovic 2002
Kostovic and Judas, 2015

Emergence of cortical columns

- Proliferation and migration from the ventricular zone follows an inside-out spatio-temporal sequence

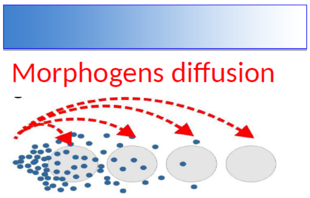




- “Radial unit hypothesis: the radial development could endow the emergence of cortical columns with functional specificity.

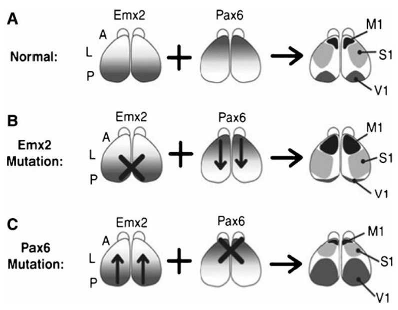
Genetic guidance

- Cortical regionalization / patterning (protomaps): effects of morphogens, of transcription factor genes



Gradients of secreted molecules generate a positional information.

If these molecules constrain genetic expression (transcription factor, mRNA silencing, …) and induce cellular differentiation, then the gradient results into a genetic patterning, i.e. a region-specific genetic expression.

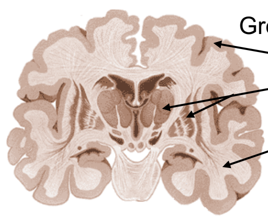


- Interaction between genetic patterning and activity-dependent patterning: “intrinsic” and “extrinsic” factors

Adapted from slides by Florent Meyniel, NeuroSpin
Stiles and Jernigan, 2010

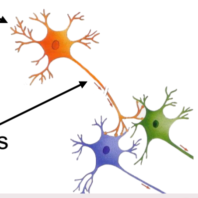
Development of brain connectivity

- Distant connections between brain regions, through fascicles of axons composing the white matter

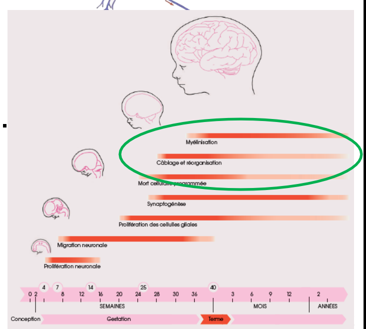


Grey matter: neuronal soma
cortex
central grey nuclei

White matter:
axonal fibers of neurons



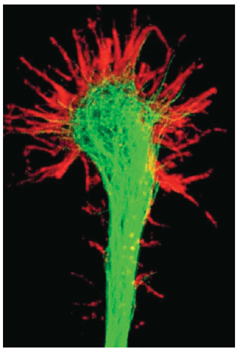
- During development, too many axonal connections are initially formed. They are further pruned during the early post-natal period (→ 1 year?) according to functional activity, environmental stimulation…



Axonal growth

- Pioneering axons, fasciculation process
- Growth cone: to explore the brain tissue and environment
- Axonal growth: guided by molecular signals to target cells
- Axons make transient contacts with a huge number of target cells, then *pruning* (e.g. corpus callosum) :
  → the excess of connections in the network are removed to reach mature configuration.
- Developing axons grow fastly, which is not the case during adulthood anymore.

Growth cone (sensory neuron)



actin filaments (accumulated in filopods)

microtubules

Pre-natal connectivity

- Transient fetal patterns of connectivity, different from post-natal connectivity
- Prenatal development: coordinated and regulated by interactions with several histogenetic events (proliferation, migration, cells aggregation, molecular specification of neuronal phenotypes, cell death, myelination…)

conception	early fetal period	middle fetal period	early pre-term period	late pre-term period	term

0 — 9 — 15 — 23-24 — 28-29 — 34 — 39 w PC

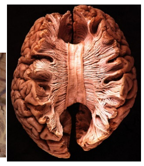
White matter bundles

Long bundles:

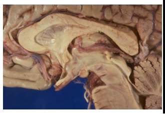
– Projection fibers between cortex and thalamus, midbrain, spinal cord, central grey nuclei

– Cortico-cortical association fibers:
  - between regions within an hemisphere (e.g. arcuate fasciculus)

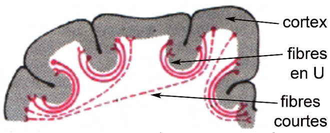
  - between regions of the two hemispheres (e.g. corpus callosum)



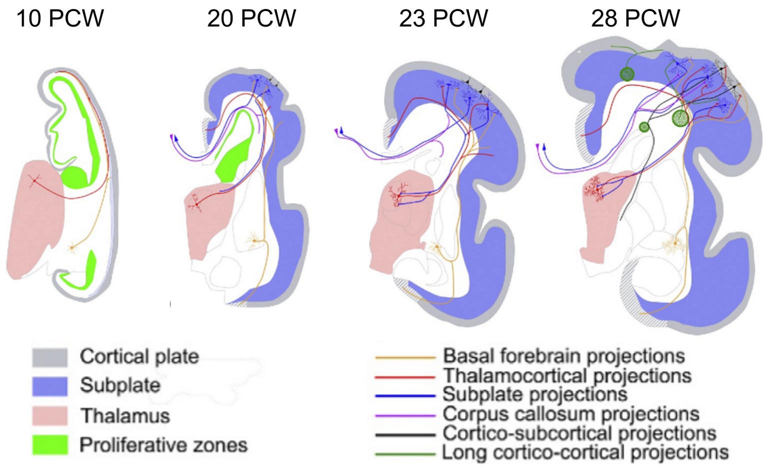
– Fibers of the limbic system (e.g. fornix)



+ Short cortico-cortical fibers, U fibers



Development of connections

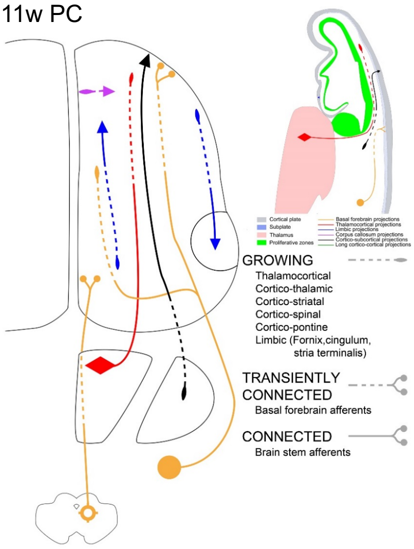


Through the subplate, an early cortical circuitry is transiently active (e.g. relay for thalamo-cortical fibers + connections from subplate neurons).

Judas & Kostovic, 2014

Early fetal period (9-15w PC)

11w PC



Judas & Kostovic, 2014

- Major pathways are growing and pathfinding within the intermediate zone. Some afferent (e.g. thalamo-cortical fibers in the internal capsule) and efferent (cortico-subcortical) fibers are already observed.
- Before penetrating into the cortical plate, thalamo-cortical fibers make connections with neurons of the subplate zone, that develops from 13PCW.
- Several limbic bundles (originating from amygdala, hippocampus, cingulate gyrus) are observed (e.g. cingulum).

Middle fetal period (15-23w PC)

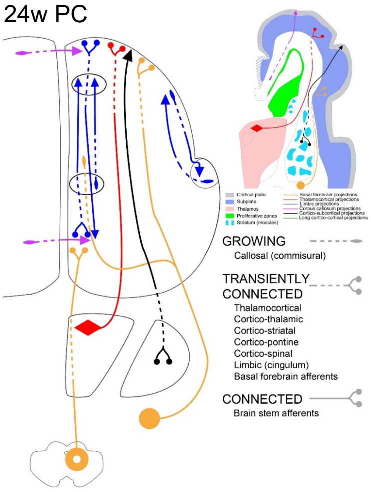
Subplate neurons are:
- targets for the growing afferent fibers
- origins for early efferent fibers
- constituting an early cortical circuitry that is transiently active.

- Major efferent pathways penetrate their targets in the striatum, the pons and the spinal cord.

- Periventricular cross-roads are developing, notably with the growth of cortico-cortical callosal and associative fibers (uncinate and inferior longitudinal fasciculi) within the intermediate zone.

Early pre-term period (24-28w PC)

24w PC

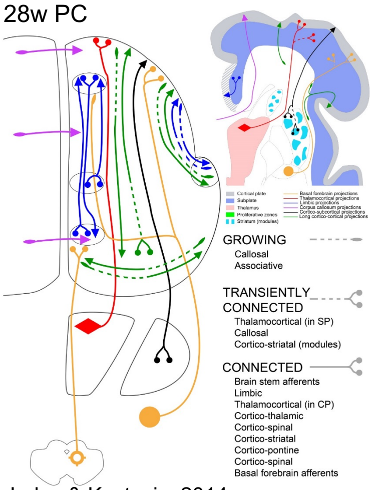


Judas & Kostovic, 2014

- Afferent fibers that were waiting in the subplate start making connections within the cortical plate in most brain regions, leading to the establishment of the permanent connectivity with neurons of the future cortical layer IV.
- A transient fetal circuitry still exists within the subplate, and this compartment reaches its maximum volume and thickness around 30PCW.
- Limbic cortico-cortical connections are well developed in the cingulate, entorhinal and hippocampal cortices.
- In the lateral neocortex, long cortico-cortical pathways are growing while short connections are little developed.
- Sleep / vigilance states are appearing.

Late pre-term period (29-34w PC)

28w PC



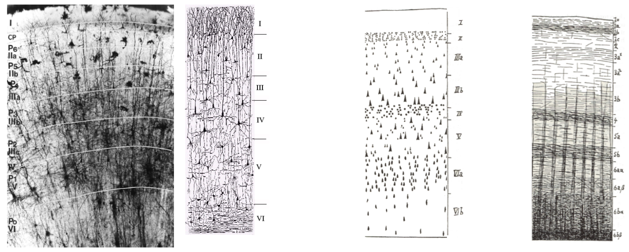
Judas & Kostovic, 2014

- Sensory thalamo-cortical pathways are synaptically active.
- Long associative and commissural bundles are quickly developing, likely originating from pyramidal neurons of cortical layer III.
- Short cortico-cortical fibers are growing and entering the cortex through the remnant subplate.

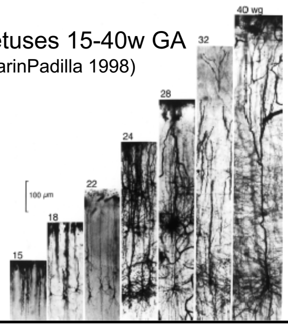
- Important apoptosis of neurons and axons (e.g. callosal fibers) regulated by neurotrophic factors depending on activity

Intra-cortical connectivity

Mature cortex: neuronal membranes (Golgi staining) cell bodies (Nissl) myelin (Weigert)

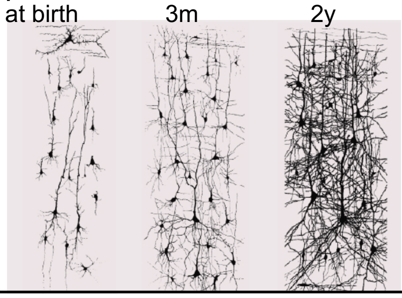


Fetuses 15-40w GA
(MarinPadilla 1998)



Development of dendritic arborization

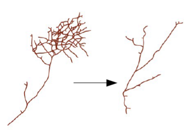
Infants at birth 3m 2y

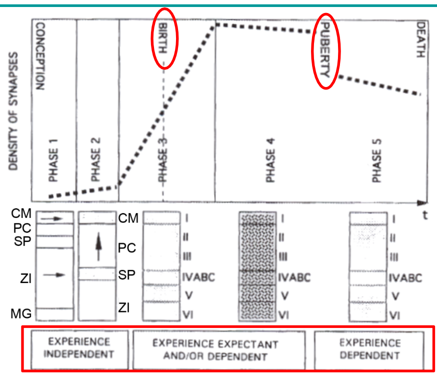


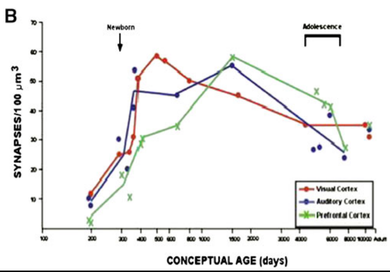
development

Synaptogenesis

- Begins after neuronal migration and axonal growth
- From middle gestation to adolescence
- 5 successive phases of formation and pruning, including:
  - exuberant production during the peri-natal and early post-natal period
  - strong elimination at puberty
- Variability according to brain regions
- Influence of electrical activity, sensory stimulations… and so early disturbances (e.g. prematurity)







Huttenlocher et al, Bourgeois 1996

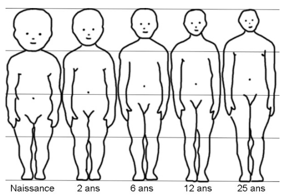
2. Brain development after birth

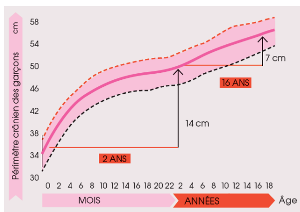
Jessica Dubois, Brain development

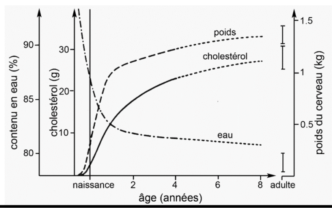
2/8 After birth

Specificities of the human species

- Important developmental processes during gestation
- A relatively large and organized brain at birth, with an early architecture of networks
- But still a very immature brain: intense changes to come during infancy
- Considerable sensori-motor and cognitive advances during a very long post-natal period of development
- Permitting progressive and successive phases of learning



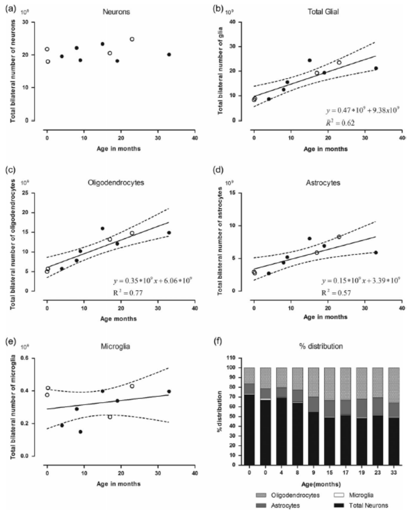


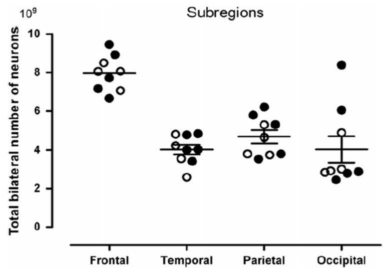


2/8 After birth

Brain cellular content at birth

From term birth to 3 years:
- stable number of neurons, differences across lobes
- increase in oligodendrocyte and astrocyte numbers





Kjær et al, Cerebral Cortex 2016

Jessica Dubois, Brain development

2/8 After birth

Connectivity at birth

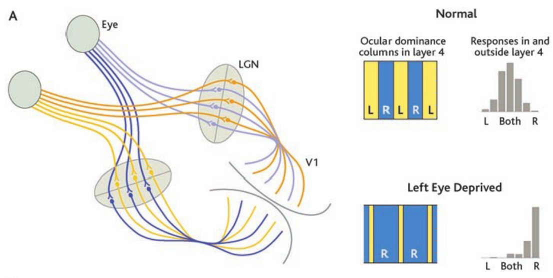
- Main long-distance connections are in place.
- U-fibers further develop, and cortico-cortical connectivity is reorganized by several processes including the development of dendritic arborization, the overproduction of synapses and dendritic spines and their later elimination.
- Pruning of axonal fibers like callosal connections also probably extends until the end of the first post-natal year.

Jessica Dubois, Brain development

Functional segregation

- Activity-dependent changes and “hebbian” plasticity in the developing cortex:
  “cells that fire together work together”
- Activity-dependent pruning of neuronal connections

The canonical example of ocular dominance columns

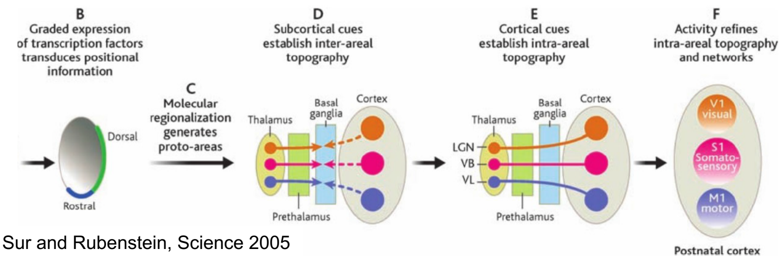


Sur and Rubenstein, Science 2005

Functional segregation

The cortical regionalization and the development of sensory maps depend on a complex sequence of intrinsic and extrinsic factors. It combines two mechanisms:

- “protomap”: hypothesis emphasizing the role of molecular signaling of neural progenitors
- “protocortex”: hypothesis emphasizing the cortex homogeneity, and its functional segregation based on differential input activity and interactions with the environment.

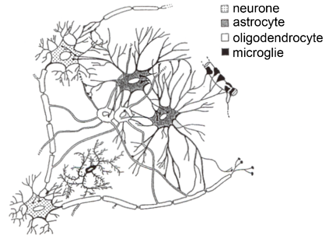


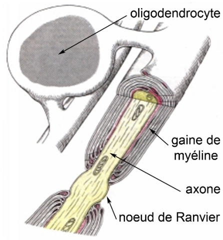
Sur and Rubenstein, Science 2005

2/8 After birth

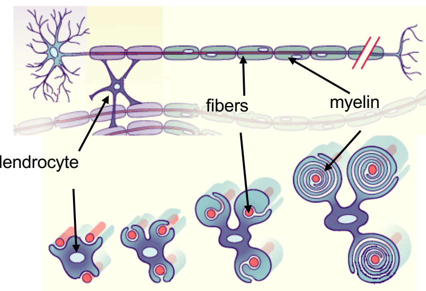
Fiber myelination

- Another important post-natal process
- Role of oligodendrocytes
- Myelin sheath and speed of neural impulse conduction





- Myelination stages:
  - "pre-myelination" (proliferation of glial cells, oligodendrocyte expansions…)
  - "true" myelination (ensheathment of myelin)



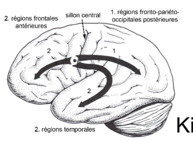
2/8 After birth

The progression of myelination

- Early maturation of primary sensori-motor pathways
  Late and protracted maturation of associative pathways
- This asynchrony is assumed to be related with the progression of functional acquisitions.

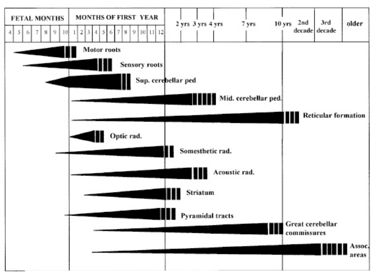
Post-mortem myelin staining

Flechsig, 1920



Kinney, 1988

Cycles of myelination



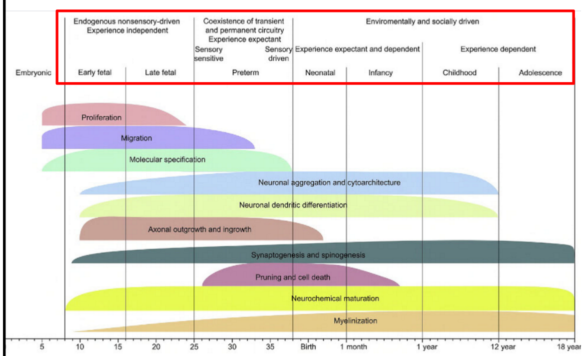
Yakovlev and Lecours, 1967

Critical periods of development

- Characterized by massive plasticity
- Required to consolidate the architecture
- Based on interactions with the environment (evoked activity)
- Limited in time
- Different timelines and patterns across brain functions
- Followed by a “freezing” of the system?
- Later plasticity is far less important, but still exists (important for the adaptation to the environment)

Role of activity and stimulation

Successive types of neural activity: endogenous (non-sensory driven), sensory-sensitive, sensory-driven, experience-expectant, experience-dependent



Kostovic and Judas.
Brain Mapping: An Encyclopedic Reference 2015

Period	Circuit	Type of activity
Neonate	Permanent, with transient elements	Sensory-driven, centered on layer V
2-6 mo	Permanent with transient elements	Sensory-driven, columnar processing
7-12 mo	Initial cognitive circuit	Environmental driven, local circuit
12-24 mo	Cognitive	Socially driven, centered on layer III

earlier?

Gazzaniga, The cognitive neuroscience. 4th ed. Chap 2

Early cognitive processing in specific brain networks highlighted by recent neuroimaging studies

3. Studying brain development *in vivo*

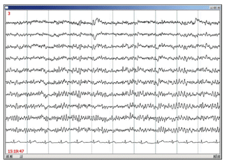
The revolution of neuroimaging

- Key aspects characterizing the developing brain:
  - early architecture of brain networks in newborns
  - different and asynchronous progression of maturation across brain functions in infants

- How can we relate the behavioral acquisitions with brain developmental changes?
  → *in vivo* and *non-invasive* exploration of the brain with neuroimaging

Measuring brain activity in infants

- ***Electroencephalography*** EEG
recording neural activity
☺ Temporal resolution
☹ Spatial localization



- ***Magnetoencephalographie*** MEG
recording neural activity
☺ Temporal resolution, spatial localization
☹ Motion sensitivity, adult systems

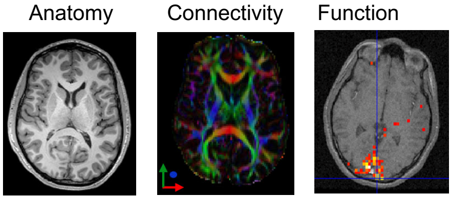
- ***Near infra-red spectroscopy*** NIRS
recording hemodynamic responses
% blood oxygenation (~fMRI)

Imaging the human brain

- ***Magnetic Resonance Imaging*** MRI: non-invasive technique!

Brain: water H_2O
Different modalities

Anatomy | Connectivity | Function



T1w, T2w | Diffusion MRI | Functional MRI

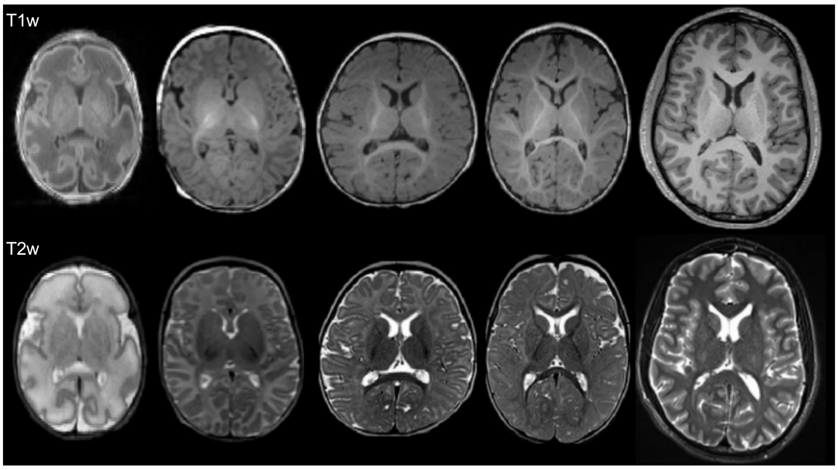
☺ Spatial localization
☹ Scanner noise, motion sensitivity
☹ For fMRI: temporal resolution, indirect measure of neural activity

→ For infants imaging: short acquisition times and dedicated sequences

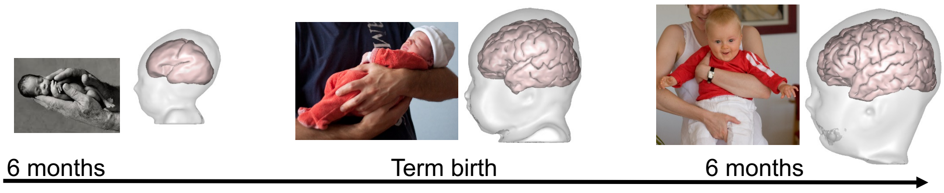
4. MRI of the brain *structural* development

The developing brain

Preterm 7 months	After term birth 1 month	4 months	8 months	adult



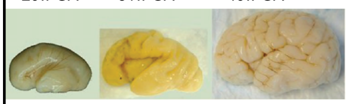
Outline of the studied mechanisms



6 months | Term birth | 6 months

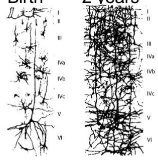
CORTEX Folding

20w GA | 31w GA | 40w GA

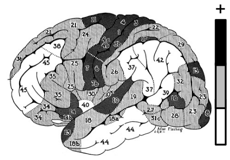


Microstructure

Birth | 2 years



Maturation

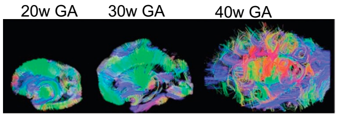


Flechsig, 1901, 1920

WHITE MATTER

Development of connectivity

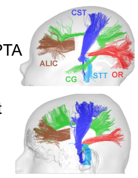
20w GA | 30w GA | 40w GA



Takahashi *et al*, 2012

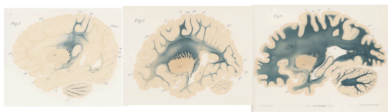
6w PTA

adult



Myelination

birth | 4 months | adult

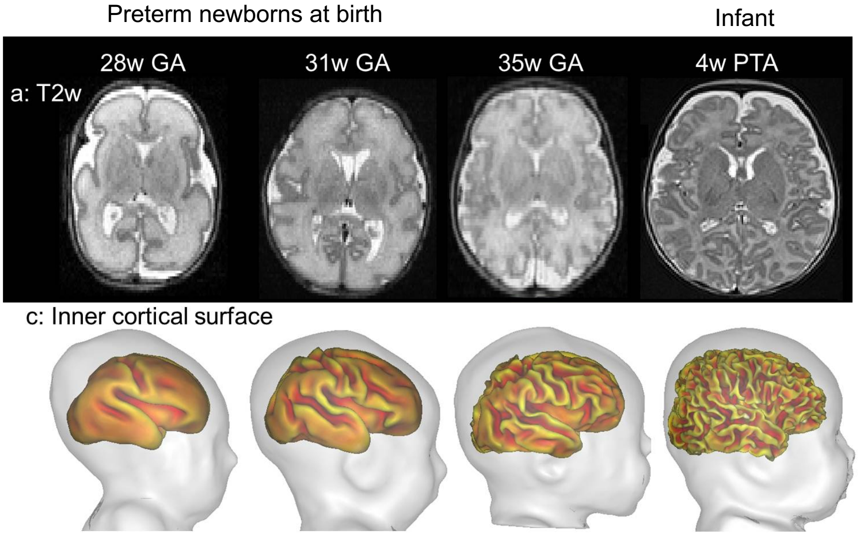


4. MRI of the brain *structural* development

- Brain folding
- Cortical growth
- Cortical microstructure
- White matter connectivity
- White matter maturation

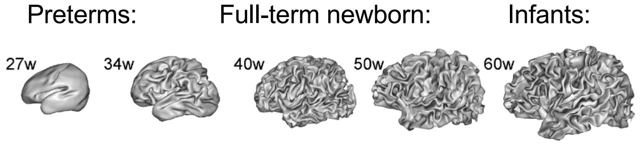
Cortical folding

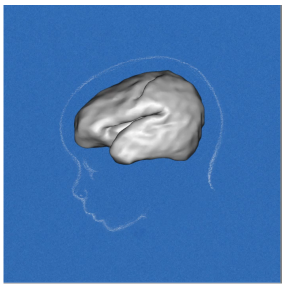
A marker of brain growth, resulting from the interaction between the growth of cortex and white matter?



Dubois and Dehaene-Lambertz, Brain Mapping 2015

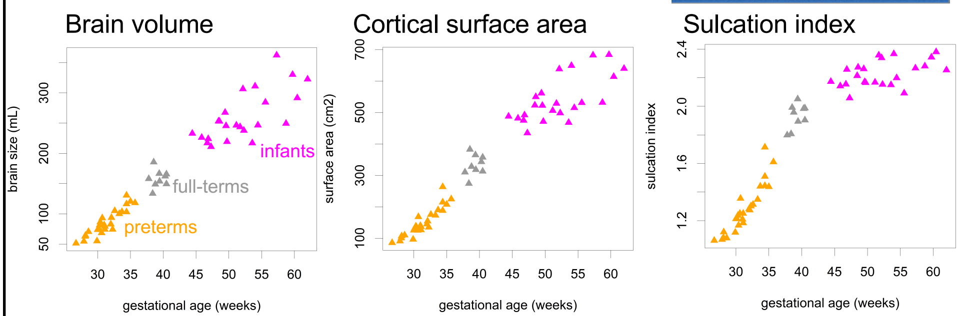
Development of cortical surface





Intense progression of folding between 30 and 40w PMA

Renaud Chabrier
Universcience

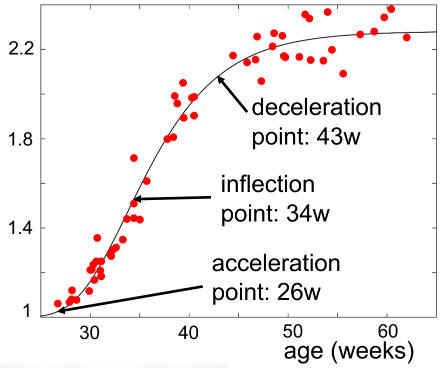


Dubois *et al*, IEEE ISBI 2016

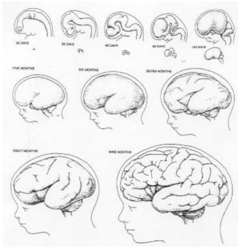
Evolution of cortical folding

The sulcation index is the slowest at the start and end of the time period.

It highlights successive critical points, but not necessarily the successive waves of primary, secondary and tertiary folding.



39w — tertiary folds
32w — secundary folds
14w — primary folds

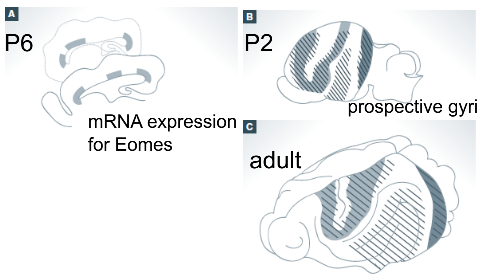


Cowan 1979

Origins of folding?

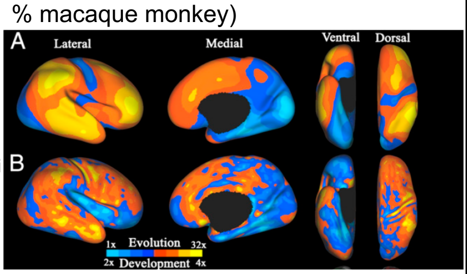
- Folding organization around stable points (“growth seeds”)
- Differential growth of tissues (grey and white matter) with distinct mechanical properties (e.g. elasticity)
- Tension of glial and axonal fibers?
- Genetic control (% phylogeny)

Patterns of gene expressive % prospective location of cortical folds in the ferret brain



Fernandez et al, EMBO 2016

Evolutionary cortical expansion (human % macaque monkey)

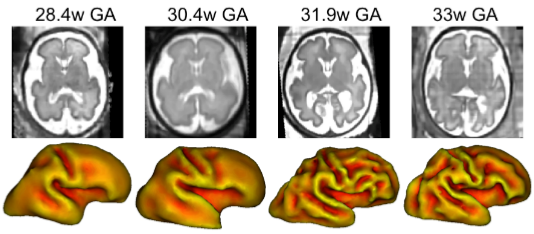


Vs human post-natal cortical expansion

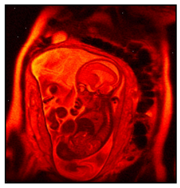
Hill et al, PNAS 2010

Early differences in folding

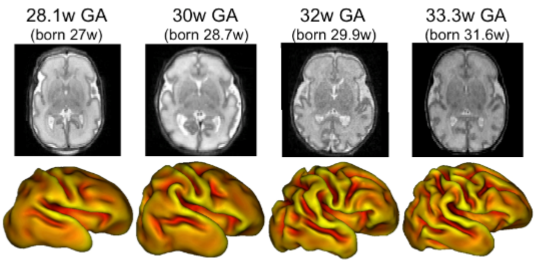
Fetuses



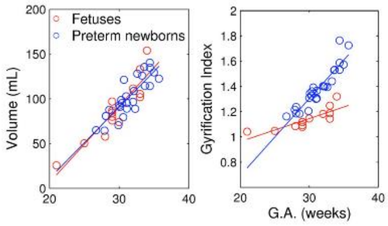
For equivalent age:
- similar brain volume and rate of sulci appearance
- but different trajectories in parameters of cortical morphology.



Preterms ***close to birth***



The transition from *in* to *ex utero* has a major impact on folding.

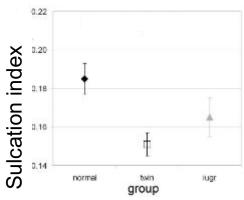


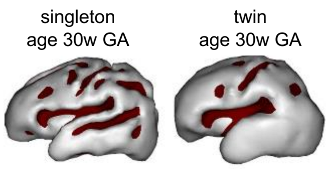
Coll. J. Lefèvre, Pr N. Girard (Marseille University Hospitals, INT)
Lefèvre *et al*, Cerebral Cortex 2016

Early impairment in folding

Comparison between preterm newborns at birth

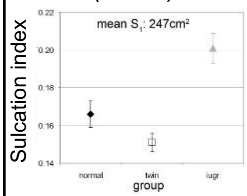
– Harmonious delay in twins

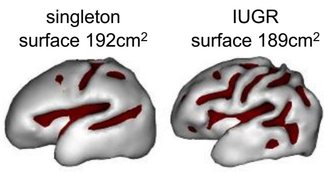




For equivalent age: cortical surface and folding are lower (delay ~2 weeks)

– Dysharmonious delay in newborns with intra-uterine growth restriction *(IUGR)*



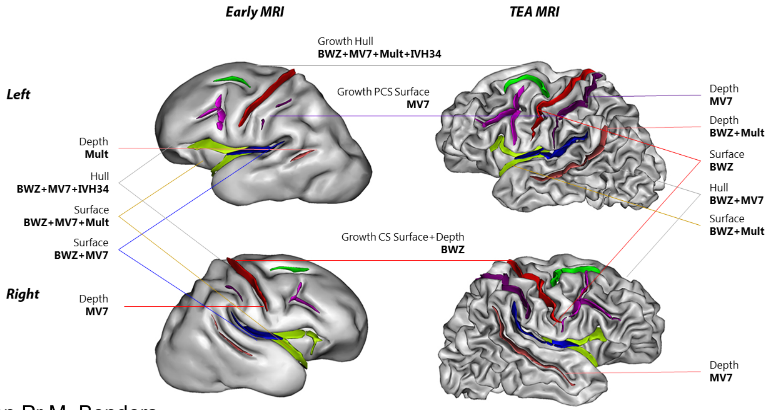


For equivalent cortical surface: folding is too high (folding is less delayed than surface growth)

Dubois *et al*, Brain 2008

Early impairment in folding

Preterm newborns at 30w and 40w PMA
Major impact of birth weight, multiple pregnancy, severity of illness (prolonged mechanical ventilation)



Collaboration Pr M. Benders
(Utrecht University Hospitals)

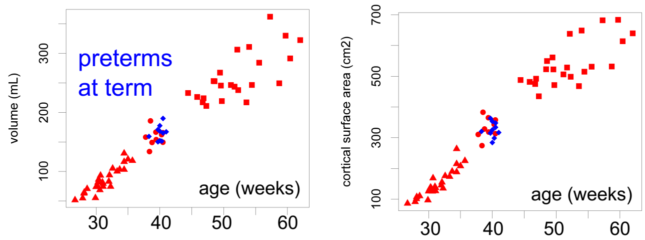
→ Sulci developing the earliest are the most affected by clinical factors.

Kersbergen *et al*, Neuroimage 2016

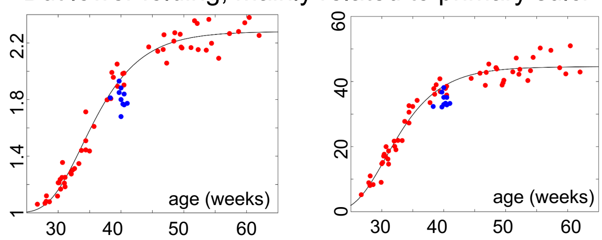
Folding and prematurity

'Healthy' preterm infants at term equivalent age % 'typical' newborns:

Similar brain size and cortical surface

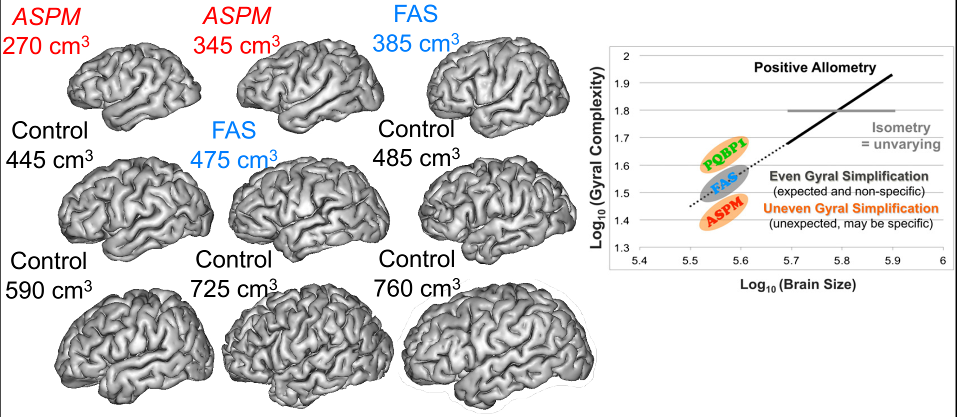


But lower folding, mainly related to primary sulci



Folding disturbances

Microcephalies: gyral simplification mainly results from brain size reduction (notably in fetal alcohol syndrome FAS), with an additional negative (vs positive) disease effect for severe microcephalies related to ASPM (vs PQBP1).



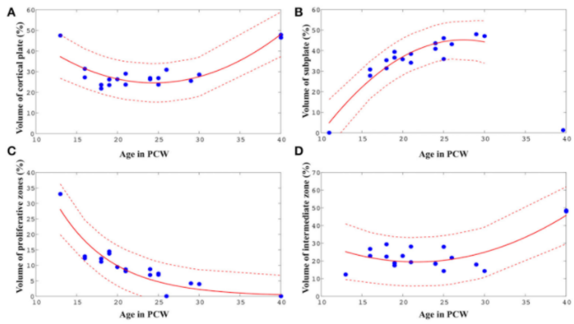
Germanaud et al, Neuroimage 2014

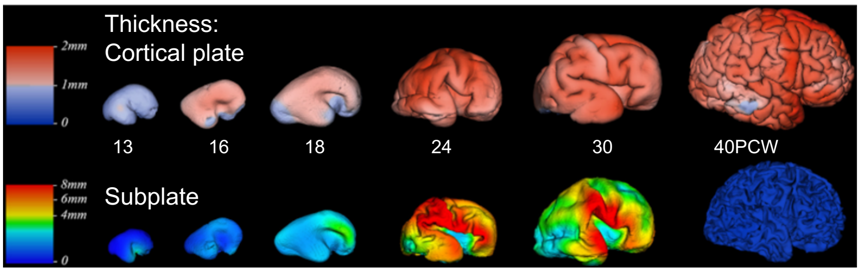
4. MRI of the brain *structural* development

- Brain folding
- Cortical growth
- Cortical microstructure
- White matter connectivity
- White matter maturation

Growth of brain compartments

Post-mortem MRI of fetal specimen:
Identification of subplate and cortical plate

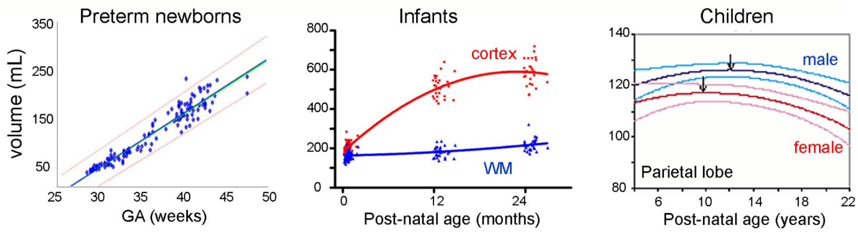




Vasung et al, Front Neuroanatomy 2016

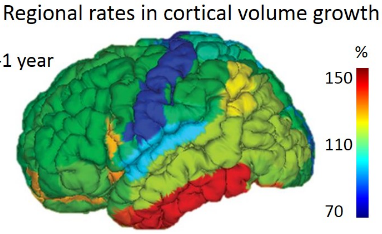
Cortical growth

a. Changes in the volume of cortex during childhood



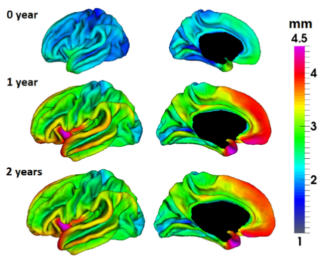
Kuklisova-Murgasova et al 2011 Knickmeyer et al 2008 Giedd et al 1999

a. Regional rates in cortical volume growth



Gilmore et al 2012

Changes in cortical thickness



Li et al, J. Neurosci. 2015

Dubois and Dehaene-Lambertz, Brain Mapping 2015

4. MRI of the brain *structural* development

- Brain folding
- Cortical growth
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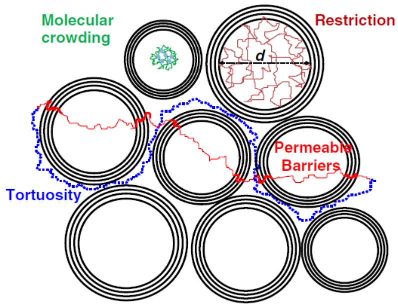
- White matter maturation

These macrostructural changes are the visible marker of the microstructural evolution, marked by synaptic outburst and pruning, modifications in dendritic branching, and fiber myelination.

Diffusion MRI

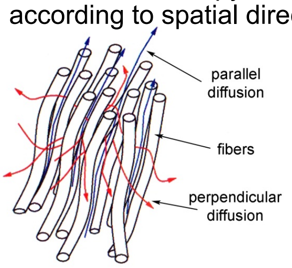
Brownian motion (free diffusion)

Hindered diffusion in brain tissue

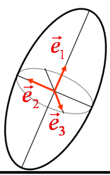


Le Bihan and Johansen-Berg, Neuroimage 2012

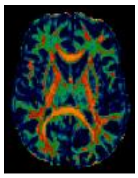
Diffusion anisotropy: diffusion differs according to spatial directions



Tensor modelling:
diffusion tensor imaging (DTI)



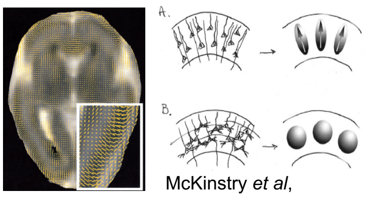
Map of anisotropy



Development of microstructure

- Radial organization of the cortex during the preterm period (early anisotropy) which disappears with the development of dendritic arborization

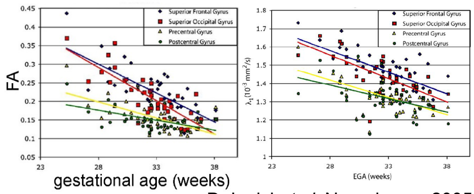
26w GA



McKinstry *et al*, Cereb Cortex 2002

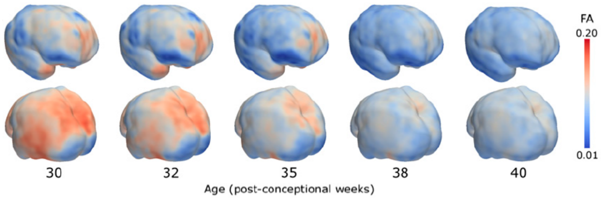
Diffusion tensor imaging DTI

anisotropy FA   longitudinal diffusivity $\lambda_{//}$



Delpolyi *et al*, Neuroimage 2005

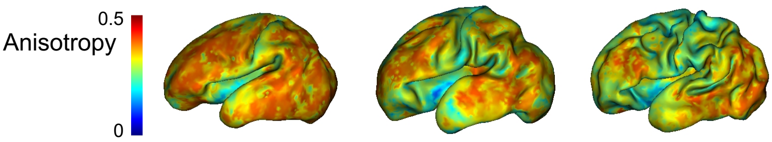
- Variations across brain regions



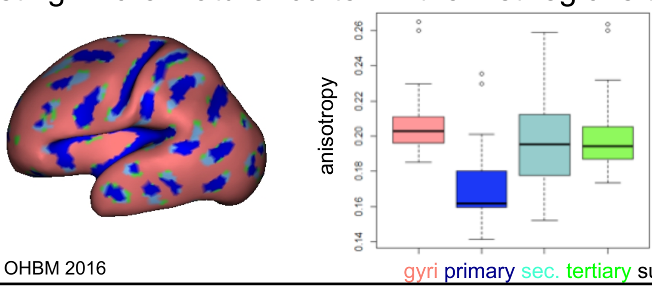
Ball *et al*, PNAS 2013

The preterm cortical microstructure

- Relationships between folding and microstructural development?
- Differential decrease in anisotropy across brain regions



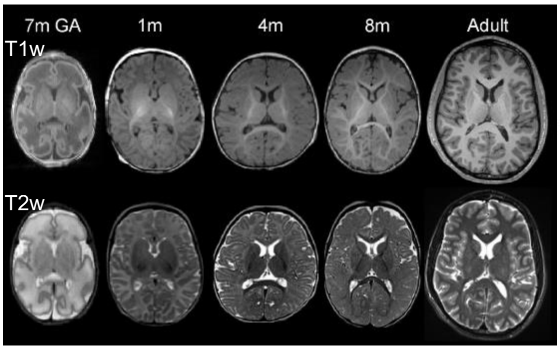
- Lower anisotropy in primary sulci than in other folds and gyri, suggesting "more mature" cortex in the first regions to fold.



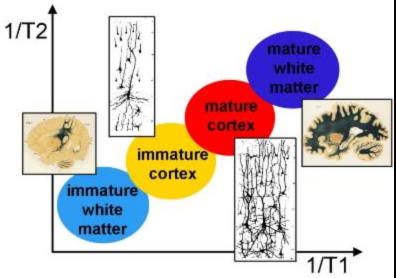
Zomeno *et al*, OHBM 2016

Maturation during infancy

T1 and T2 relaxation times show huge decreases during development



Larger changes in white matter than in grey matter

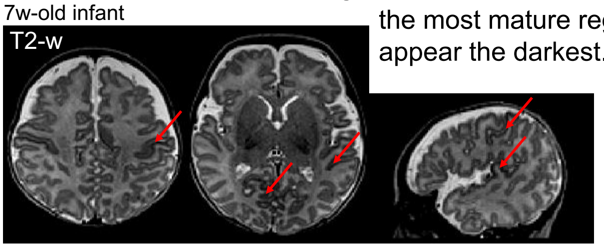


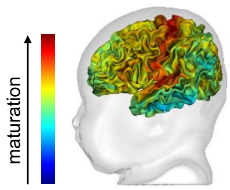
Dubois *et al*, Neuroscience 2014

Cortical maturation

- Differences of T2w signal across cortical regions in infants: the most mature regions (e.g. primary cortices) appear the darkest.

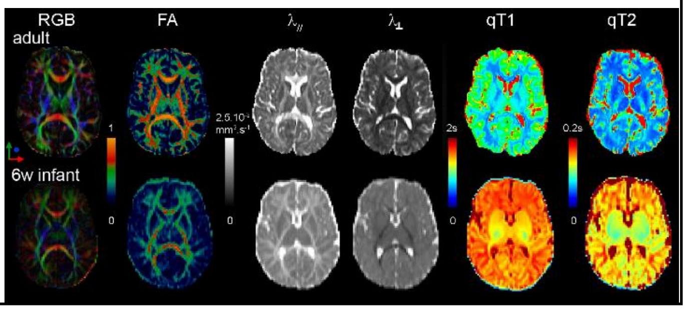
7w-old infant





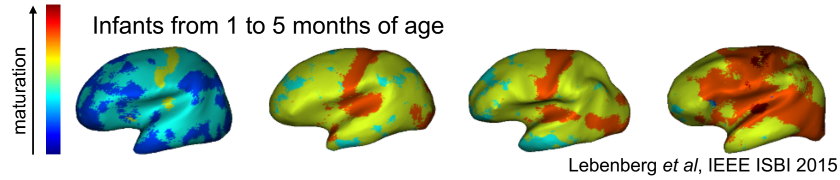
Leroy *et al*, J. Neuroscience 2011

- Multi-parametric MRI: DTI, quantitative T1 and T2
  → complementary information



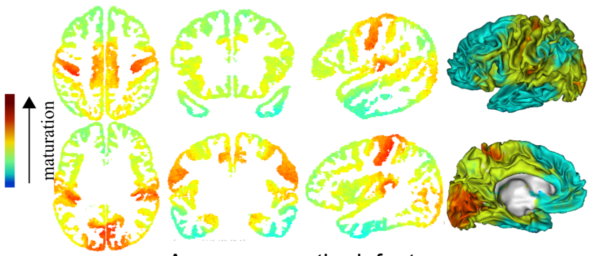
Asynchrony of maturation

- Clustering cortical regions according to maturational properties (no hypothesis on infants age or spatial localization)



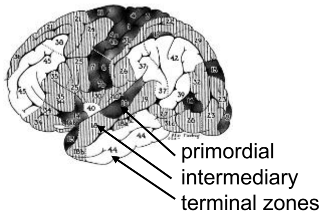
Lebenberg *et al*, IEEE ISBI 2015

- Primary sensori-motor regions mature before associative regions



Average over the infants group

Flechsig myelin maps (1920)



Measuring cortical maturation

Which processes do we measure with MRI during infancy?

- Density of neurons (< 1 year), dendritic arborization and synaptogenesis?
- Density of glial cells (++ during the first years)
- Myelination of intra-cortical fibers
- Associated with changes in cortical thickness: increase from 1.3 mm in newborns to 1.5-5.5 mm during childhood, followed by a decrease during adolescence, asynchronously across brain regions.

Influence of several factors

Numerous factors affect early cortical development:

- genes (monozygotic vs dizygotic twins): heritability of cortical volume (but decreasing with age); environmental influences on surface measures; cortical thickness: early-developing regions show greater genetic effects during early childhood, while later-developing regions seem more heritable in adolescents.
- birth weight (even in children born full term, a longer duration of gestation -until 41w GA- seems beneficial), nutrition, stress, toxics
- interaction between prenatal environment and genetic expression (e.g. fetal alcohol exposure in twins) → epigenetic factors
- sex: in relation to body mass index, hormones (cerebral androgen receptor signaling) and sex chromosome gene dosages
  [boys are more vulnerable than girls to early developmental disturbances (e.g. worse outcome in case of premature birth)]
- socio-economic status, parental education → environmental factors

Longitudinal studies should be preferred to assess developmental trajectories, in relation to cognitive performances.

4. MRI of the brain *structural* development

- Brain folding
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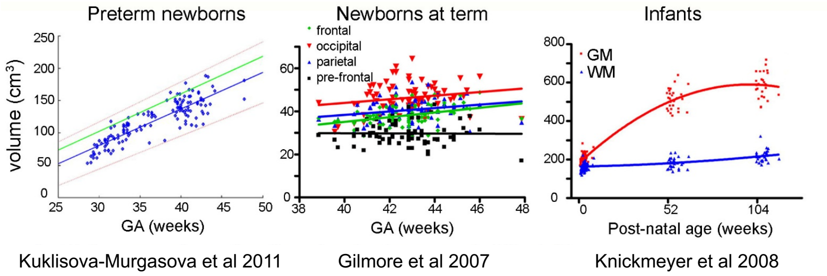
- Cortical microstructure
- White matter connectivity
- White matter maturation

Growth of white matter

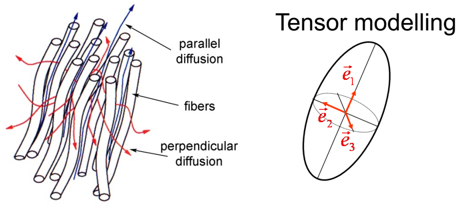
- Volume of white matter



- Development of connections (mostly prenatally)
- Followed by intense maturation (myelination) until adulthood, leading to major volume increase

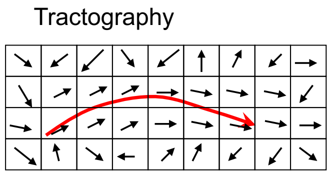
Tractography of bundles

- Diffusion imaging

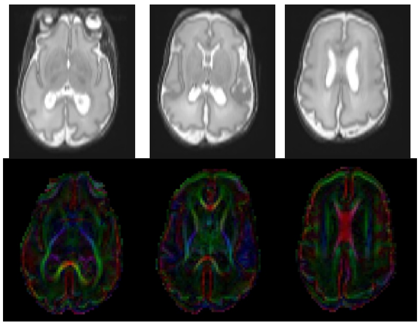


- Reconstruction of white matter bundles:
  Whole-brain tractography
  Individual regions to select bundles of interest

PTK-Connectomist software
C. Poupon's team, NeuroSpin

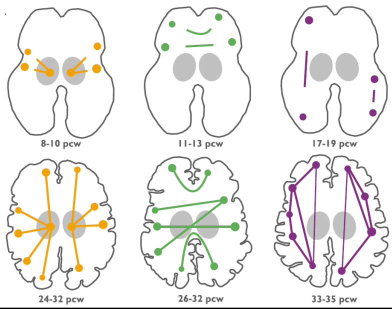


Connectivity in preterm newborns



Preterm 30w PMA

Collaboration Pr M. Benders
(Utrecht University Hospitals)

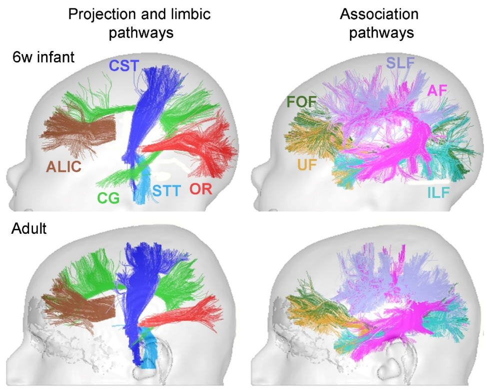


Projection fibers
Commissural fibers
Association fibers

Keunen et al, Neuroimage 2017

Early organization of bundles

At birth, the major bundles are already observed with diffusion MRI and tractography → a similar architecture of brain networks in infants and adults



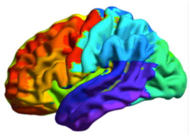
AF arcuate fasciculus
ALIC anterior limb of the internal capsule
CG cingulum
CST cortico-spinal tract
FOF fronto-occipital fasciculus
ILF inferior longitudinal fasciculus
OR optic radiations
SLF superior longitudinal fasciculus
STT spino-thalamic tract
UF uncinate fasciculus

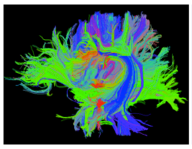
infants 3-22w
MRI at 3T
b=700s.mm^{-2}
30 directions
1.8mm iso

Dubois *et al*, Neuroimage 2006
Dubois *et al*, Neuroscience 2014

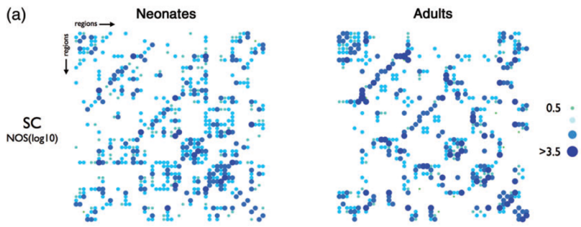
The developing 'connectome'

- Connectivity matrix: between pairs of brain regions





- In preterms at 30w PMA, networks already show similar architecture and properties compared to adults.



- Networks are further refined until term equivalent age.
- Some post-natal changes are observed, mostly during the first 2 years.

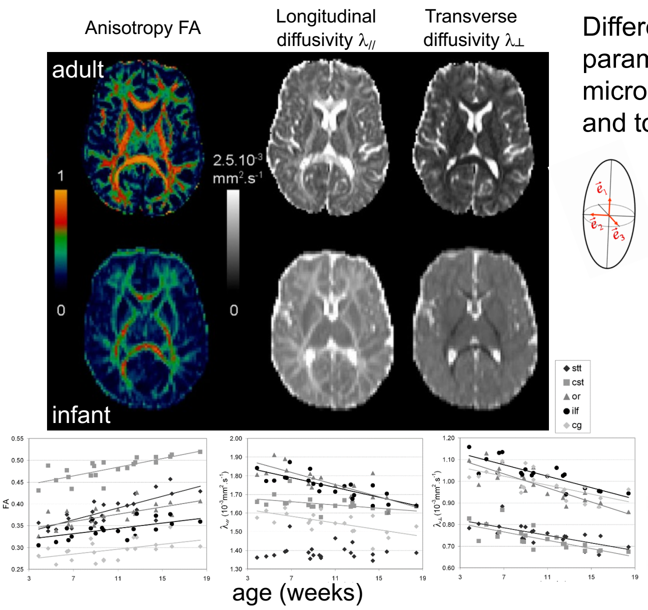
van den Heuvel *et al*, 2014; Ball *et al*, 2014; Yap *et al*, 2011; Hagmann *et al*, 2010

4. MRI of the brain *structural* development

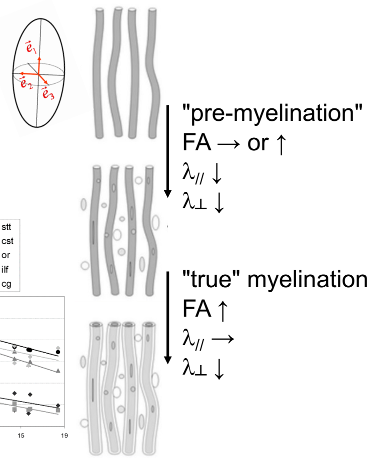
- Brain folding
- Cortical growth
- Cortical microstructure
- White matter connectivity
- White matter maturation

4/8 Structural development

DTI of white matter maturation



Different sensitivity of DTI parameters to the bundles microstructure (compactness) and to stages of maturation



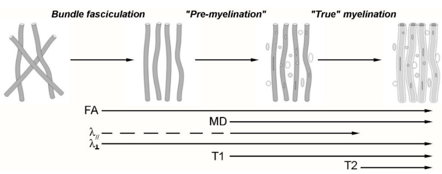
Dubois *et al*, Human Brain Mapping 2008

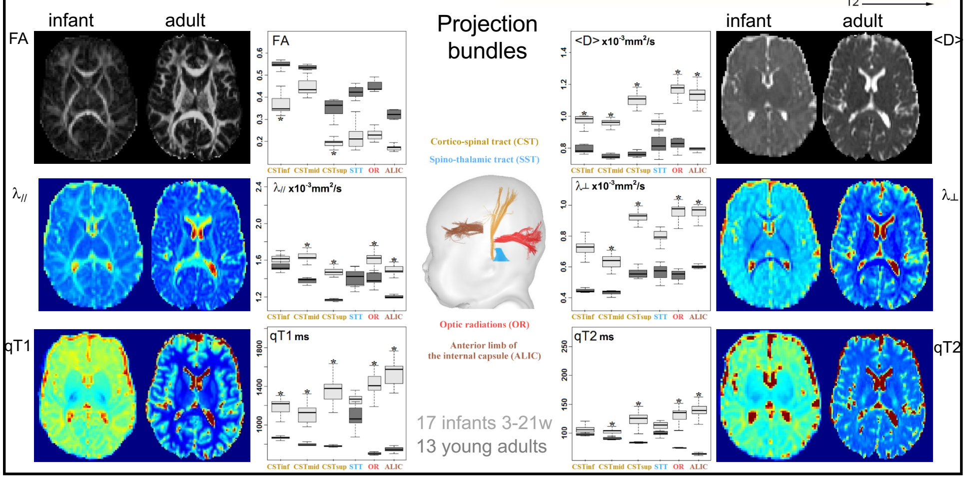
Jessica Dubois, Brain development

4/8 Structural development

Multi-parametric MRI of maturation

Successive stages of maturation and complementarity of MRI parameters





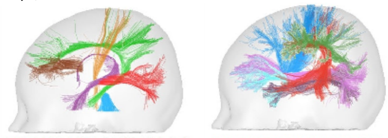
Quantifying the bundles maturation

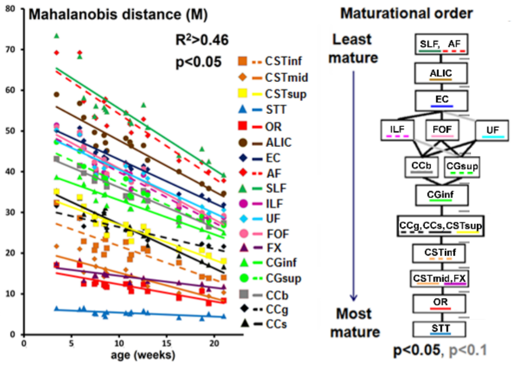
- Comparison between immature vs mature bundles
- Taking into account the adult inter-subject variability of each MRI parameter, and the correlations between MRI parameters
- "Mahalanobis distance" to the adult stage based on (T1, T2, $\lambda_{//}$, $\lambda\perp$):

$$M^2(\vec{x}) = (\vec{x}-\vec{\mu})^T \cdot \Sigma^{-1} \cdot (\vec{x}-\vec{\mu})$$

$\vec{x}$ in each infant

$\vec{\mu}, \Sigma$ in the adult group





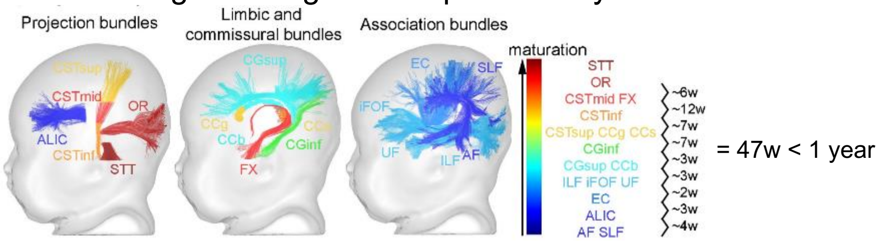
- Relative maturation delays: for a bundle *b*

$$M(b, age) = M_0 \cdot \exp(-c \cdot (age - age_0(b)))$$

Kulikova *et al*, Brain Structure and Function 2015

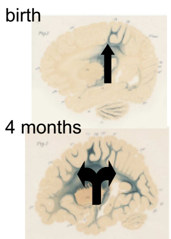
Asynchrony in maturation

- Intense changes during the first post-natal year

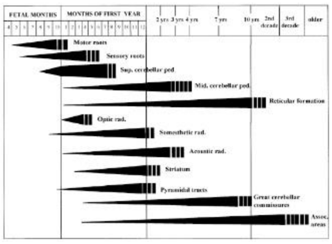


Dubois *et al*, Brain Mapping: An Encyclopedic Reference 2015

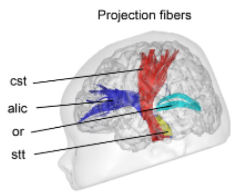
- Consistency with post-mortem and previous DTI studies



Flechsig, 1920



Yakovlev and Lecours, 1967



Dubois *et al*, Human Brain Mapping 2008

4/8 Structural development

Mapping the myelinated white matter

- *Modelling* 3 compartments of water:
  - myelin-related water
  - intra/extra-cellular water
  - free water (CSF)

  with specific $T1_c$ and $T2_c$ characteristics and different fractions f_c

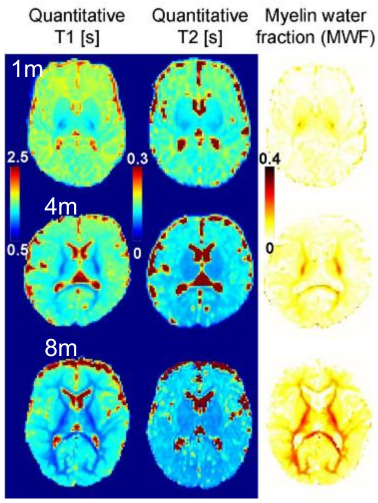
  $$\sum_{c=1}^{3} f_c = 1 \text{ inside each voxel}$$

  (Lancaster *et al*, 2003; Deoni *et al*, 2011)

- Dedicated strategy:

  1) "calibration" of $T1_c$ and $T2_c$ in adults (myelin-related water: $T1_{MW}$ ~ 357ms, $T2_{MW}$ ~ 18ms)

  2) estimation of f_c in infants based on short acquisition protocol (<6min) and fast post-processings (<5min)

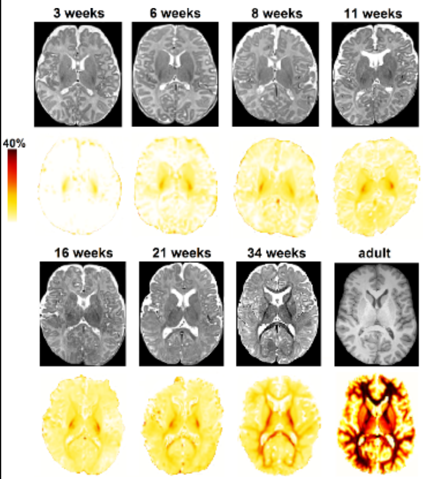


MRI at 3T

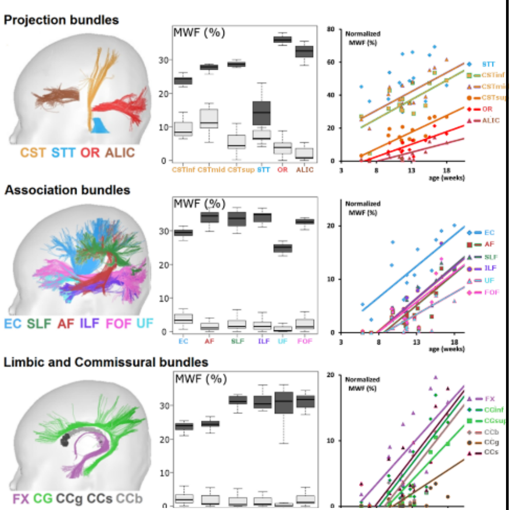
Kulikova *et al*, Plos One 2016

4/8 Structural development

Myelinated white matter



Different myelination across bundles



→ Intense changes during the first post-natal year

Kulikova *et al*, Plos One 2016

Myelination and brain networks

Myelination and neural development are related in a complex way:

- Myelination impacts electrical activity which also controls its induction (Barres and Raff 1993; Demerens *et al*, 1996; Gyllensten and Malmfors 1963; Kinney *et al*, 1988; Tauber *et al*, 1980).
- By increasing the conduction speed, myelination enables to decrease transfer times early on (at constant distance), or compensate for brain growth later on (at constant processing time).
- Oligodendrocytes and myelin might inhibit the neural growth and pruning, playing a role in the network stabilization.

For a review Dubois *et al*, Brain Plasticity 2017

Myelination and brain plasticity

'Remodeling myelination' (plastic regulation):

- Myelin is not simply a static structure
- Oligodendrocytes are responsive to individual axons and adjust myelination parameters actively
- Myelination can modulate information flow in neural circuits through several mechanisms:
  (i) new myelination of unmyelinated axons or unmyelinated segments of myelinated axons
  (ii) myelin replacement
  (iii) thickening or thinning of existing sheaths
  (iv) lengthening or shortening of existing sheaths
  (v) myelin retraction

Chang et al, Nature Neuroscience 2016

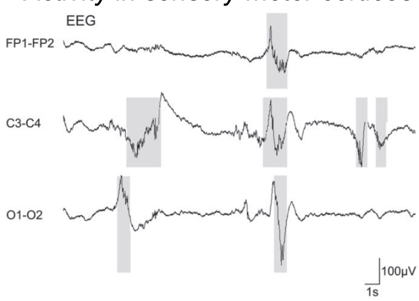
5. Neuroimaging of early *functional* activity

- EEG activity
- Resting-state functional connectivity
- Imaging of metabolic changes

Early electrical activity

- During the pre-term period, the default EEG state is "silence".
- Endogen electrical activity and "sensory-driven" activity are critical for wiring and refining the developing circuits (Penn and Shatz 1999).
- Spontaneous thalamo-cortical activity in primary sensory regions is generated by sensory periphery in the immature brain (e.g. retinal waves).

Activity in sensory-motor cortices

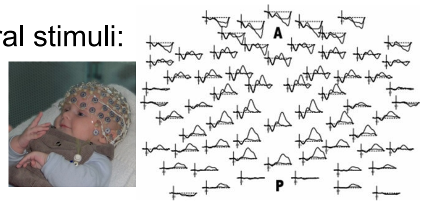


Milh *et al*, Cerebral Cortex 2006

- Dominant EEG pattern of rapid oscillatory activity in preterms from 24w GA: "delta-brush" / "spontaneous activity patterns" (SATs)
- Activity generated by the cortical plate or by the subplate? (subplate: transitory compartment that relays thalamo-cortical projections until 24-28w PC)

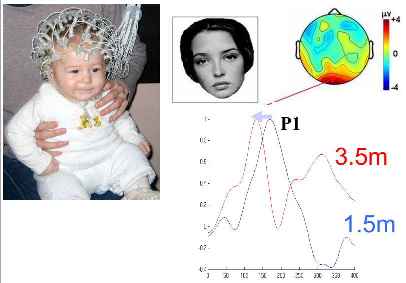
Stimulus-evoked potentials

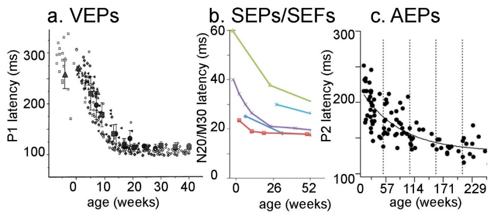
• Averaging EEG responses for several stimuli:
visual-evoked potentials VEP
somatosensory-evoked potentials SEP
auditory-evoked potentials AEP



• Major changes in the patterns of responses (peaks, amplitudes…)

• Decrease in the latency with age, mainly due to the myelination of white matter pathways that conduct the neural information.





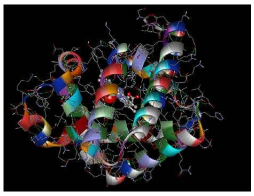
5. Neuroimaging of early *functional* activity

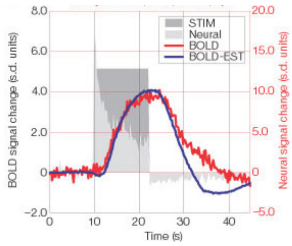
- EEG early activity
- Resting-state functional connectivity
- Imaging of metabolic changes

Hypothesis: Two regions belong to the same functional network if their activities fluctuate with correlated rhythms.

Brain activity and fMRI

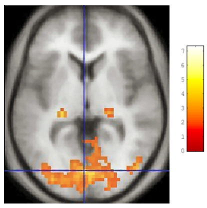
- BOLD effect (*blood oxygen level dependent*):
  Different magnetic properties of oxy- vs deoxy-hemoglobin.
- Detecting brain activations with fMRI:
  In each image voxel: compare the temporal evolution of MRI signal with the timing of stimuli.
  Statistical maps: all voxels where such analysis shows similarities between BOLD response and stimulation.
  → Indirect measure of neuronal activity





Logothetis *et al*, 2001

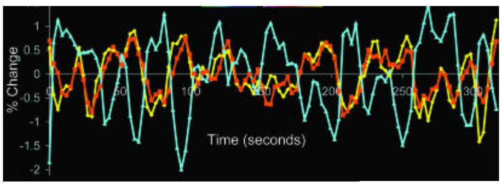
Visual stimulation in adults



statistical significance

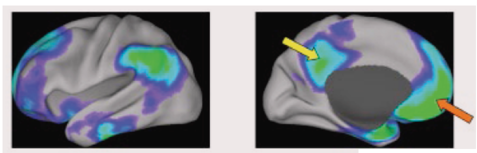
Functional connectivity and rs-fMRI

- Intrinsic brain activity during *resting-state* (rs)
- Slow spontaneous fluctuations of BOLD signal in each cortical region. Temporal correlations of these fluctuations between distant regions.



Fox *et al*, 2005

- In the adult brain:
  several main networks
  e.g. the *default-mode network*: prevailing during the inactive vigilance state, its activity decreases as soon as the brain is sollicitated by a specific task.

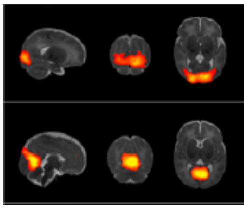


Raichle *et al*

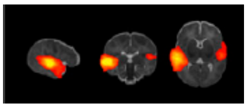
Connectivity networks in babies

- At 40w PMA (term birth), the main networks are observed.

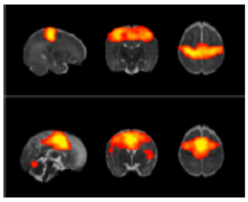
visual



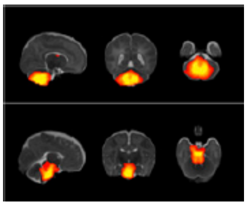
auditory



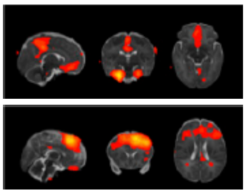
somatosensory
motor



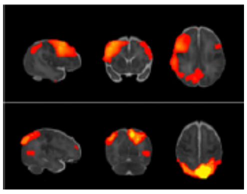
cerebellum, midbrain
and thalamus



default-mode
executive control



dorsal visual stream



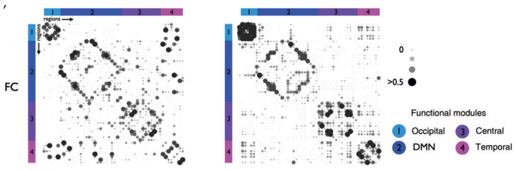
Doria *et al*, 2010; Smyser *et al*, 2010; Fransson *et al*, 2009, 2011;
Thomason *et al*, 2014; van den Heuvel *et al*, 2014
For a review Dubois, Kostovic and Judas, Brain mapping 2015

The early functional connectivity

- In preterm newborns from 26w PMA, functional networks involve several cortical regions, thalamus, cerebellum.

Matrix of functional connectivity

Newborns Adults

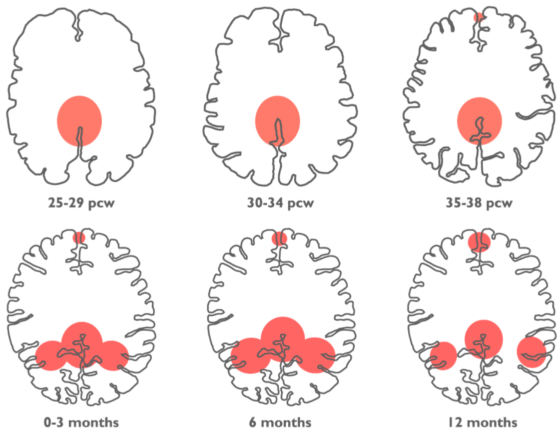


- Then the connectome architecture develops intensively (e.g. increase in inter-hemispherical connectivity).
- The maturation sequence differs across networks:
  1) primary sensori-motor and auditory networks
  2) visual network
  3) “default-mode” network
  4) executive control network

Doria *et al*, 2010; Fransson *et al*, 2009, 2011; Gao *et al*, 2009, 2014;
Smyser *et al*, 2010; Thomason *et al*, 2014; van den Heuvel *et al*, 2014

The developing default mode network

Associated with self-awareness, future planning, mind wandering, the "theory of mind"…



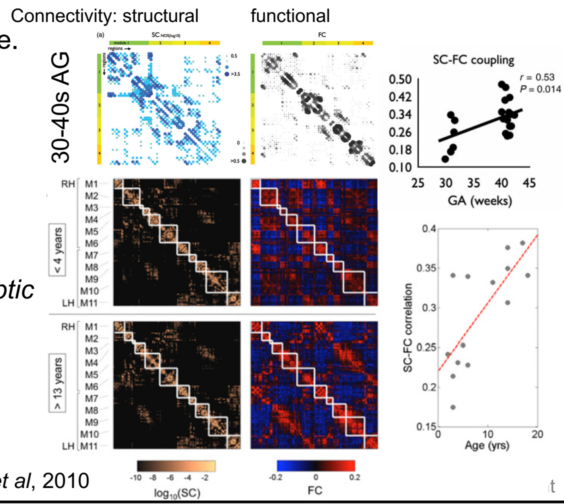
In the adult brain: it extends to the posterior cingulate cortex, ventral and dorsal medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex and the hippocampus regions.

Keunen et al, Neuroimage 2017

Structural vs functional connectivity

Functional connections might be partly related to structural connections :

- These measures are correlated in preterms from 30w PMA, and the coupling is reinforced with age.
- Structural measures would rely on *mono-synaptic connections.*
- Functional measures would also include *poly-synaptic connections* (Smyser *et al*, 2011).



van den Heuvel *et al*, 2014; Hagmann *et al*, 2010

Meanings of functional connectivity?

- In preterms, resting-state fMRI, EEG and NIRS might reflect distinct mechanisms regarding the development of functional connectivity (Omidvarnia *et al*, 2013).

- Functional connections related to high-amplitude EEG events would provide an endogenous guidance for the development of early "sensory-driven" activity.

5. Neuroimaging of early *functional* activity

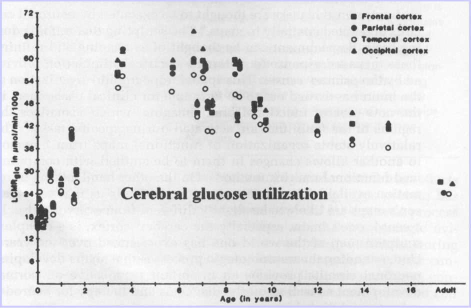
- EEG early activity
- Resting-state functional connectivity
- Imaging of metabolic changes

5/8 Functional activity

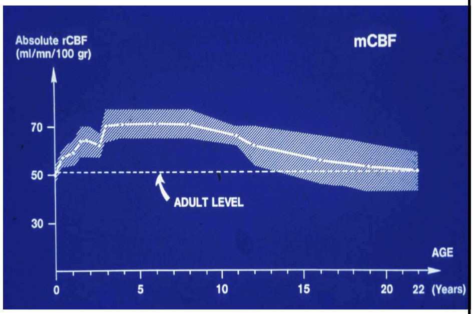
Intense metabolic changes

Cerebral glucoce utilization

Cerebral blood flow



FDG-PET, Chugani et al

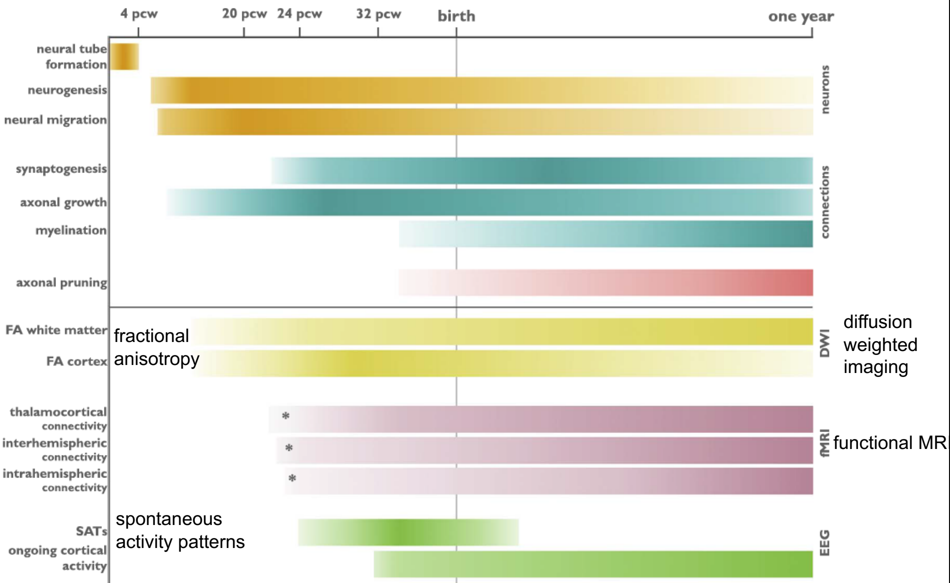


Xe-SPECT, Chiron et al

- Neuronal differentiation
- Neurotransmitter modulation (e.g. the switch from an excitatory role of GABA in immature neurons to its classical inhibitory role Ben-Ari et al 1997)
- Synaptogenesis

5/8 Functional activity

Developmental processes and neuroimaging

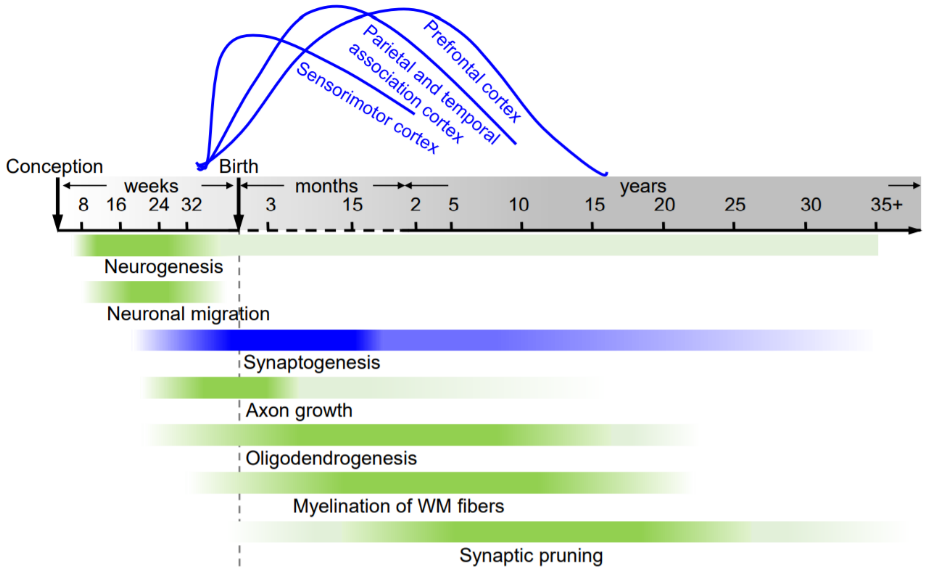


* Earlier prenatal imaging data are not available

Keunen et al, Neuroimage 2017

5/8 Functional activity

Similarities and differences across functions



Ouyang et al, Neuroimage in revision

6. Examples of neuroimaging studies on the developing sensori-motor sytem

Newborns can visually recognize the shape of an object that they have previously manipulated with their right hand, out of sight.
(Streri and Gentaz, Neuropsychologia 2004).

The somatosensory and motor systems

- Somatosensory system: the earliest sensory system to develop, mediates biological and social interactions with the mother during early life, supposed to scaffold the development of other sensory systems (vision, audition).
- Motor system: develops in parallel and in close interaction. The first physiological responses are observable from 14 weeks of gestational age: far before the cortex is developed.

Sensori-motor connections

- The peripheral sensory transmission becomes functional very early, even though the afferent input from the skin to the spinal cord is not matured yet during the last trimester.
- Spino-thalamic ascending pathways are assumed to be present from the second trimester of pregnancy.
- Sensory pathways seem to convey information from the skin to the thalamus even before the infant becomes viable for *ex utero* life.
- Developmental changes in electrophysiologial responses (somatosensory evoked potentials SEP) of preterm babies might primarily depend on the development of thalamo-cortical connections, which penetrate the cortical plate from 24 PCW (Krsnik et al, Frontiers in Neuroscience 2017).
- Motor pathways include initially contra-lateral and ipsilateral connections; the latter ones are further pruned during development.

Early sensori-motor activity (EEG)

- Cortical sensori-motor responses are detectable from 24w PMA.

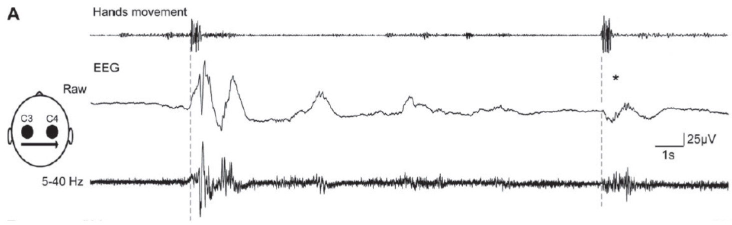
Cerebral Cortex Advance Access published September 1, 2006

Cerebral Cortex
doi:10.1093/cercor/bhl069

Rapid Cortical Oscillations and Early Motor Activity in Premature Human Neonate

Mathieu Milh[1], Anna Kaminska[2,4], Catherine Huon[3], Alexandre Lapillonne[3], Yehezkel Ben-Ari[1] and Rustem Khazipov[1]

- Delta-brush: dominant EEG pattern of rapid oscillatory activity in the human cortex during the third trimester of gestation.
- Premature neonates (29-31w PMA): DBs following sporadic hand and foot movements, and following direct hand and foot stimulation.
- *Specific* DBs in the corresponding cortical areas, suggesting early *somatotopy*.

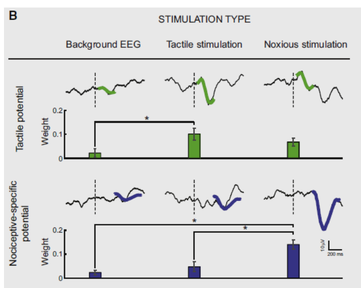


Tactile responses (EEG)

A Shift in Sensory Processing that Enables the Developing Human Brain to Discriminate Touch from Pain

Lorenzo Fabrizi,[1,6,*] Rebeccah Slater,[1,3,6] Alan Worley,[4] Judith Meek,[5] Stewart Boyd,[4] Sofia Olhede,[2] and Maria Fitzgerald[1]

Current Biol 2011



- Infants 28-45 wGA: transition in brain responses from *nonspecific* neuronal bursts to *modality specific*, localized, evoked potentials.
- Hypothesis that the *nonspecific* neuronal bursts triggered by heel stimulation in preterm infants might gradually mature into tactile and nociceptive-specific potentials in the full-term infants.
- Critical period after which the somatosensory circuitry has matured sufficiently to produce predominantly specific potentials? 35-36 wGA for nociceptive processing, 36-37 wGA for tactile processing. This suggests that specific neural circuits necessary for discrimination between touch and nociception might emerge from 35-37 wGA.

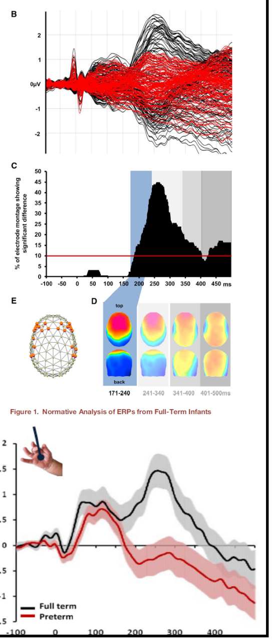
Early perinatal experiences (EEG)

The Dual Nature of Early-Life Experience on Somatosensory Processing in the Human Infant Brain

Current Biol 2017

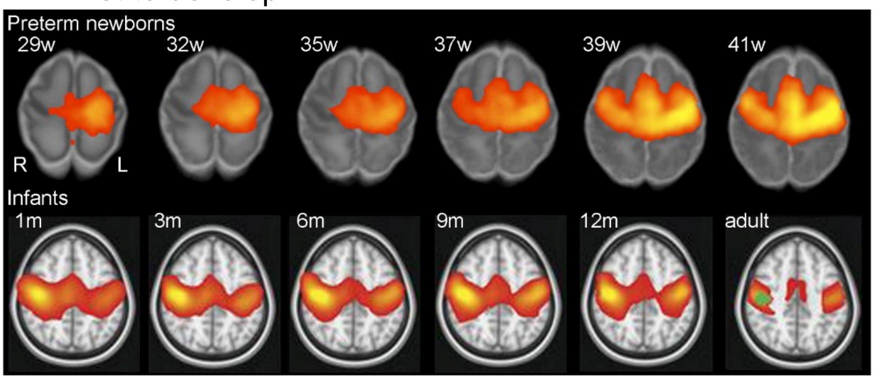
Nathalie L. Maitre,[1,2,8,*] Alexandra P. Key,[2,3] Olena D. Chorna,[1] James C. Slaughter,[4] Pawel J. Matusz,[5] Mark T. Wallace,[2,3] and Micah M. Murray[2,5,6,7]

- Characterization of cortical responses to light touch (%sham) in full-term infants → data-driven analytical framework
- In preterms at the time of discharge from the hospital: the degree of prematurity at birth determines the extent to which brain responses to light touch are attenuated → role of altered postnatal experiences and/or interruptions in the normal sequence of brain maturation by preterm birth itself?
- When controlling for prematurity and analgesics:
  - supportive experiences (breastfeeding, skin-to-skin care, massage, physical or occupational therapy sessions, parental holding) are associated with stronger brain responses
  - painful experiences (e.g. skin punctures, tube insertions) are associated with reduced responses even for these non-painful tactile stimuli.



Functional connectivity (rs-fMRI)

The primary sensori-motor network is one of the first to develop.



Increased spatial specialization throughout development?

Doria *et al*, 2010; Fransson *et al*, 2009, 2011; Gao *et al*, 2009, 2014; Smyser *et al*, 2010; Thomason *et al*, 2014; van den Heuvel *et al*, 2014

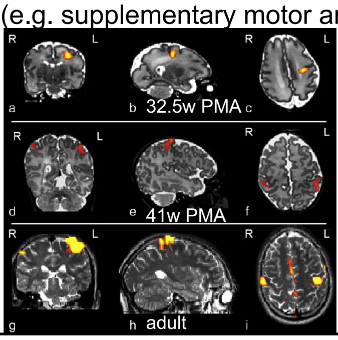
Early activations (fMRI)

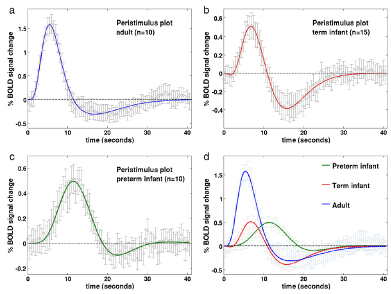
Development of BOLD signal hemodynamic responses in the human brain

Tomoki Arichi [a,b], Gianlorenzo Fagiolo [c], Marta Varela [c], Alejandro Melendez-Calderon [d], Alessandro Allievi [d], Nazakat Merchant [a,b], Nora Tusor [a,b], Serena J. Counsell [a], Etienne Burdet [d], Christian F. Beckmann [e,f], A. David Edwards [a,b,*]

Neuroimage 2012

- Preterm infants at 32-35w and at 38-44w PMA. Passive movement (1s)
- Relatively similar localization of responses compared to adults (mostly activations in contro-lateral central regions)
- With increasing age:
  Maturation in the peak characteristics (decreasing time, increasing amplitude)
  Trend towards co-activation of the ipsilateral SI and associated sensori-motor areas (e.g. supplementary motor area SMA)





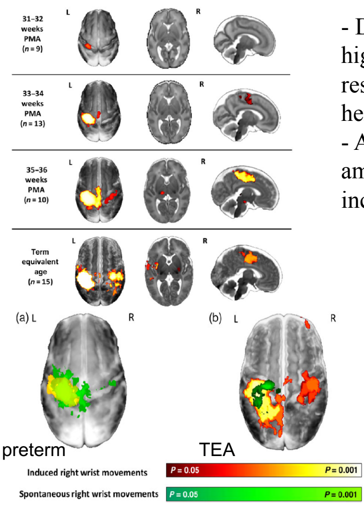
Early activations (fMRI)

Maturation of Sensori-Motor Functional Responses in the Preterm Brain

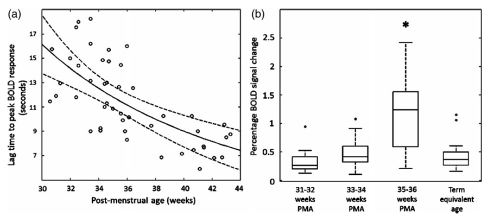
Alessandro G. Allievi[1,†], Tomoki Arichi[1,3,†], Nora Tusor[3], Jessica Kimpton[3], Sophie Arulkumaran[3], Serena J. Counsell[3], A. David Edwards[1,2,3] and Etienne Burdet[1]

Cerebral Cortex 2016

30 -> 43w PMA
Alternating blocks of passive wrist flexion/extension (0.33-Hz) and rest (24s)
Spontaneous wrist movement: measure of displacement



- During the preterm period, maturational trend : faster, higher amplitude, and more spatially dispersed functional responses (increasing integration of the ipsilateral hemisphere and sensori-motor associative areas).
- At term equivalent age: decrease in both response amplitude and interhemispheric functional connectivity + increase in spatial specificity



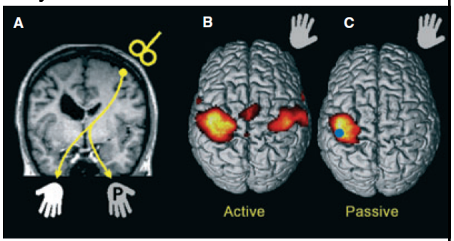
Reorganization of representations

Reorganization after pre- and perinatal brain lesions J Anat 2010

Martin Staudt

- ***Somatosensory network***: Ascending thalamo-cortical projections might form 'axonal bypasses' around periventricular white matter lesions to reach their original cortical target regions. When the post-central gyrus is affected, no reorganization in primary somatosensory cortex (S1) is observed.
- ***Motor network***: When a unilateral brain lesion disrupts the projections of one hemisphere during the period of fiber withdrawal, the ipsilateral projections from the contra-lesional primary motor cortex (M1) persist (this hemisphere takes over motor control).
- ***Dissociation*** of S1 and M1 representations into different hemispheres can be observed in some individuals with cerebral palsy.

Patient with a unilateral periventricular lesion:
A: TMS of the unaffected hemisphere: movement of both hands
B: Active movement of the paretic hand: activations in both contra-lateral and ipsilateral central regions
C: Passive movement of the paretic hand: activations in the affected hemisphere only.



7. Examples of neuroimaging studies on the developing visual sytem

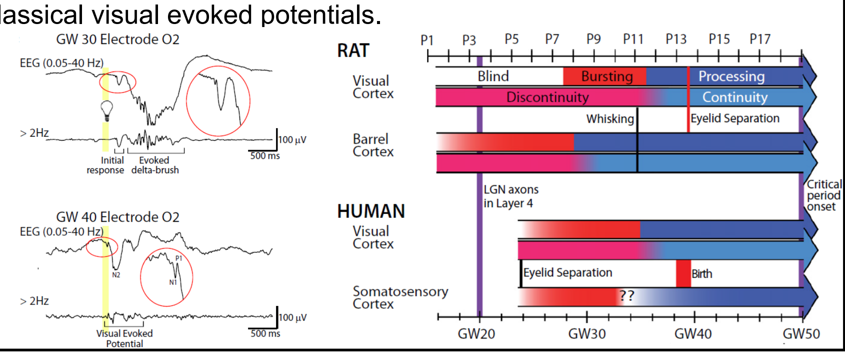
Early visual activity (EEG)

A Conserved Switch in Sensory Processing Prepares Developing Neocortex for Vision

Neuron 2010

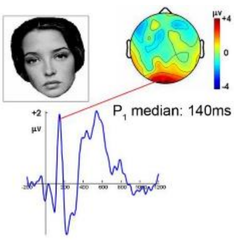
Matthew T. Colonnese,[1,*] Anna Kaminska,[2,3,4] Marat Minlebaev,[1] Mathieu Milh,[1] Bernard Bloem,[1] Sandra Lescure,[4,5,6] Guy Moriette,[4,5,6] Catherine Chiron,[3,4,7] Yehezkel Ben-Ari,[1] and Rustem Khazipov[1]

- Preterms between 27 and 34w GA: light flashes evoke occipital visual responses consisting of two large amplitude, slow, negative deflections. The second contains rapid oscillations (5-20 Hz) and resembled spontaneously occurring delta brushes.
- Between 34 and 36w GA: switch between these immature responses and classical visual evoked potentials.

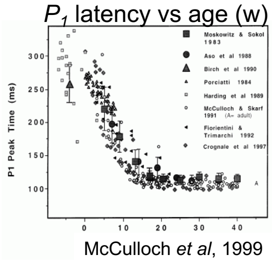


Speed of visual responses (EEG-MRI)

- Visual-evoked potentials

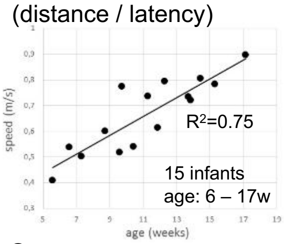


P₁ latency vs age (w)



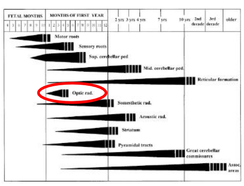
McCulloch *et al*, 1999

Conduction speed of the visual information (distance / latency)

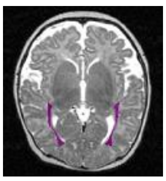


- Relating structural and functional maturation?

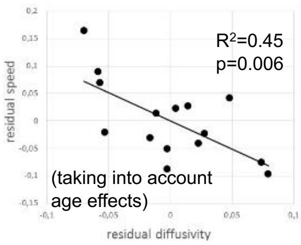
Fiber myelination



Yakovlev and Lecours, 1967



DTI in the optic radiations

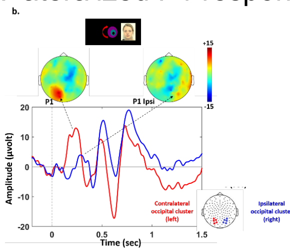


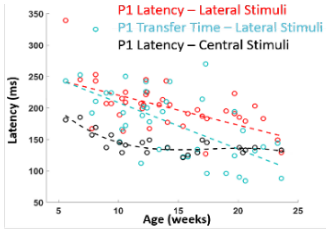
Dubois *et al*, J. Neuroscience 2008

Speed of visual responses (EEG-MRI)

- Lateral stimuli: lateralized P1 responses and inter-hemispheric transfer

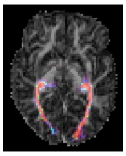
13 infants
age: 7 – 22w

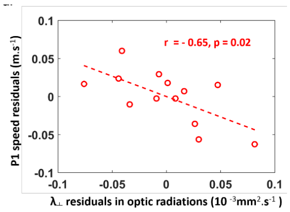




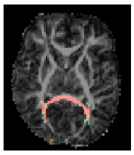
- Relating structural and functional maturation?

Optic radiations and P1 speed

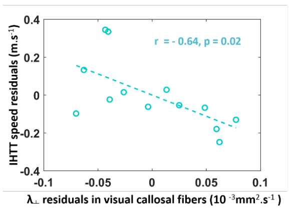




Visual callosal fibers and transfer speed



(taking into account age effects)

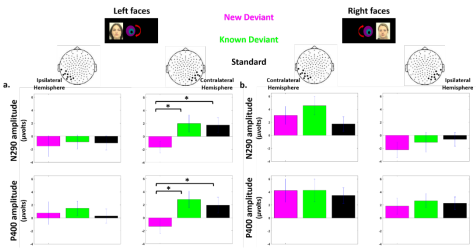


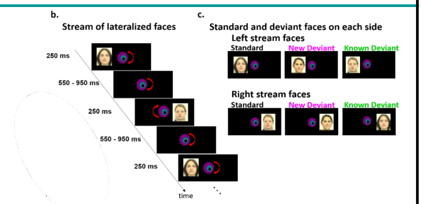
Adibpour *et al*, Nature Hum Behav in press

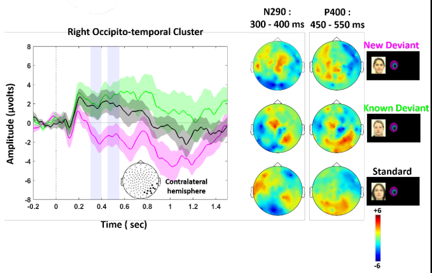
Face discrimination (EEG)

- 1- to 5-month-old infants looking at lateralized face stimuli that differ in left and right hemi-fields.

- For *left* face stimuli:
  N290 and P400 responses in right occipito-temporal regions differ for new-deviant stimuli (% standard), but not for known-deviant stimuli (presented before in the right hemi-field).







N290, P400: classical ERP responses to faces in infants

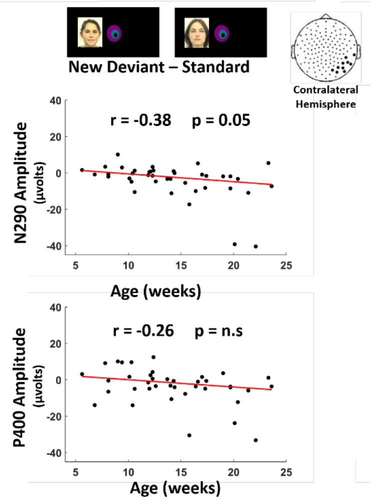
Adibpour *et al*, Nature Hum Behav in press

Face discrimination (EEG)

These results suggest:

- an efficient discrimination of faces
- an efficient inter-hemispheric transfer of information
- an asymmetry in face processing in favor of the right hemisphere.

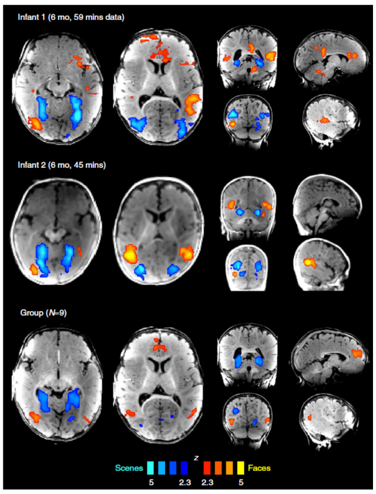
- Face discrimination also gradually improves with age.



Adibpour *et al*, Nature Hum Behav in press

High-level visual regions (fMRI)

- 4-6-month-old infants
- Preferential responses of extrastriate regions to abstract categories (faces and scenes), as in adults.
- Further refinement throughout development since activity patterns differ between infants and adults.

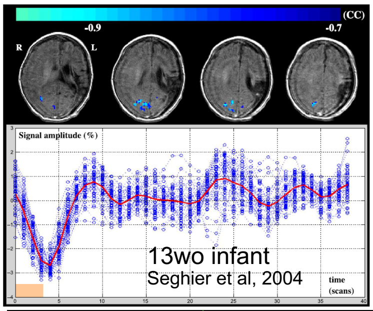


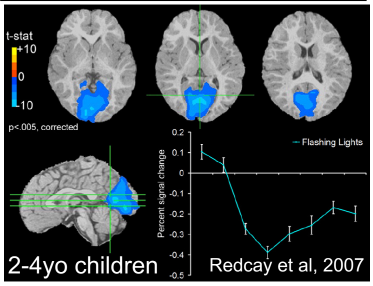
Deen et al, Nature Com 2017

Early visual activations (fMRI)

Older studies:

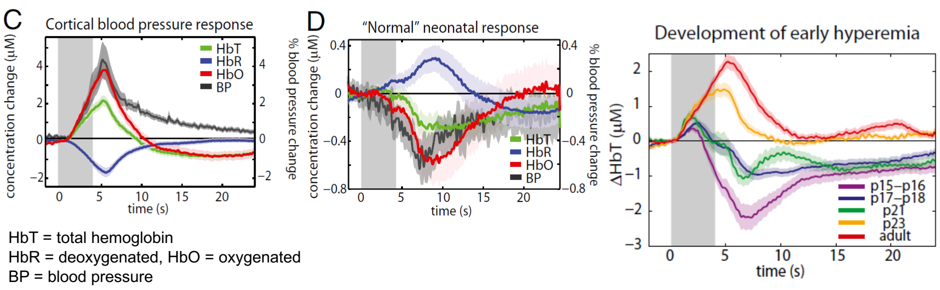
- fMRI in infants and children (flashing lights, checkerboards)
- Similar localization in occipital regions compared with adults
- But negative amplitude (<4 years?)





Early sensory activations (fMRI)

Mechanisms responsible for inverted hemodynamic responses?
In neonatal rats (somatosensory stimulation, recording with multispectral optical intrinsic signal imaging), complex interplay of:
- immature autoregulation: blood pressure fluctuations dependent of stimulus amplitude
- neurovascular coupling: dependent on a global, delayed constriction process, present from early on, and on a localized initial hyperemia (=increase of blood flow) that develops gradually.



HbT = total hemoglobin
HbR = deoxygenated, HbO = oxygenated
BP = blood pressure

Kozberg et al, 2013

8. Examples of neuroimaging studies on the developing auditory system and language network

Early development of language

At birth, neonates already perceive some characteristics of speech-related stimuli:

they recognize the prosody of their native language, their mother voice…

During the first post-natal year, the infant capacities to process speech are booming:

- they learn the distribution of sounds used in their native language, the rules that govern their combination into words…
- they improve their articulatory control to converge to a babbling that is specific to their native language
- they integrate the auditory, visual, and motor aspects of speech in their efforts to imitate adults' utterances.

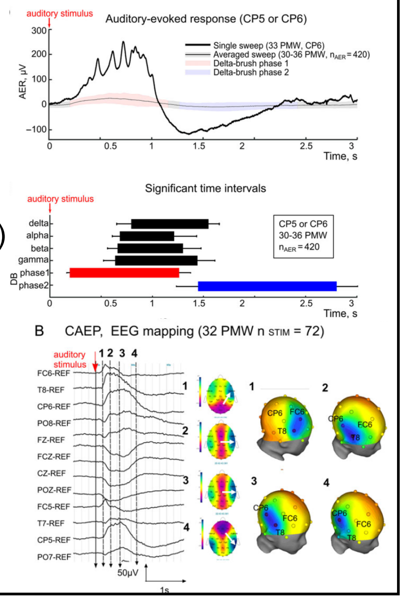
How the early architecture and maturation of the brain linguistic network endow them with such abilities?

Early auditory activity (EEG)

Cortical Auditory-Evoked Responses in Preterm Neonates: Revisited by Spectral and Temporal Analyses

A. Kaminska[1,2], V. Delattre[1,3], J. Laschet[1], J. Dubois[4], M. Labidurie[1], A. Duval[1,3], A. Manresa[5], J.-F. Magny[6], S. Hovhannisyan[6], M. Mokhtari[7], L. Ouss[8], A. Boissel[5], L. Hertz-Pannier[1,3], M. Sintsov[9], M. Minlebaev[9,10], R. Khazipov[9,10] and C. Chiron[1]

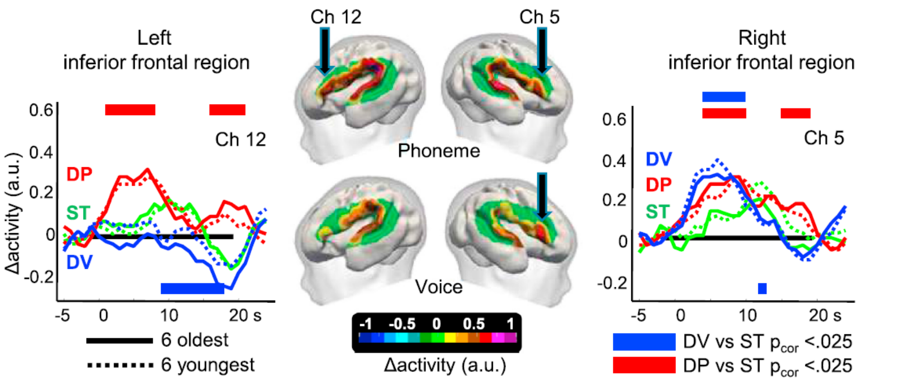
Cerebral Cortex 2017



- In all preterms between 30 and 33 PMW: auditory-evoked delta-brush (DB)
- Rate decrease until full term
- EEG power from delta to gamma frequency bands over the middle and posterior temporal regions.
- The delta component of DBs correspond to the late part of cortical auditory-evoked potentials (CAEP).

Early auditory responses (NIRS)

- Preterm newborns 28-32 PMW
- Discrimination of deviant phonemes and deviant voices
- Different lateralization of responses

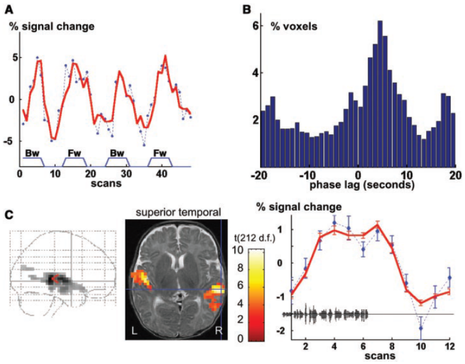


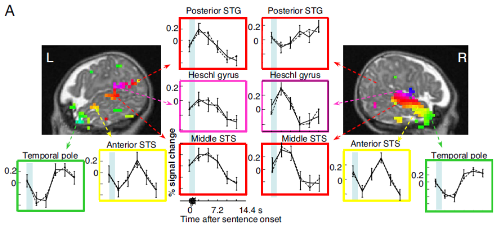
DP deviant phonemes
DV deviant voices

Mahmoudzadeh *et al*, PNAS 2012
Dehaene-Lambertz and Spelke, Neuron 2015

Early activations to speech (fMRI)

- fMRI in 2-3 month-old infants (language stimuli)
- Relatively similar localization of activations compared with adults (perisylvian cortical regions)
- Differences in the response characteristics among brain regions in terms of timing and amplitude
- Asymmetry of responses across hemispheres

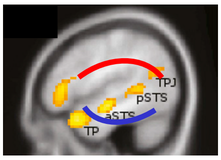




Dehaene-Lambertz et al, Science 2002
Dehaene-Lambertz et al, PNAS 2006

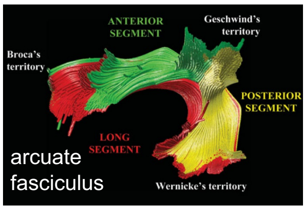
Multiple pathways for language

- How do these regions collaborate during early stages?
- Pathways connecting these regions: are they organized similarly in infants and adults? Do these pathways mature differently during infancy?
- Two processing streams (Hickok and Poeppel, Cognition 2004)
  - Dorsal pathway ~ phonological processing, links between the sensorial aspects of speech (hear a sound, see a face speaking) and the motor aspect (articulate a sound)
  - Ventral pathway ~ semantic processing

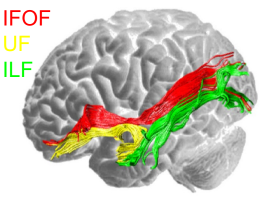


Pallier et al. PNAS 2011

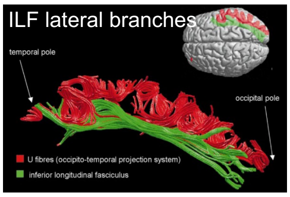
- Anatomical bundles for linguistic pathways



Catani et al. Annals Neurology 2005



Catani et al. Cortex 2008



Catani et al. Brain 2003

Linguistic bundles (diffusion MRI)

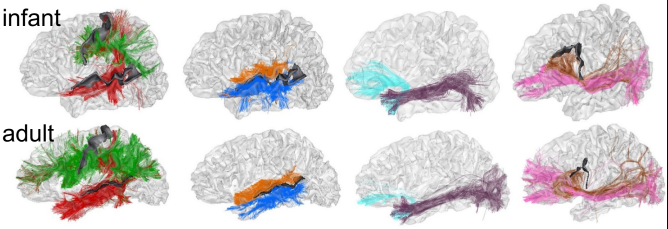
- Similar trajectory of bundles in 1 to 5-month olds and adults

- Dorsal pathway: AF arcuate fasciculus, SLF superior longitudinal
- Ventral pathway: MLF / ILF medial, inferior longitudinal fasciculus, ILFlat lateral branches, UF uncinate fasciculus, IFOF fronto-occipital fasciculus, EC extreme capsule

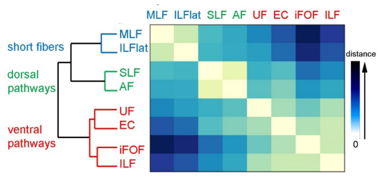
AF SLF MLF ILFlat ILF UF iFOF EC

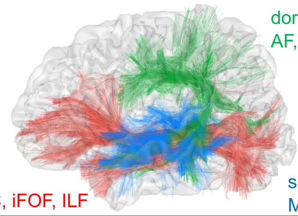
infant

adult



- Similar microstructural properties with segregation between short fibers, the dorsal and ventral bundles

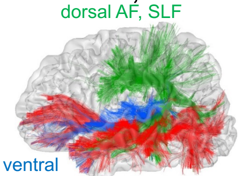


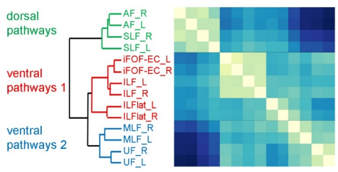


Dubois *et al*, Cerebral Cortex 2016

Different maturation (diffusion MRI)

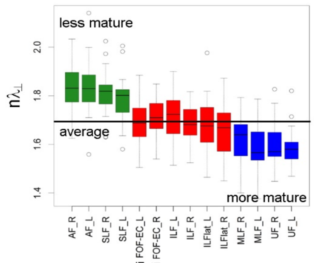
- Bundles clustering in infants, based on $\lambda_{\perp}$ normalized to the adult *mature stage*



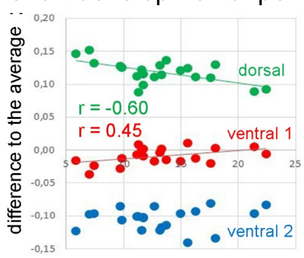


- Maturation asynchrony

The maturation of dorsal bundles is delayed.



But this delay decreases over this short developmental period.



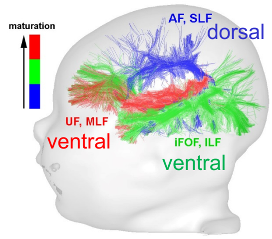
Dubois *et al*, Cerebral Cortex 2016

development

Different maturation of pathways

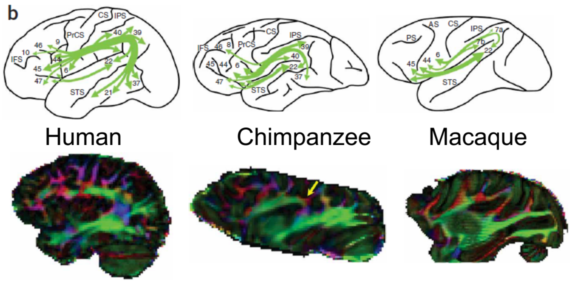
Language pathways show asynchronous maturation in the infant brain:

- The ventral pathway starts maturing first, in agreement with previous studies in non-human primates and hypotheses from evolutionary-developmental biology.



Dubois *et al*, Cerebral Cortex 2016

The ventral pathway shows higher stability than the dorsal pathway in the primates evolution.

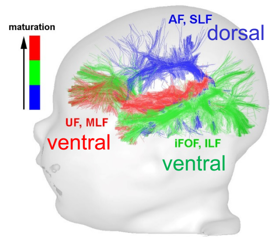


Rilling et al. Nat Neurosci 2008, Front Evol Neurosci 2012

Different maturation of pathways

Language pathways show asynchronous maturation in the infant brain:

- The ventral pathway starts maturing first
- Nevertheless the ***maturation of dorsal pathway catches up*** during the first post-natal months.



Dubois *et al*, Cerebral Cortex 2016

This fast development might be related to the language advances at this age, in particular to the development of speech cross-modal representations (need to integrate the *sensory* and the *motor* aspects of speech to imitate the adults' production).

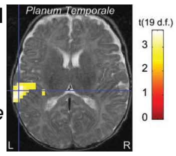
8/8 Auditory system

Lateralization of the language network

- Early lateralization in langage perception :
  - Advantage of right ear for sound processing in newborns
  - Higher brain activity to speech listening in left than right superior temporal regions

3mo infants, fMRI

planum temporale



Dehaene-Lambertz *et al*, 2002

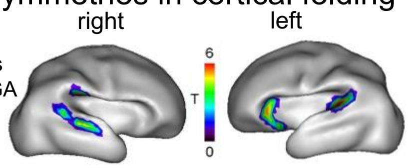
- Lateralization in pre-language production?
  - More right hand activity during “cooing” (<3 month)
  - More mouth opening on the right side during babbling (~6 month)
  - More right hand communicative pointing (~1 year)
- Is this early functional lateralization related to brain structural substrates?

8/8 Auditory system

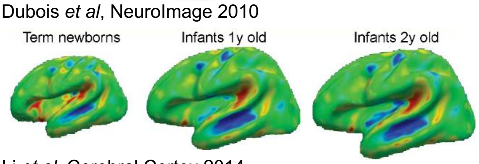
Inter-hemispheric asymmetries (MRI)

- Asymmetries in cortical folding

Preterm newborns 27-36w GA



Dubois *et al*, NeuroImage 2010

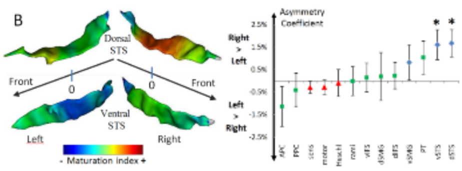


Li *et al*, Cerebral Cortex 2014

→ The right superior temporal sulcus (STS) is more folded than the left sulcus.

→ Perisylvian regions (Heschl gyrus, *planum temporale*, Broca’s region) are larger on the left side.

- Asymmetries in cortical maturation



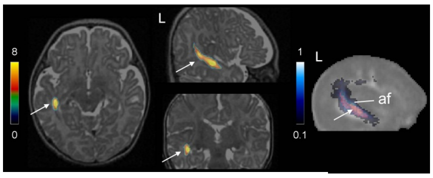
Leroy *et al*, J. Neuroscience 2011

→ The right STS gets mature earlier than the left STS.
→ Broca’s region (left side) tends to become mature earlier than the right region.

Inter-hemispheric asymmetries (MRI)

- Intrinsic left-lateralization of the arcuate fasciculus in terms of volume and compacity

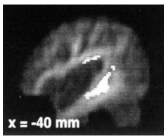
1-4 mo infants



Dubois *et al*, Cerebral Cortex 2009

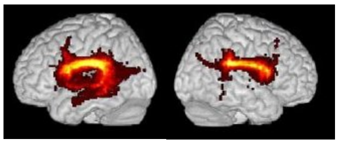
adults

anisotropy



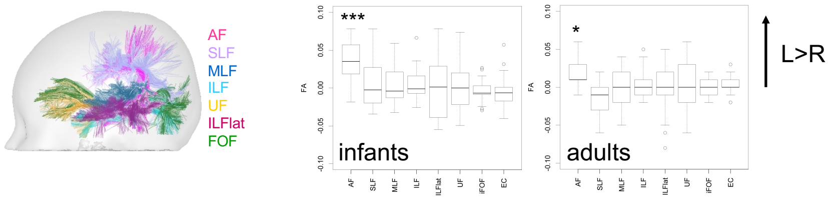
Buchel *et al*, 2004

tractography



Parker *et al*, 2005

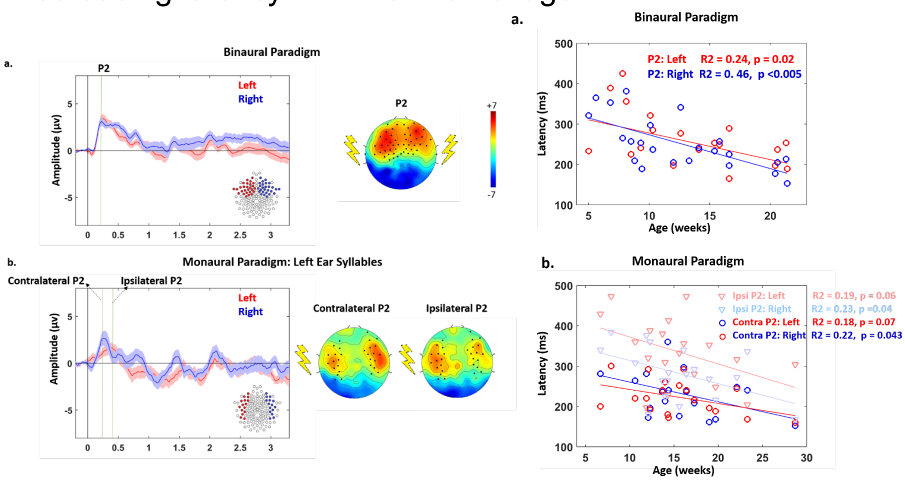
- No asymmetry in other linguistic bundles



Dubois *et al*, Cerebral Cortex 2016

Auditory responses in infants (EEG)

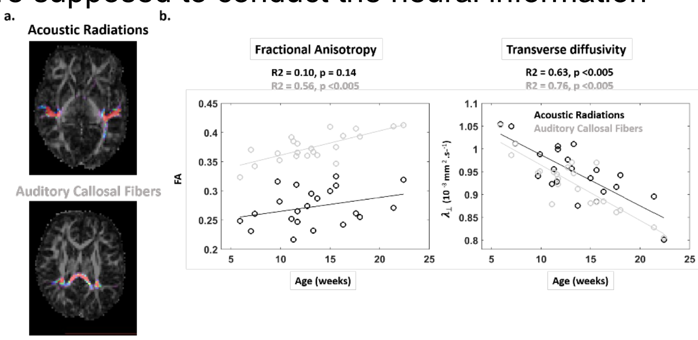
- Binaural presentation of syllables: P2 bilateral responses
- Monaural presentation: P2 contralateral & ipsilateral responses
- Decreasing latency with the infants' age



Adibpour et al, in preparation

Auditory responses in infants (EEG)

- Maturational changes in the underlying white matter pathways that are supposed to conduct the neural information

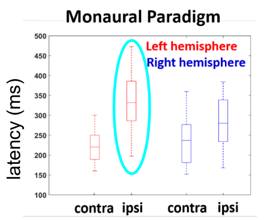


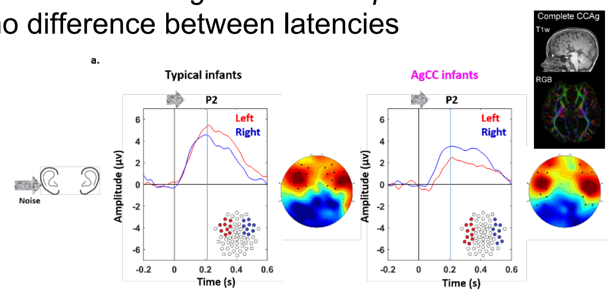
- But no direct relationships between the P2 properties and the bundles maturation
- Role of cortical maturation?

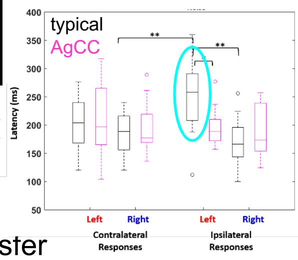
Adibpour et al, in preparation

Transfer of auditory responses (EEG)

- Slower *left ipsilateral* responses (higher latency)
- Same observation following the monaural presentation of babble noise in typical infants
- In infants with *agenesis of corpus callosum*: no difference between latencies







- *Left ipsilateral* responses might include the transter of *right contralateral* responses through callosal fibers.
- This suggests an asymmetry of transfer in favor of the left hemisphere.

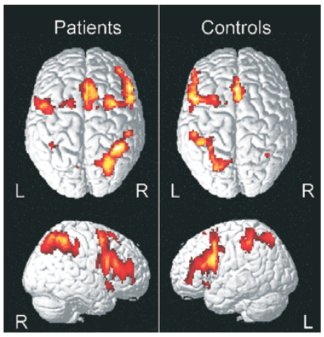
Adibpour et al, in preparation

Reorganization (fMRI)

Early lesions: Good recovery after left hemispheric lesions in children younger than 5 yo
→ "Extensive plasticity"

Reorganization of language processing in the right hemisphere, in brain regions homotopic to the classical left-hemispheric language regions.

fMRI during silent speech production



5 patients with left-sided periventricular lesions

5 healthy right-handers

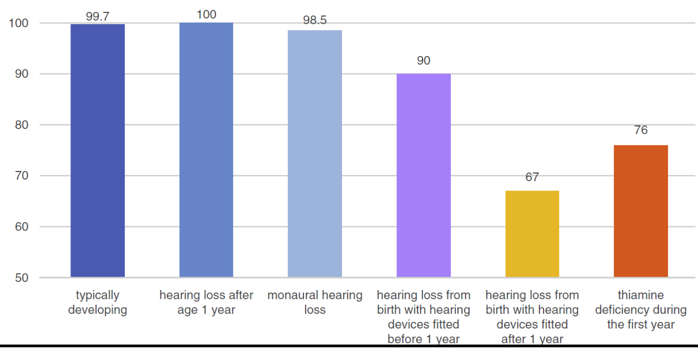
Staudt 2010

Critical period

Critical period for first language: the crucial role of language input during the first year of life Current Opinion in Neurobiol, 2015
Naama Friedmann and Dana Rusou

- The role of ***language input*** is crucial: language deficits are observed in children who did not receive the required language input because they grew in isolation or due to hearing impairment.
- A ***thiamine*** deficit only during a few weeks is also sufficient to cause later syntactic deficits without global deficiency

Comprehension of syntactic structures (%) at 9y



Conclusions

Take home messages

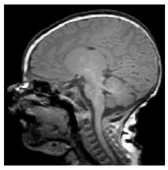
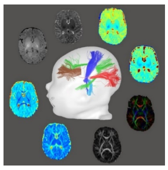
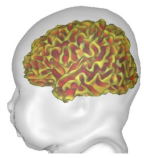
• The brain is organized early on in main networks (~ *genetic programming*). The pre-term period is crucial for the development of structural and functional architecture.
→ Major impact of *toxics* during pregnancy (e.g. alcohol), of *prematurity…*

• Networks evolve and mature intensively during infancy and all along childhood. They might be influenced by *multiple factors* (environment, learning…).
→ During development the brain *plasticity* is much higher than during adulthood.

• Obsolete dilemna *"Nature vs nurture"*

Perspectives

- From birth on, there are several evidence for audio-visual, visuo-tactile integration… But maturational timelines differ across functions: how the evolving properties of networks might still provide infants with such integration capacities?
  → Need for developmental models that integrate the spatial and temporal constraints to explore how infants process complex cross-modal information.
  (Dehaene-Lambertz and Spelke, Neuron 2015)

- Neuroimaging approaches may enable to better characterize the impact of early disturbances, to "predict" outcome in newborns with neuro-developmental disorders, to evaluate the potential efficiency of learning strategies…

But many challenges to overcome…

- ***Constraints in MRI acquisition:***

- infants spontaneously asleep vs scanner noise
- wake up and motion vs acquisition time

→ Need for dedicated acquisition sequences

- ***Constraints in MRI post-processing:***

- tissues immaturity, changing contrast during the first post-natal year
- spatial resolution: structures' size, partial volume effects

→ Need for dedicated post-processing tools

Thank you!

Questions? jessica.dubois@cea.fr www.unicog.org

Cognitive NeuroImaging Unit (INSERM), NeuroSpin (CEA, France)

G. Dehaene-Lambertz, L. Hertz-Pannier, C. Poupon,
J.F. Mangin, F. Leroy, D. Le Bihan, S. Dehaene,
S. Kulikova, P. Adibpour, J. Lebenberg, M. Zomeno, etc.

Robert-Debré Hospital (Paris)

D. Germanaud, etc.

Marseille University Hospitals, INT

J. Lefèvre, N. Girard, etc.

Geneva University Hospitals

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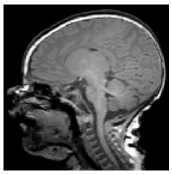

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