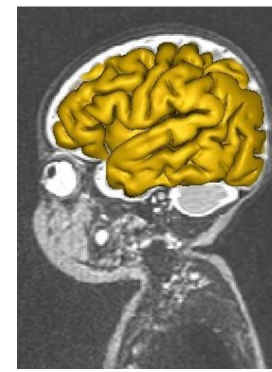
The early development of the human brain:
MRI studies of the growth and folding patterns in newborns and infants



Jessica Dubois

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CEA, NeuroSpin, Gif-sur-Yvette; Robert-Debré Hospital, Paris

Workshop *Shape analysis in Biology*, 21 November 2019

Development of the human brain



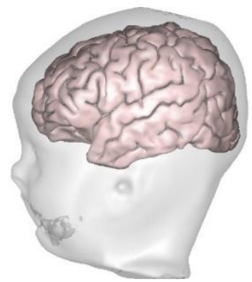

...

...

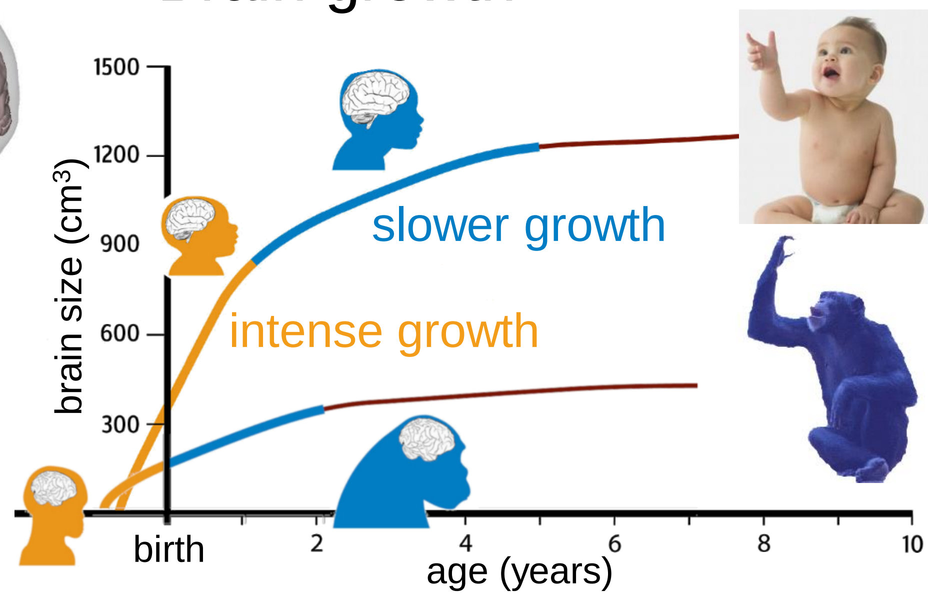
6 months of gestation

birth

6 months



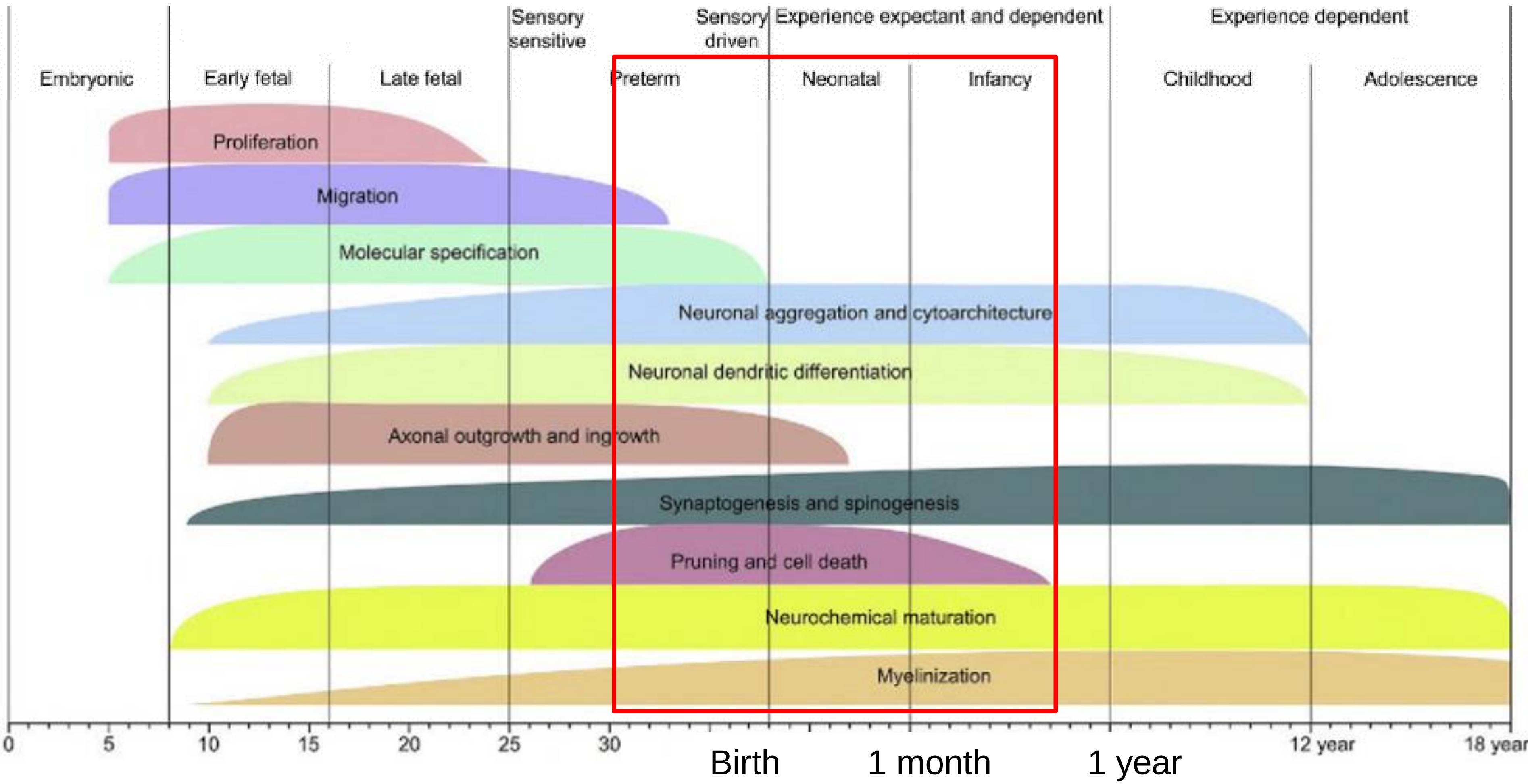
Brain growth



- Infants' early acquisitions
- Children's learnings
- Interactions between genetic determination and environment

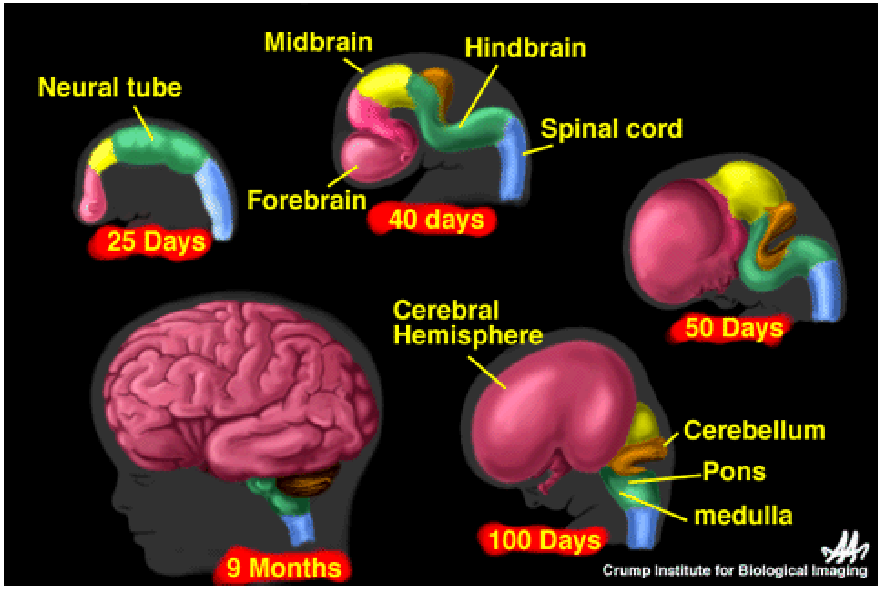
Mechanisms of brain development

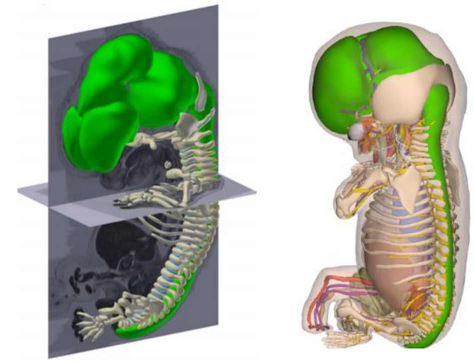
A complex progression during the pre- and postnatal periods



Kostovic and Judas. Brain Mapping: An Encyclopedic Reference 2015

Early brain development

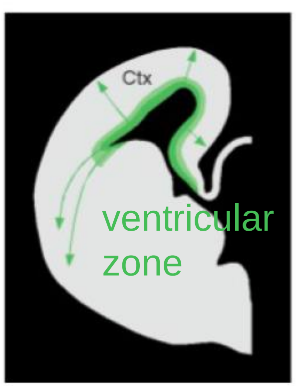


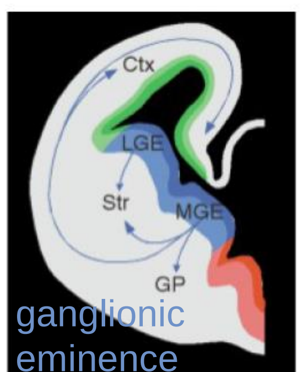


Bakker *et al*, Science 2016

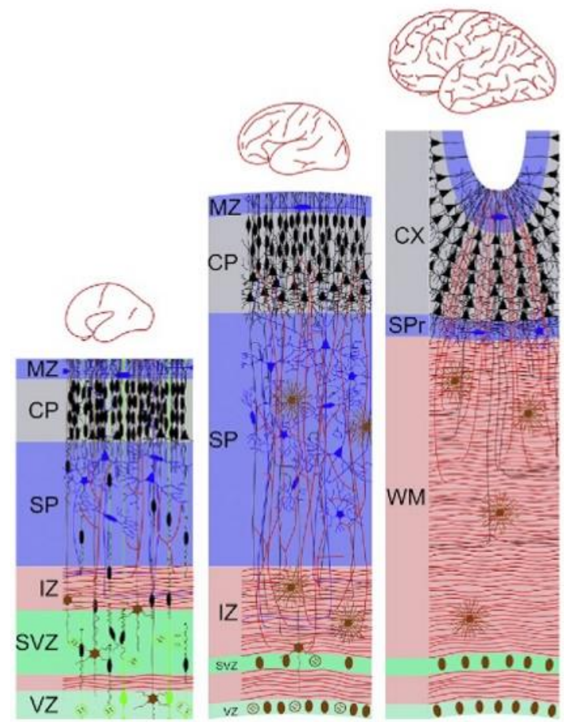
Neurogenesis and formation of the cortex

Migrations: radial (excitatory neurons) tangential (inter-neurons)





marginal zone
cortical plate
subplate
intermediate zone / white matter
proliferative zones



at term birth

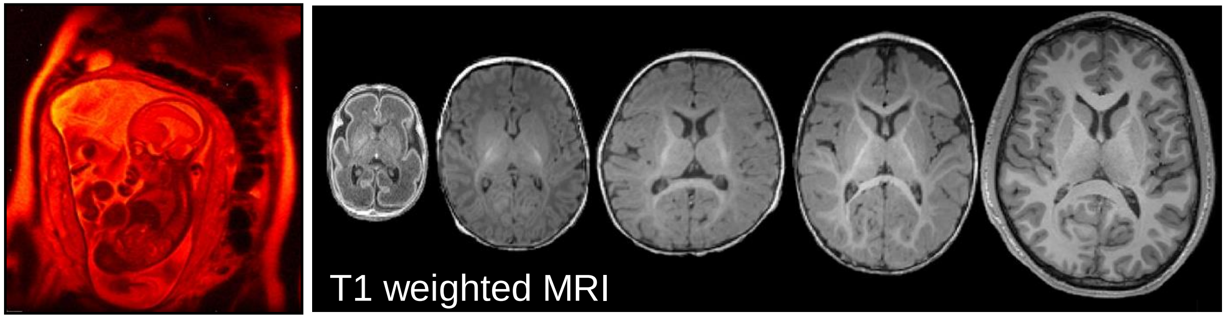
Kostovic *et al*, 2002, 2015, 2019; Stiles and Jernigan, Neuropsychol Rev 2010

MRI of brain development in infants

- Relationships between brain changes and behavioral acquisitions in infants
- MRI at 3T, different sequences < 45min

☺ Spatial localization
☹ Scanner noise, sensitivity to motion, temporal resolution

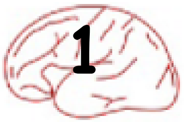
- Constraints for data acquisition
- Constraints for data post-processing



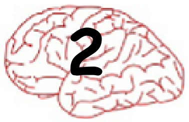
→ Studies on neurodevelopment require dedicated tools.

Dubois *et al*, Neuroscience 2014

Overview of the presentation



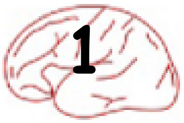
Studies on the development of brain folding with "whole-brain" analyses



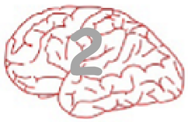
Studies based on "sulcus" objects

Relating the folding process and other developmental mechanisms

Overview of the presentation



Studies on the development of brain folding with "whole-brain" analyses

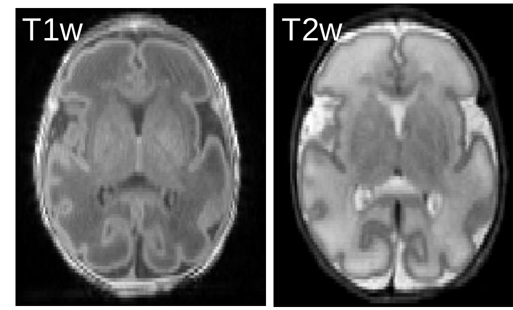


Studies based on "sulcus" objects

Relating the folding process and other developmental mechanisms

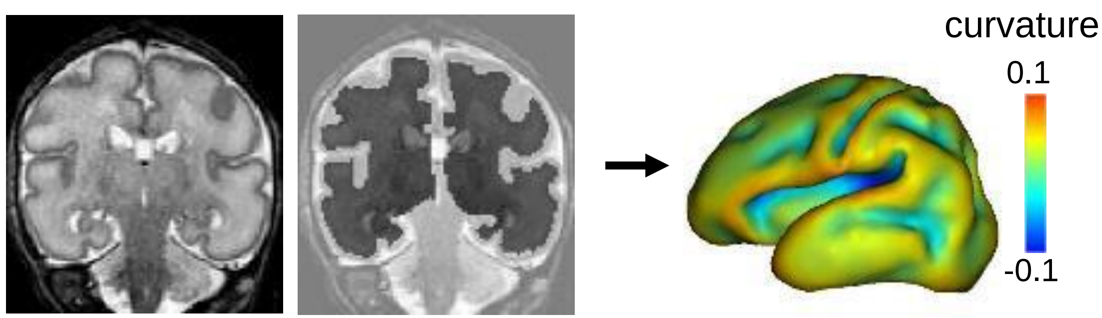
MRI data and post-processing

- T2-weighted MR images with high spatial resolution
  0.8x0.8x1.2mm^3 for preterm and full-term newborns
  1x1x1.1mm^3 for infants



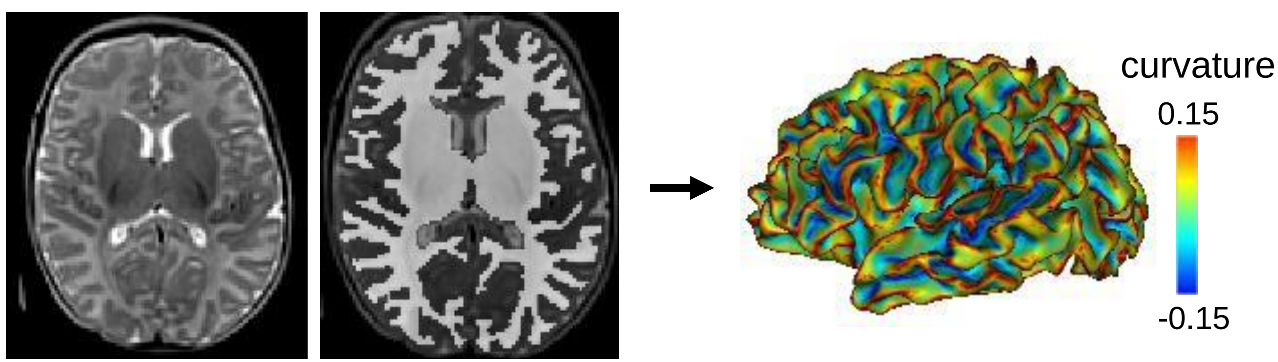
- Segmentation of inner and outer cortical surfaces with BrainVISA tools (Baby Morphologist pipeline) + manual corrections

Preterm newborns



Dubois *et al*, 2008

Infants



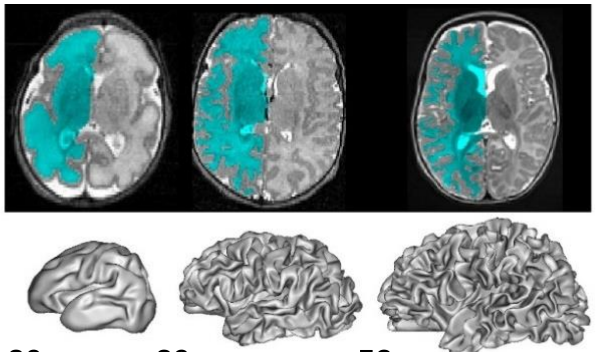
Leroy *et al*, 2011

Morphological development

newborns: preterm at term infant

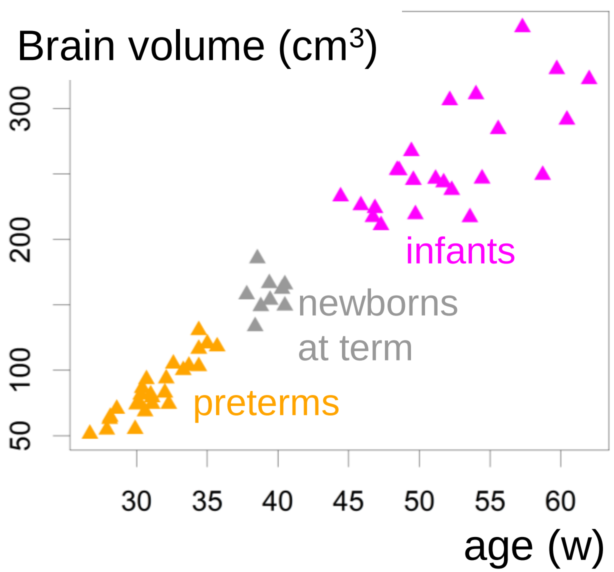
T2w images + segmentation

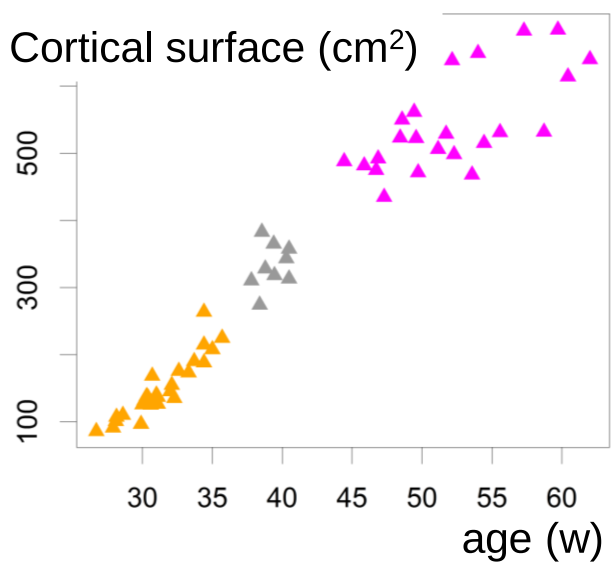
inner cortical surface

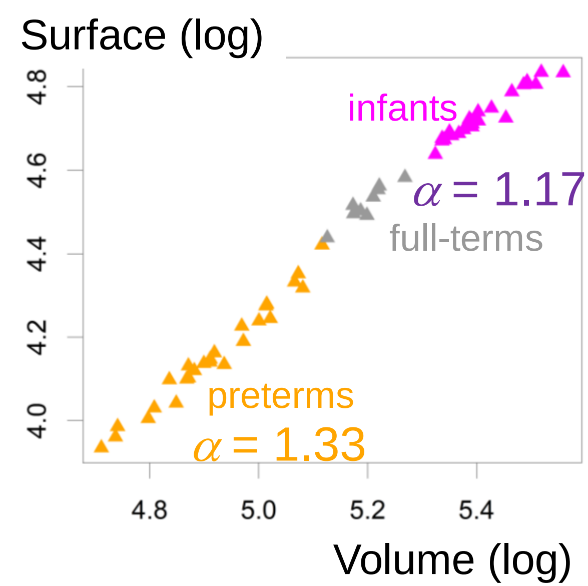


$$S = V^{\alpha}$$

$$\log S = \alpha \cdot \log V$$



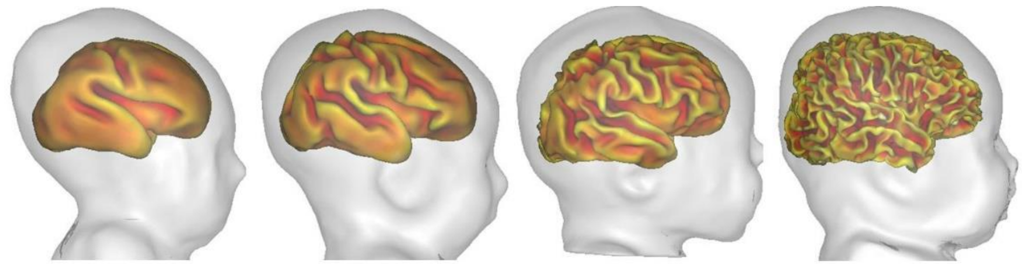




Dubois *et al*, IEEE ISBI 2016, Neuroimage 2019

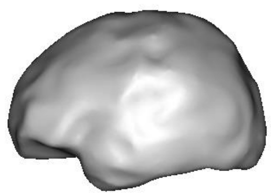
Evolution of the brain folding

Several hypotheses on the processes that might underly it



Folding index:

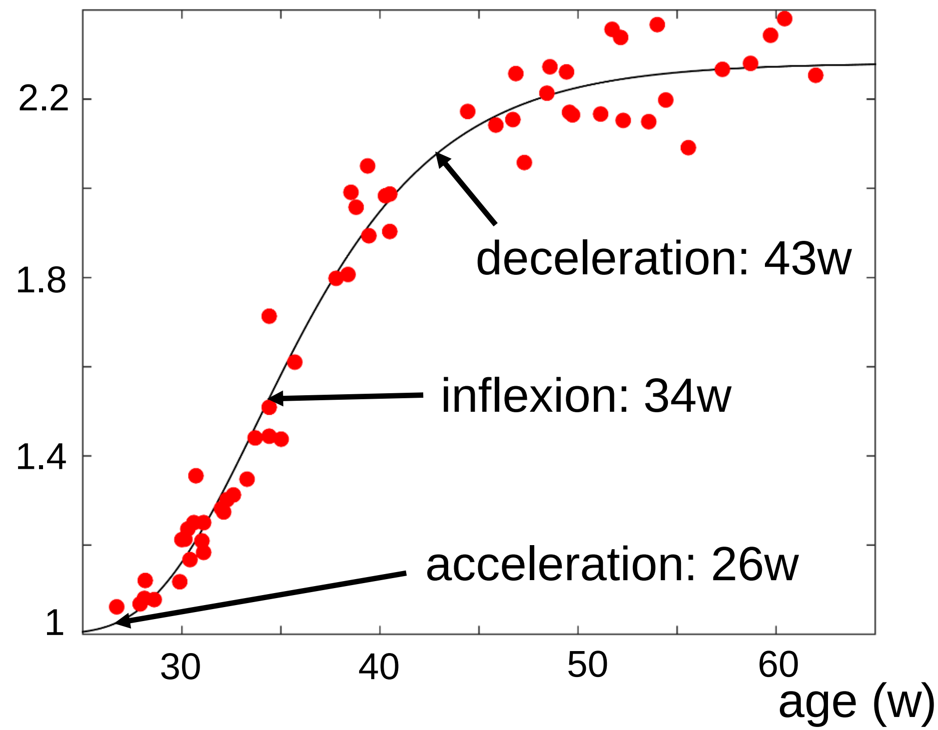
ratio between areas of
cortical surface and closed surface



Gompertz modelling:

$$K \cdot \exp(-b \cdot \exp(-a \cdot t)) + K'$$

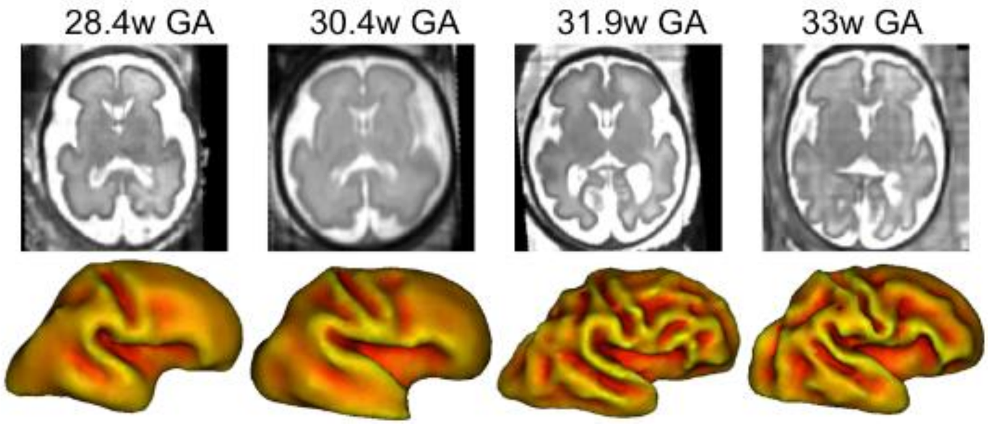
→ Intense progression between 30 and 40w of gestational age



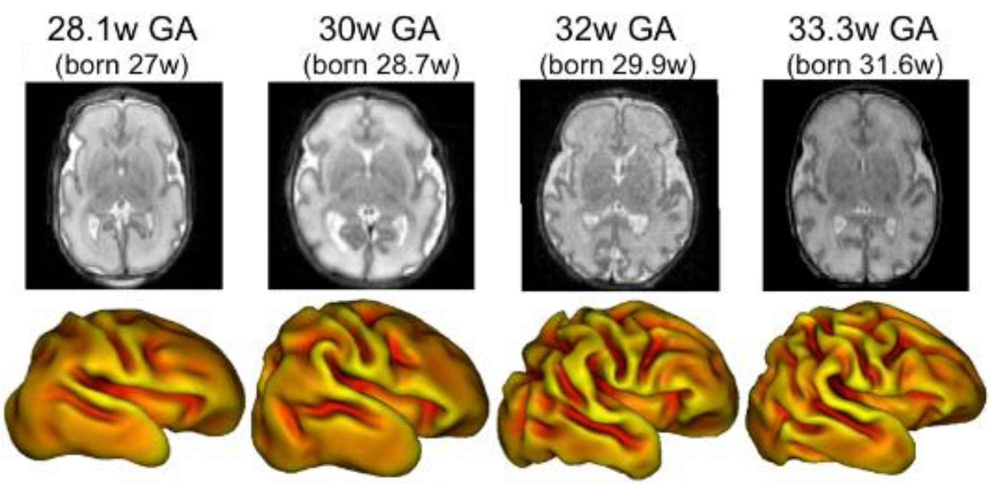
Dubois and Dehaene-Lambertz, Brain Mapping 2015
Dubois *et al*, IEEE ISBI 2016, Neuroimage 2019

Early differences in folding

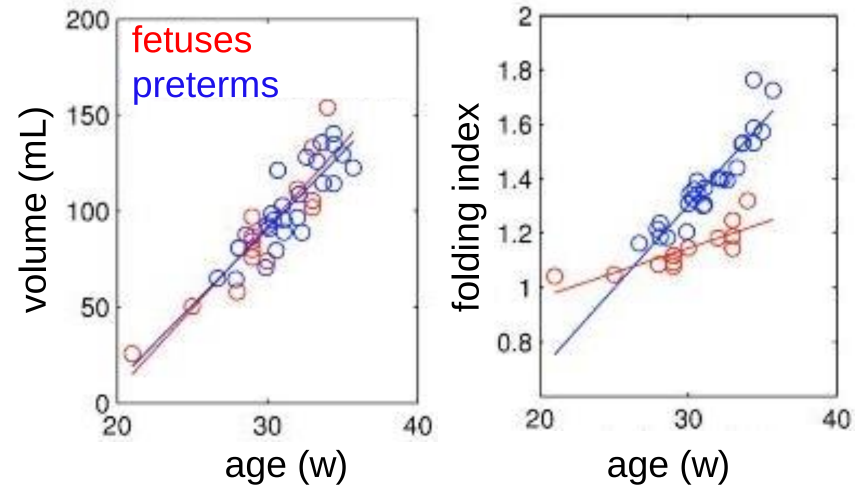
Fetuses



Premature newborns



At equivalent ages:
- similar brain volumes
- different folding trajectories

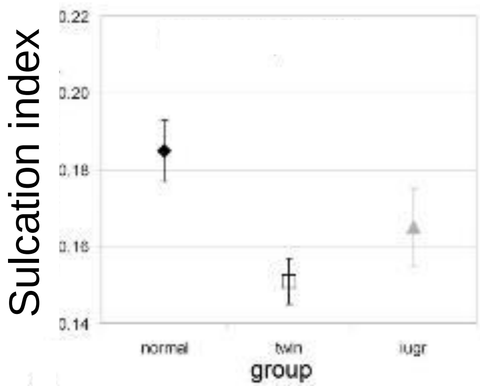


The transition from *in utero* to *ex utero* has a major impact on the folding process.

Early impairment in cortical folding

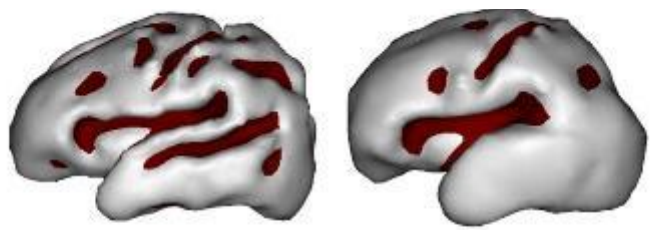
Comparison across preterm newborns close to birth

– Harmonious delay in twins



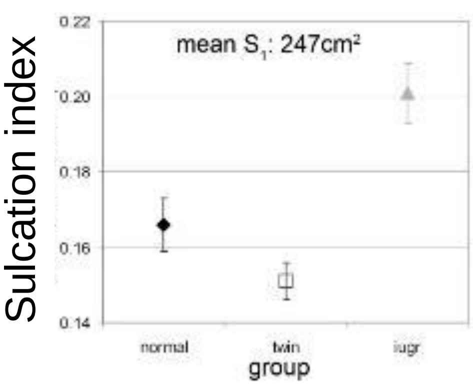
singleton
age 30w GA

twin
age 30w GA



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

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



singleton
surface 192cm^2

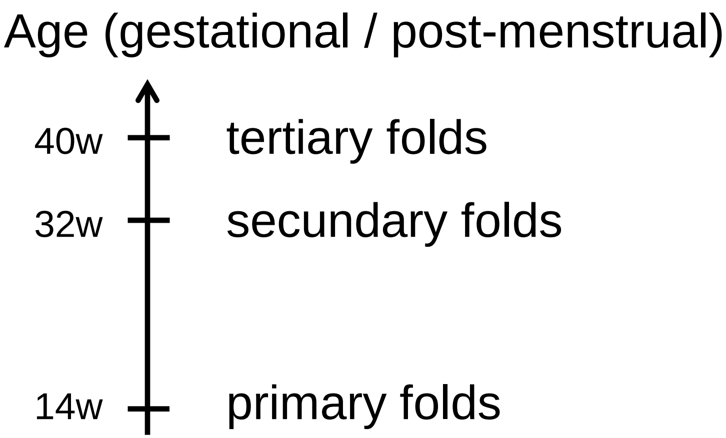
IUGR
surface 189cm^2

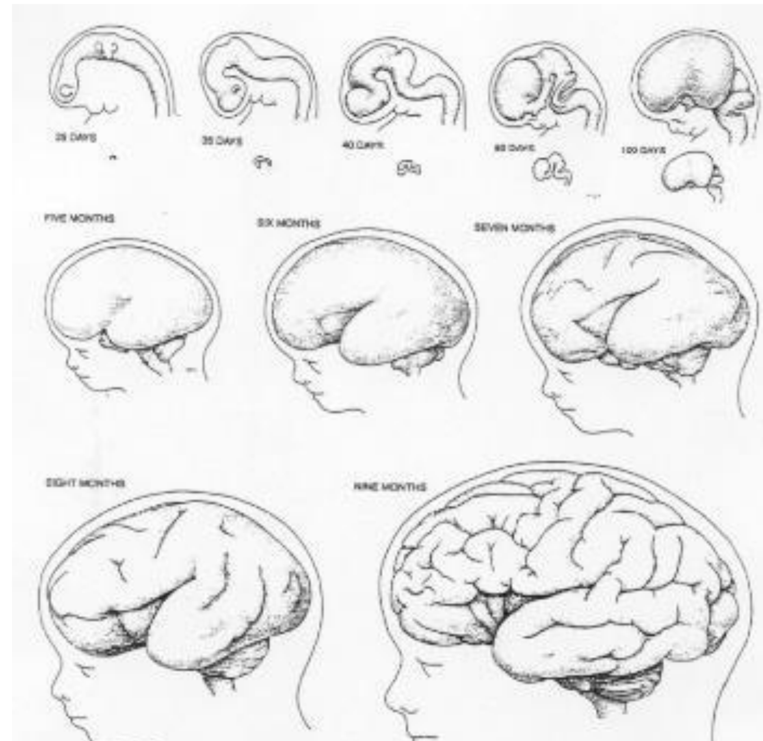
For equivalent cortical surface:
folding is too high
(folding is less delayed than surface growth)

Dubois *et al*, Brain 2008

A non-linear progression of folding

- Folds are labelled according to the age of appearance:



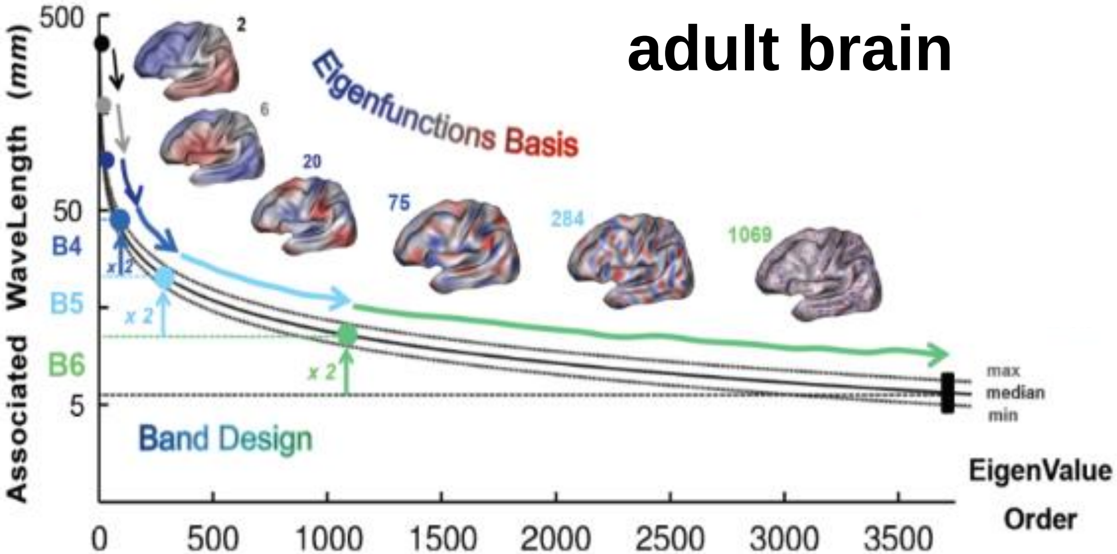

Cowan 1979

- Successive waves of folding
- Quantitative measures at the individual level?

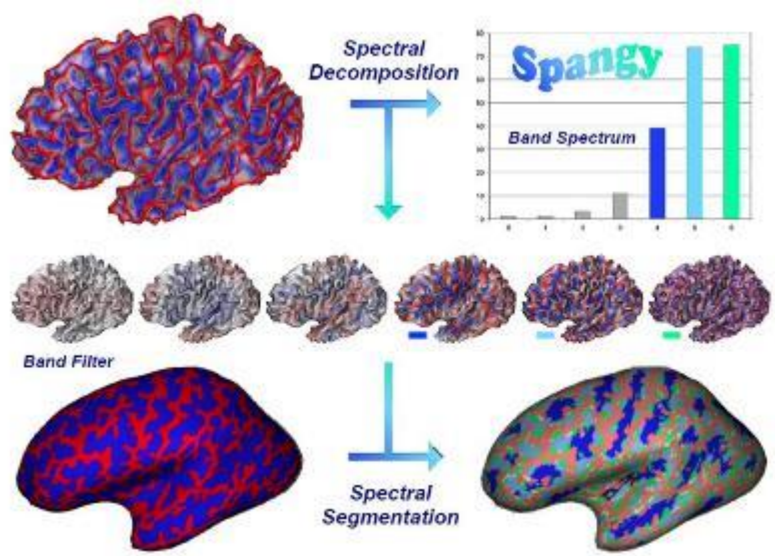
Decomposition of the brain folding

Spectral analysis of gyrification (SPANGY):

adult brain



* Decomposing the surface curvature according to spatial frequencies
* Merging into frequency bands:
- low frequency bands ~ global brain shape
- the last 3 bands (B4-6) ~ fold-related variations of curvature



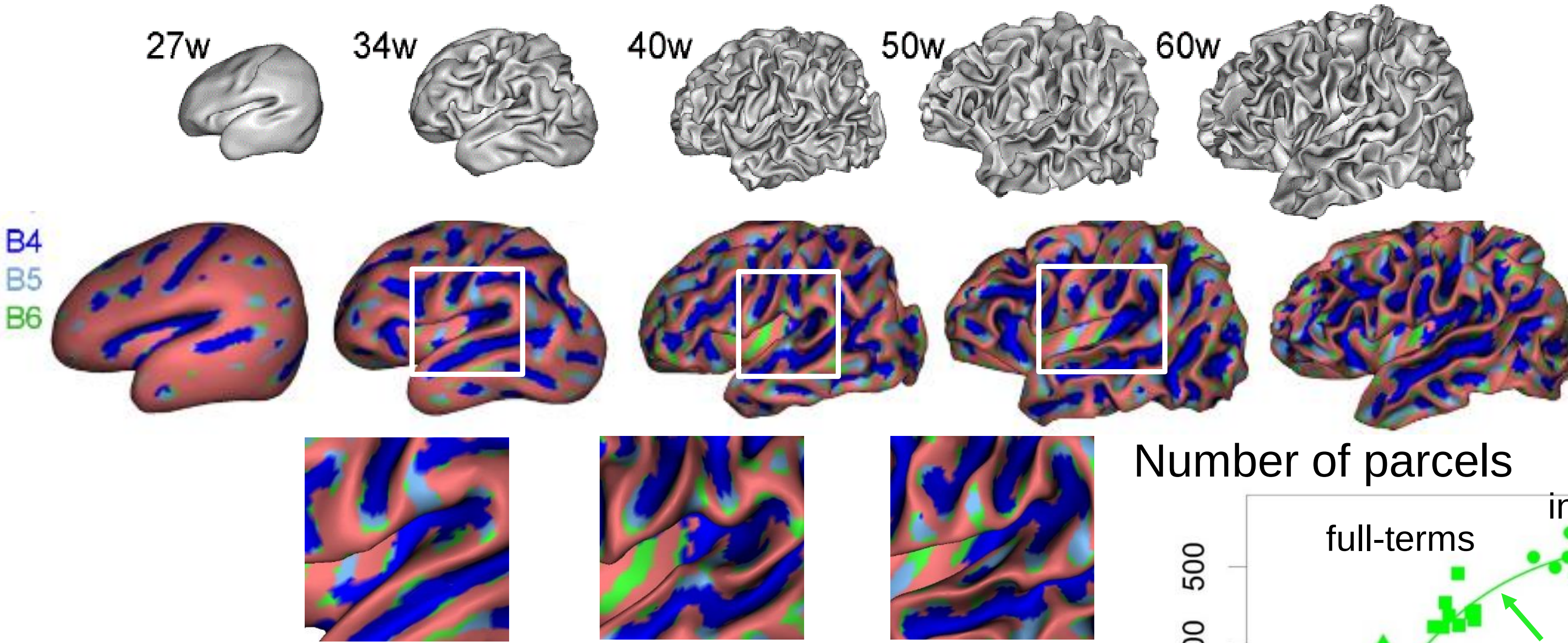
Analogy between spatial elements associated with B4, B5 and B6 bands, and developmentally-defined primary, secondary and tertiary folds?

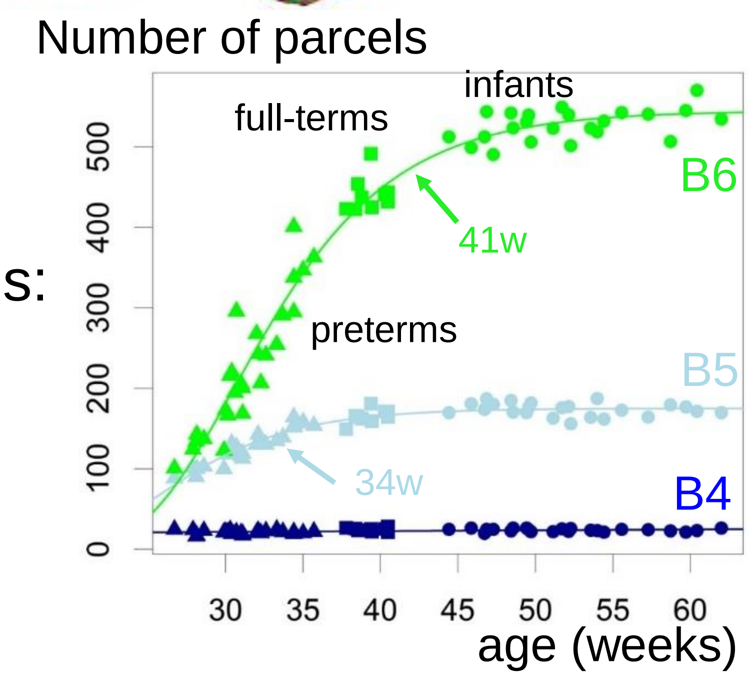
WL:
B4~56mm
B5~28mm
B6~14mm

Germanaud, Lefèvre *et al*, Neuroimage 2012

Successive folding waves

SPANGY in babies: in the ***spatial domain***





The 3 bands reveal different spatial patterns:

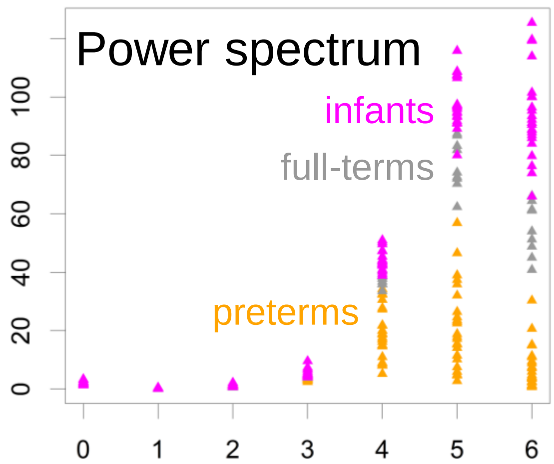
- B4 elements: the main earliest folds
- B5 and B6 elements: branches and dimples

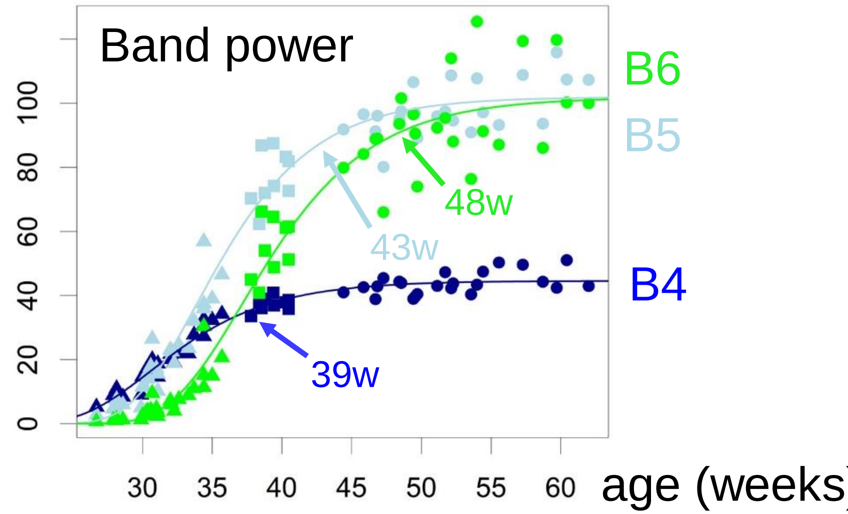
Wavelengths:	Babies	Adults
B4	17-55mm	49-64mm
B5	9-28mm	25-32mm
B6	4-14mm	12-16mm

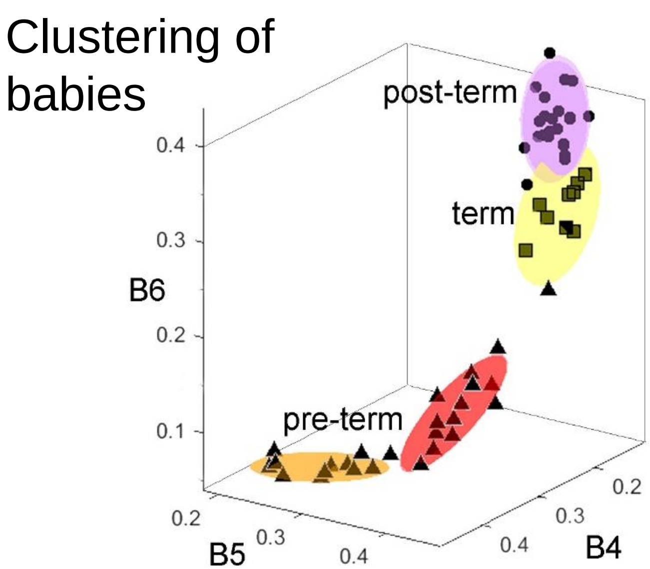
Dubois *et al*, Neuroimage 2019

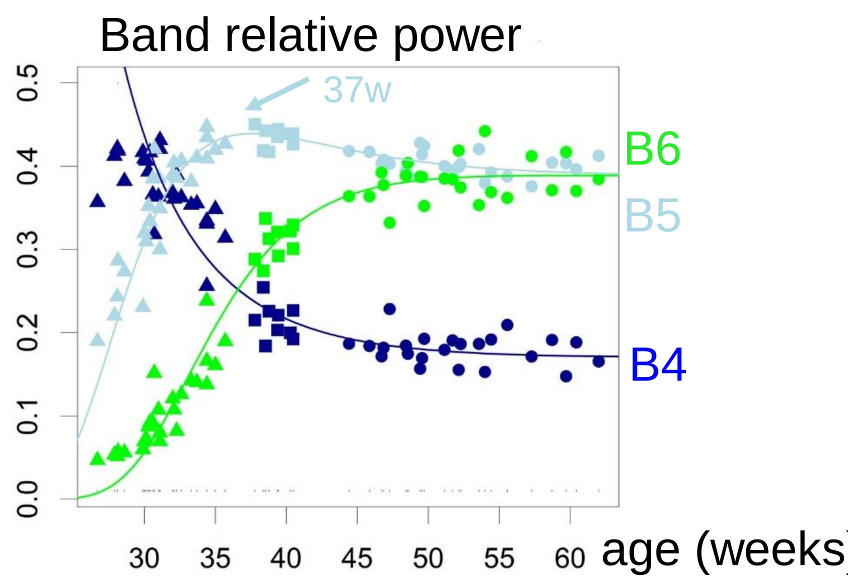
Successive folding waves

SPANGY in babies: in the ***spectral domain***





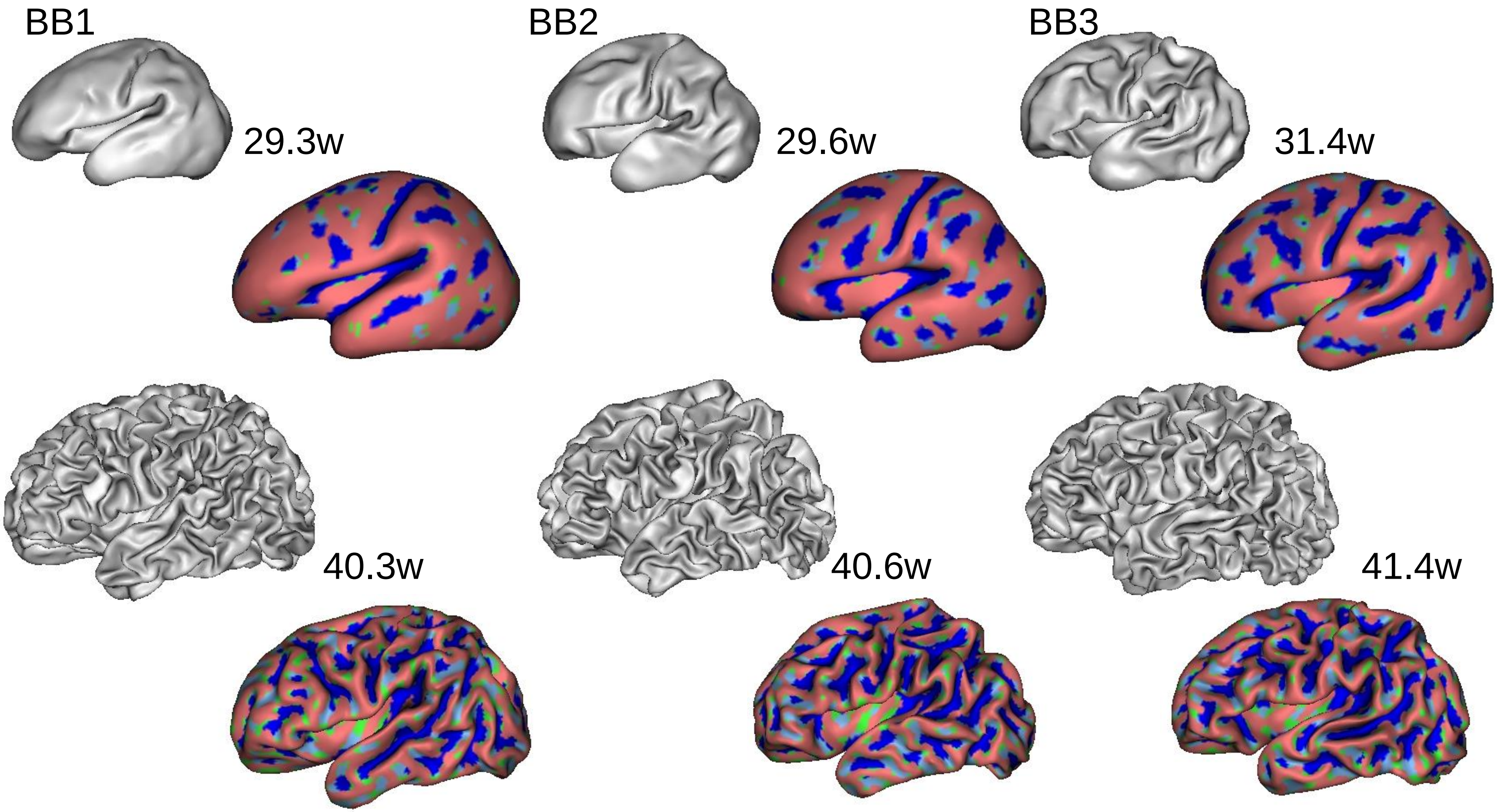




Dubois *et al*, Neuroimage 2019

Longitudinal MRI of preterm newborns

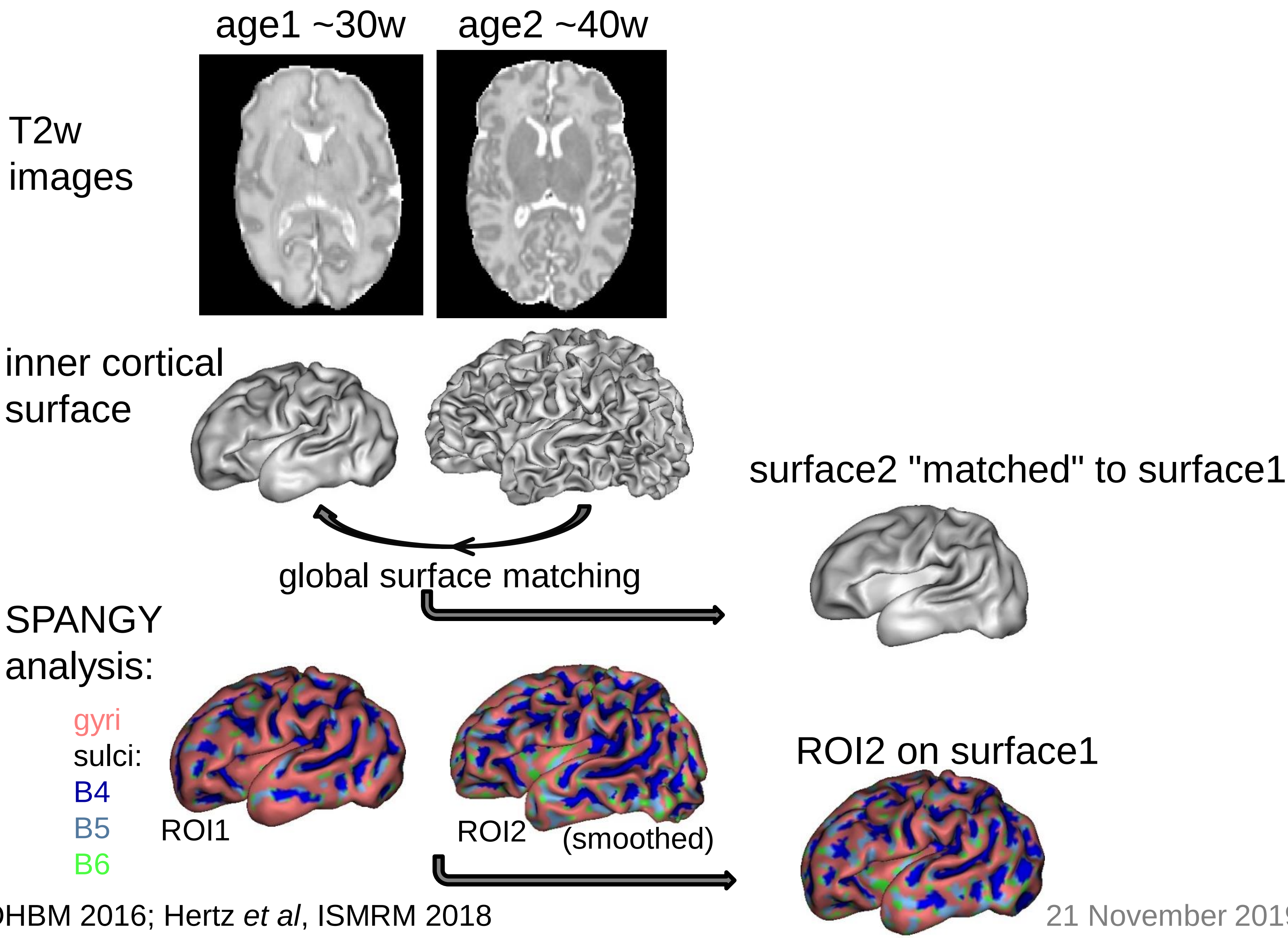
Inter-individual variability in age, folding and brain size



Zomeno *et al*, OHBM 2016; Hertz *et al*, ISMRM 2018

Longitudinal registration of surfaces

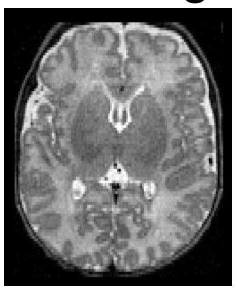
Spectral-based surface matching (A. Pepe, J. Lefèvre)

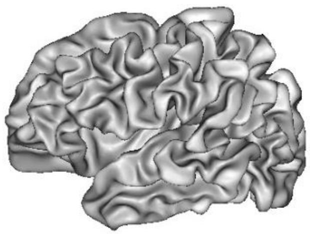


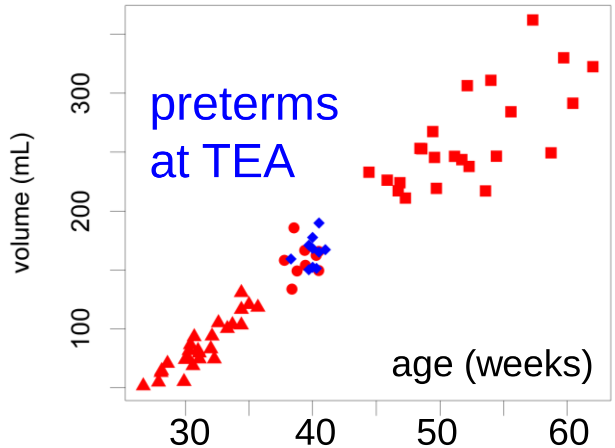
Zomeno *et al*, OHBM 2016; Hertz *et al*, ISMRM 2018

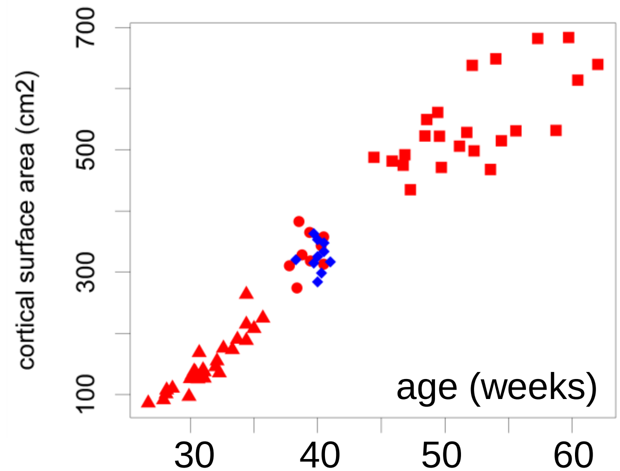
Early impairment in cortical folding

- Preterm infants at term equivalent age (TEA):
  - ✓ GA at birth: 24.5 – 31w
  - ✓ Age at MRI: 38.3 – 41w



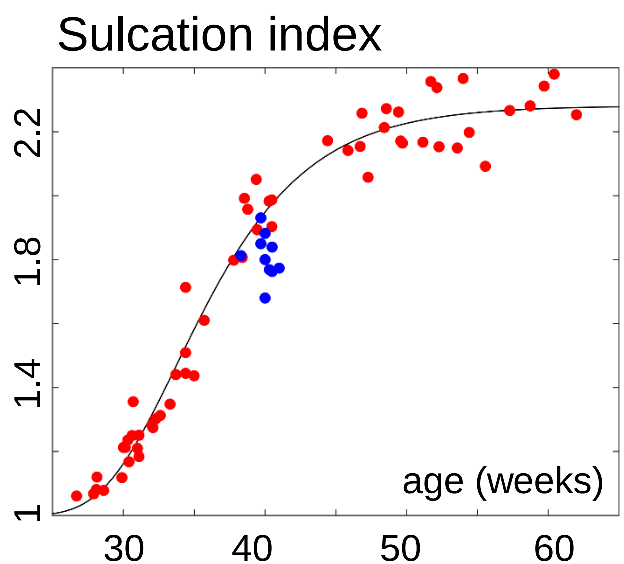


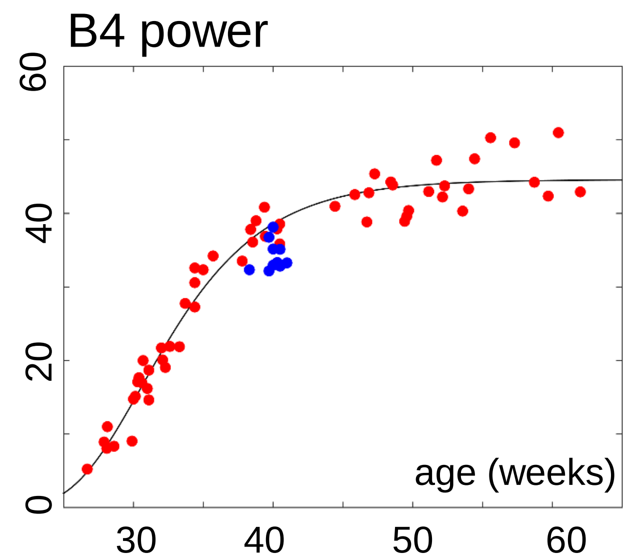




- No difference in brain size and cortical surface

- But lower folding, mainly related to lower B4 power

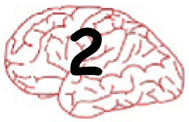




Dubois *et al*, Neuroimage 2019

Overview of the presentation

Studies on the development of brain folding with "whole-brain" analyses

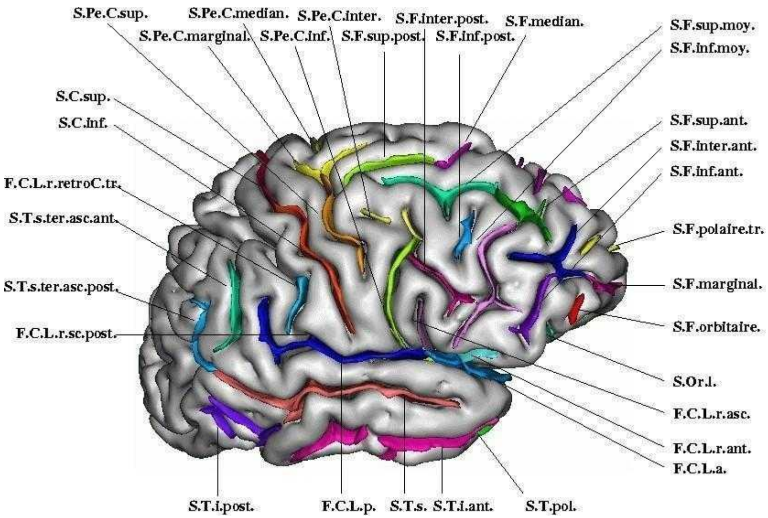


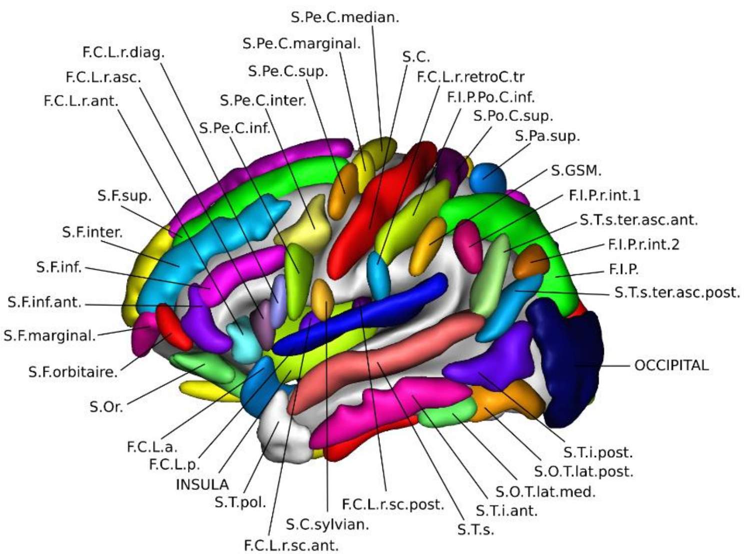
Studies based on "sulcus" objects

Relating the folding process and other developmental mechanisms

Another way to study folding

"Sulcus" objects (BrainVisa / Morphologist)

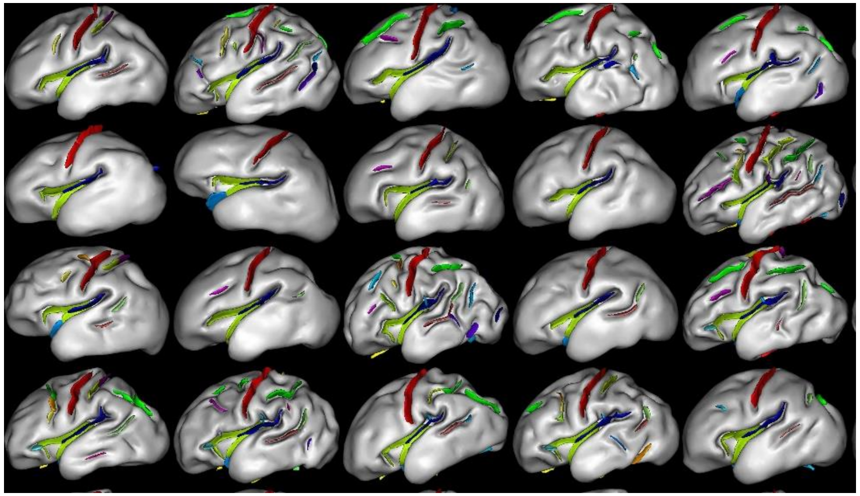




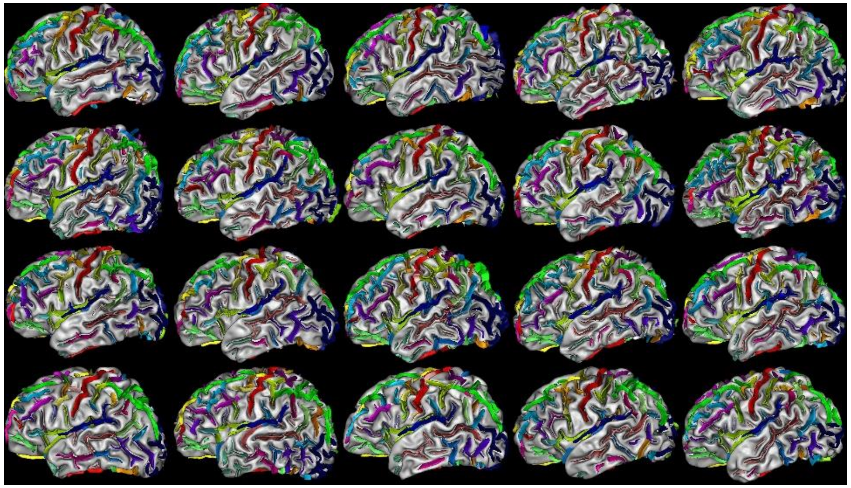
Fischer *et al*, OHBM 2012

Preterm newborns

30w



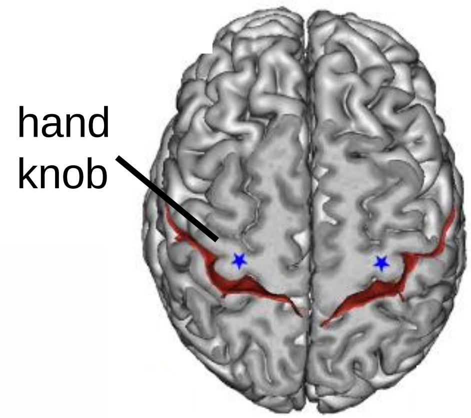
40w

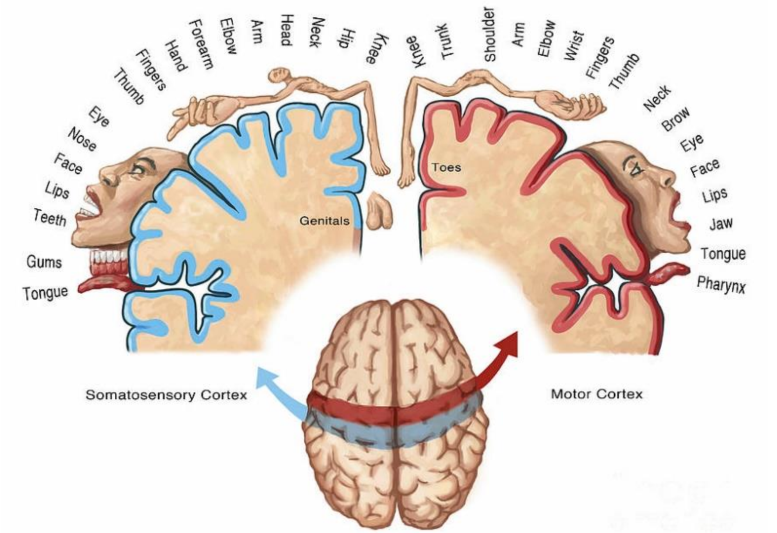


de Vareilles *et al*

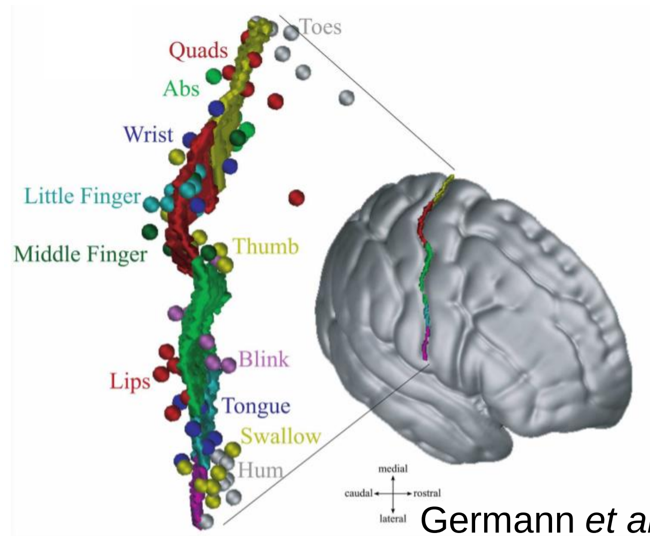
Focus on the central sulcus

- Border between pre-central gyrus (primary motor cortex) and post-central gyrus (primary somatosensory cortex)
- Link with somatotopic organization



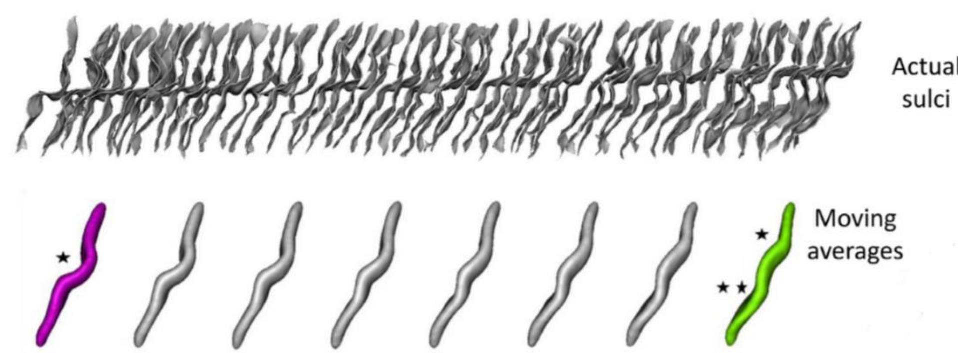


Penfield and Rasmussen, 1950



Germann *et al*, Cerebral Cortex 2019

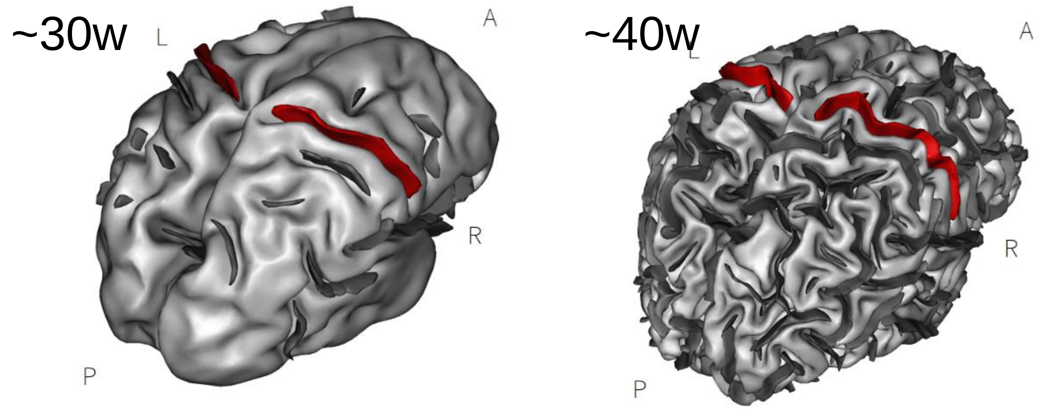
- One of the first developing sulcus
- Shape variability in the adult brain



Sun *et al*, Neuroimage 2012

Studying the shape of the central sulcus

71 preterm newborns



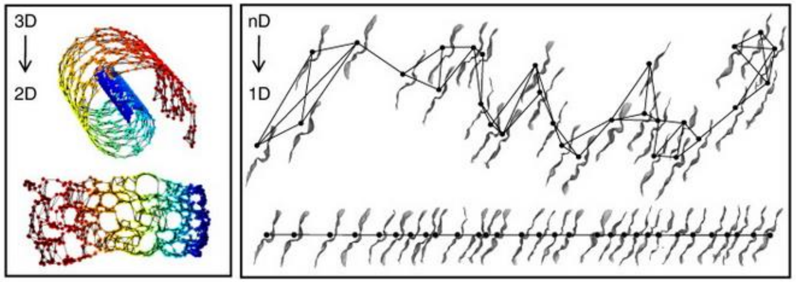
Steps to capture the variability in shape:

- Brain coregistration
- Sulcus extraction
- Sulcus pairwise coregistration (distance between each pair of sulci)
- Dimension reduction on variability matrix

$$\begin{bmatrix} d(1,1) & \cdots & d(1,284) \\ \vdots & \ddots & \vdots \\ d(284,1) & \cdots & d(284,284) \end{bmatrix}$$

71 subjects
x 2 hemispheres
x 2 acquisitions

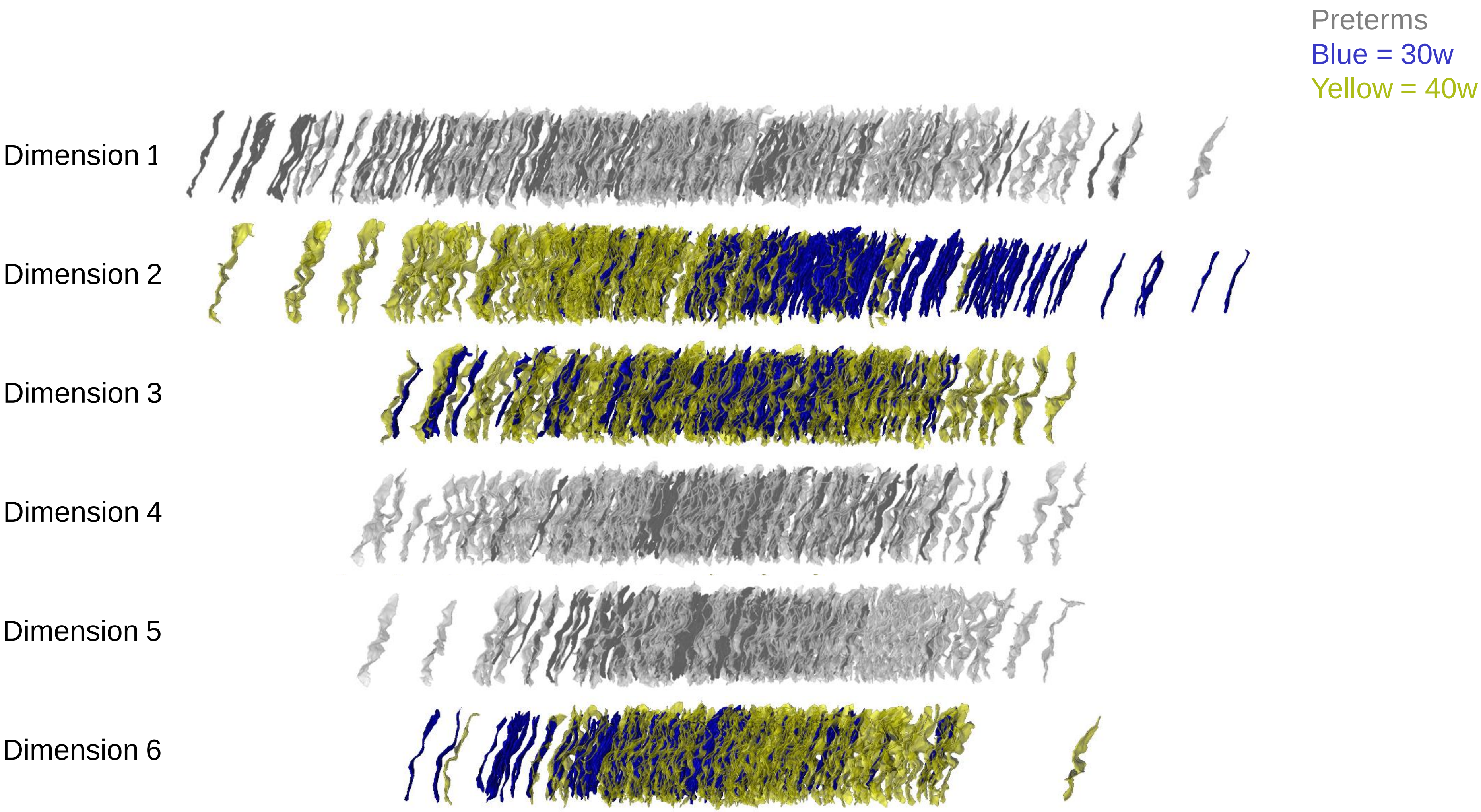
Isomap algorithm



de Vareilles *et al*, MICCAI/PIPPI 2019

Sun *et al*, Neuroimage 2012

Major variability features



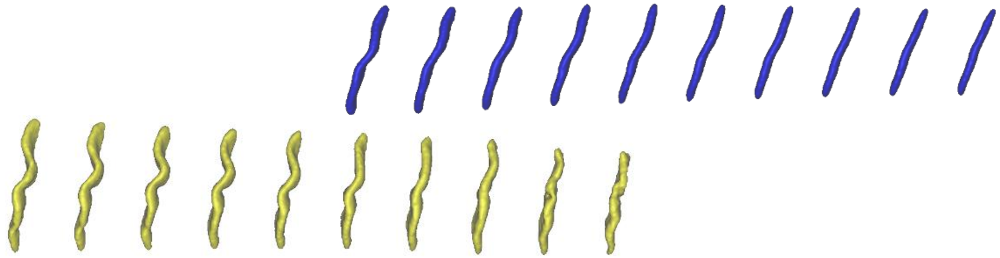
de Vareilles *et al*, MICCAI/PIPPI 2019

Major variability features

Longer and curvier sulci ← → Shorter and straighter sulci

Preterms
Blue = 30w
Yellow = 40w

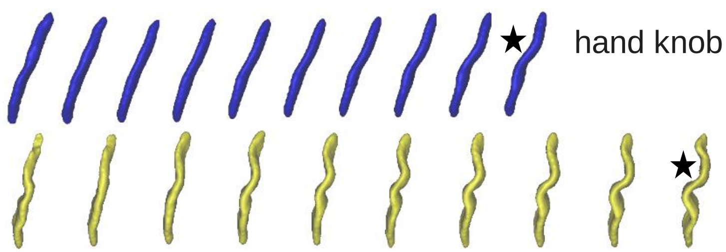
Dimension 2:
Length and development



Wilcoxon rank sum between 30w and 40w sulci:
stat = -12
p-val = 8.10^{-34}

Shallower hand knob ← → Deeper hand knob

Dimension 3:
Amplitude of the hand knob



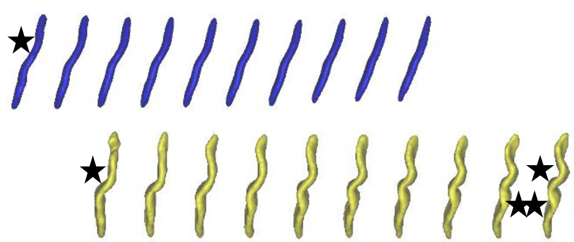
★ hand knob

★ hand knob

Pearson correlation between 30w and 40w sulci:
r=0.55
p-val=7.10^{-12}

Single knob ← → Double knob

Dimension 6:
Single to double knob



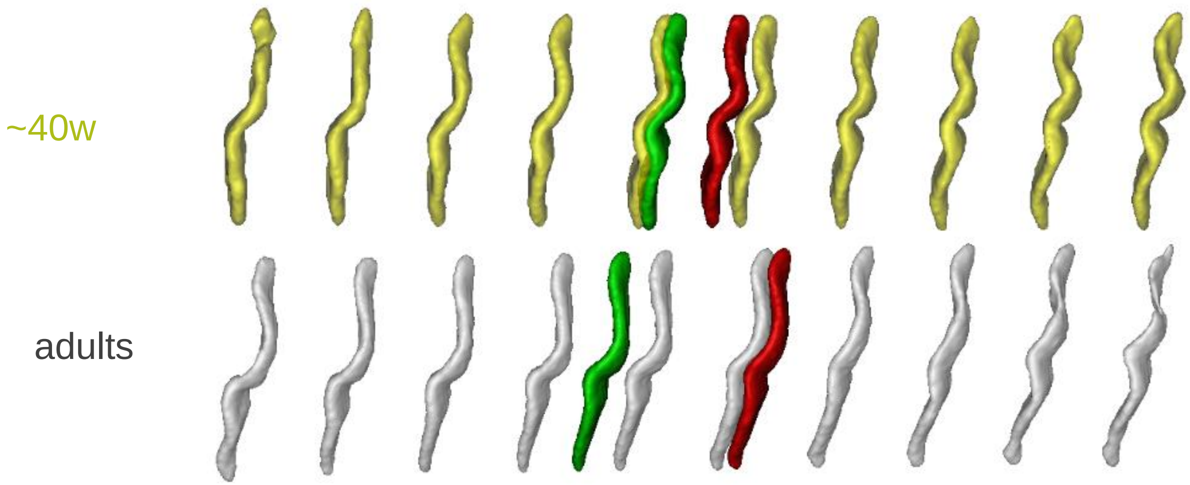
★ hand knob
★★ second knob

de Vareilles *et al*, MICCAI/PIPPI 2019

Inter-hemispherical asymmetries in folding

- Left / right asymmetry of the "single to double-knob" configuration

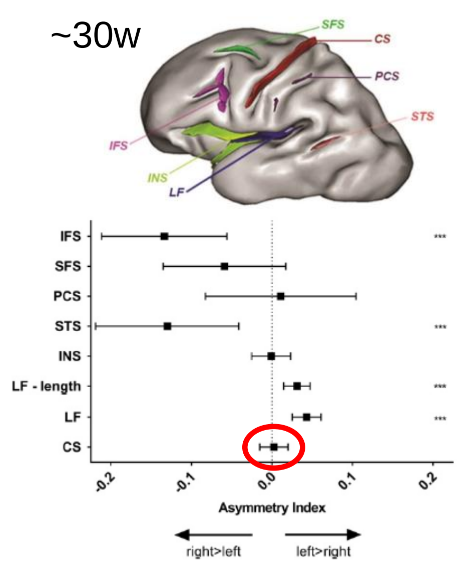
Median shape for: right sulci left sulci

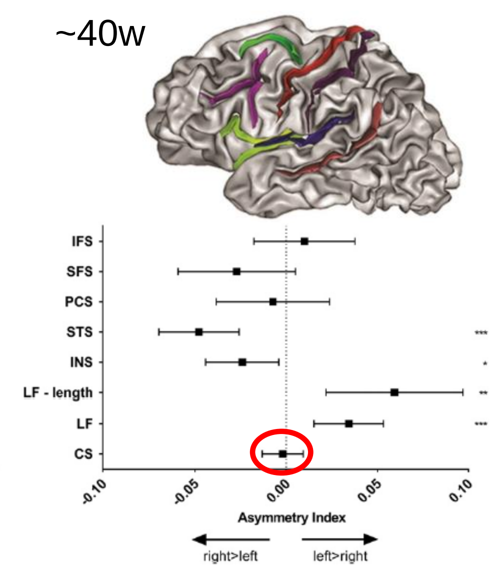


Wilcoxon signed-rank test
(left vs right):
Preterms ~40w
stat = 802 / p-val = 6.10^{-3}
Adults
stat = 1057 / p-val = 3.10^{-6}

de Vareilles *et al*, MICCAI/PIPPI 2019

- Asymmetries in the surface of sulci



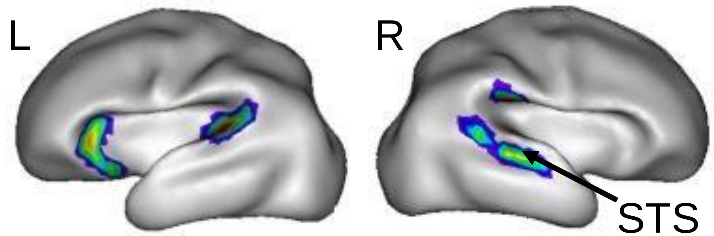


Kersbergen *et al*, Neuroimage 2016

Inter-hemispherical asymmetries in folding

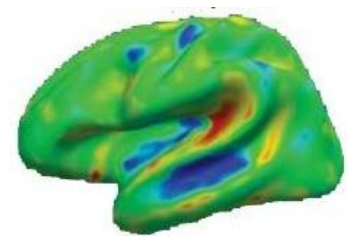
- Asymmetries in brain growth and folding

Preterm newborns



Dubois *et al*, Neuroimage 2010

Infants 0-2 years



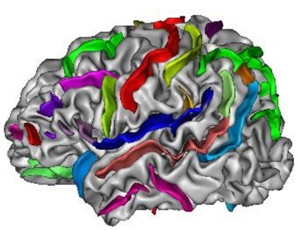
Li *et al*, Cerebral Cortex 2014

- Registration of brains with different sizes, shapes, asymmetries…

Individual data

T2w image

Sulci of interest



Cortical ribbon

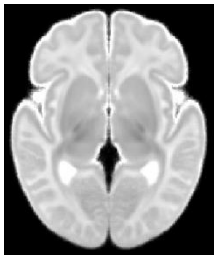
DISCO+DARTEL registration

→

native + flipped brains

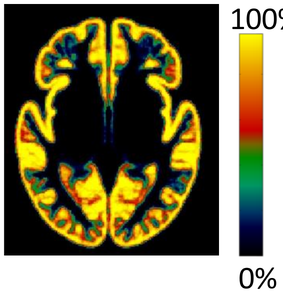
Over the group

Averaged brain



All native and flipped sulci

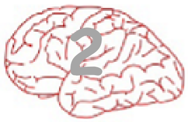
Averaged cortical ribbon



Lebenberg *et al*, Brain Structure and Function 2018
Rolland *et al*, IEEE ISBI 2019

Overview of the presentation

Studies on the development of brain folding with "whole-brain" analyses



Studies based on "sulcus" objects

Relating the folding process and other developmental mechanisms

Early development of the brain



6 months — Birth at term — 6 months

~28 weeks of gestational age — ~40w — ~26w of post-term age

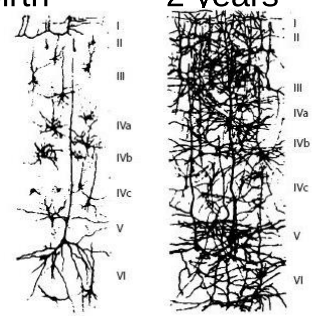
CORTEX

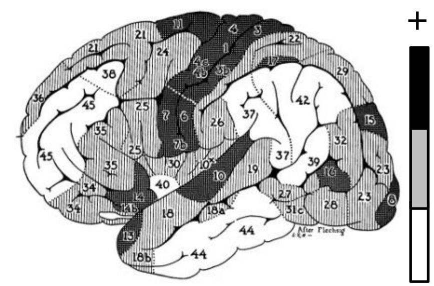
Growth and folding

20w 31w 40w

Microstructure / Maturation

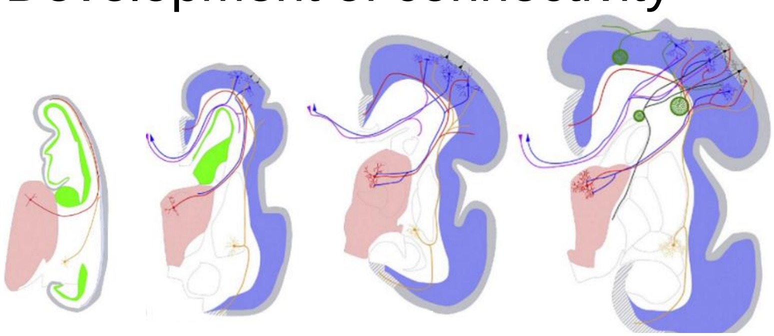
birth 2 years





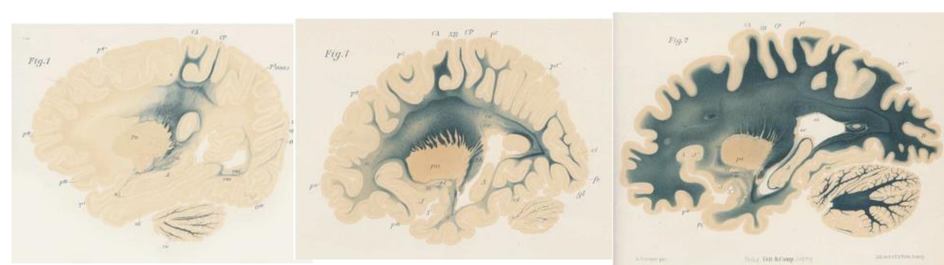
WHITE MATTER

Development of connectivity



Myelination

birth 6 months adult



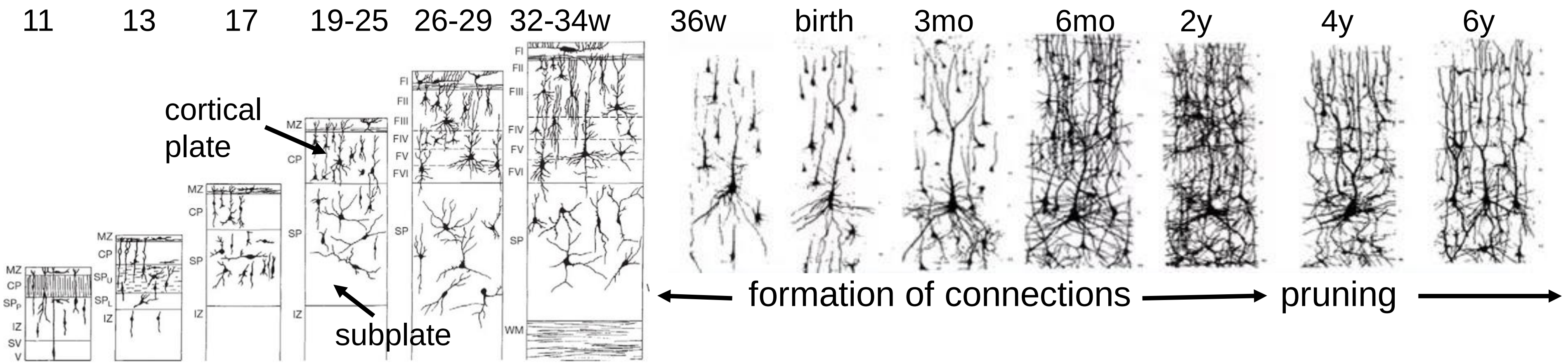
Flechsig 1901, 1920; Judas & Kostovic, 2014

Jessica Dubois, 21 November 2019

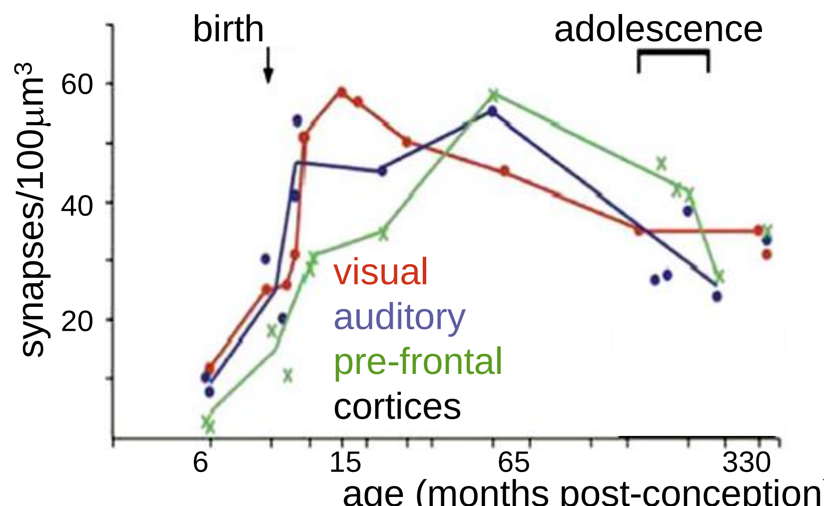
Development of the cortex

- Growth of dendritic arborization and synaptogenesis

Cortex : during gestation / after birth



- Successive phases
- Variability between brain regions

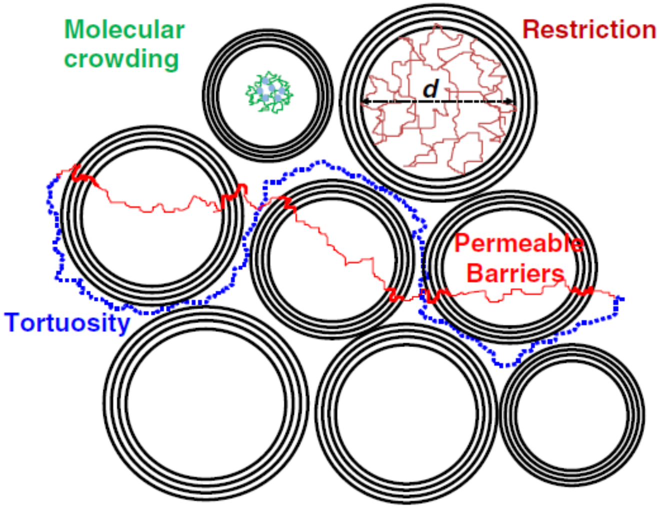


Bourgeois and Rakic 1993; Huttenlocher and Dabholkar, 1997; Stiles and Jernigan, 2010

Diffusion MRI and microstructure

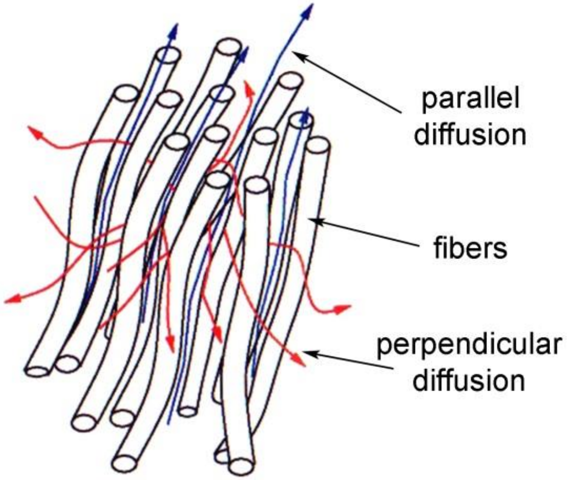
Brownian motion

Diffusion in a biological tissue

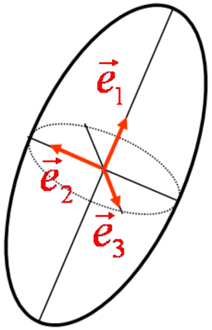


Le Bihan and Johansen-Berg, Neuroimage 2012

Diffusion anisotropy: variations among space directions



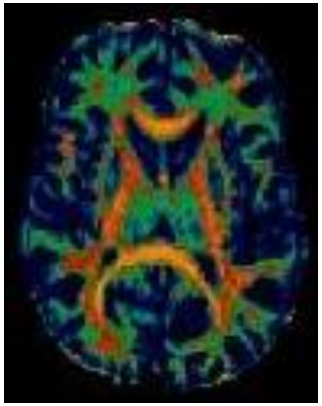
Modelling and diffusion tensor imaging (DTI)



parallel diffusivity $\lambda_{//}$

perpendicular diffusivity $\lambda_{\perp}$

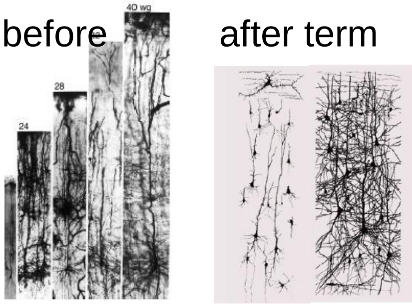
Anisotropy map



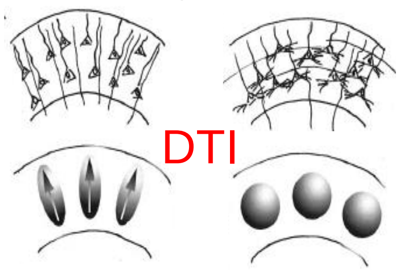
Microstructure of the cortex

During the preterm period: radial organization of the cortex that disappears with the development of dendritic arborization

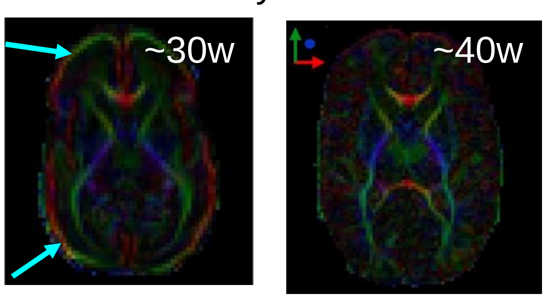
before after term



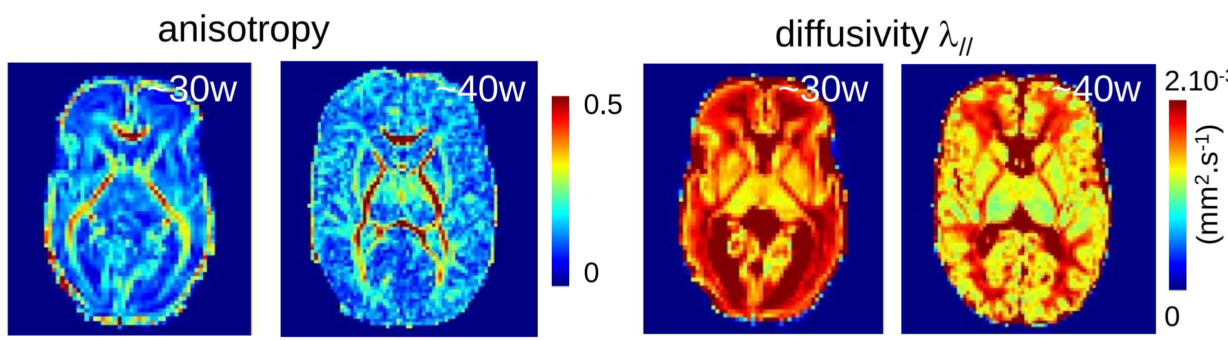
Marin-Padilla, 1998



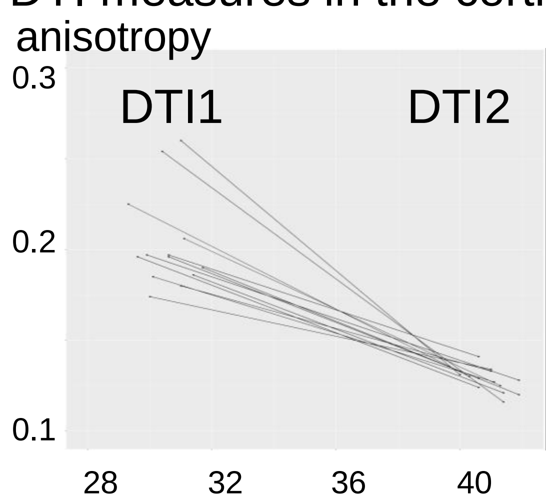
DTI directionality

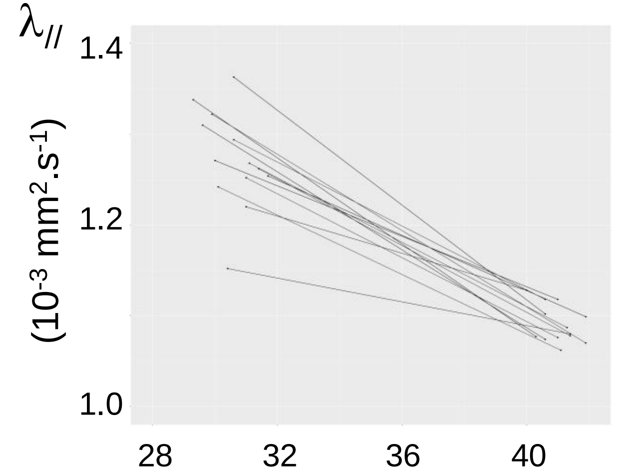


Preterm newborns



DTI measures in the cortical ribbon

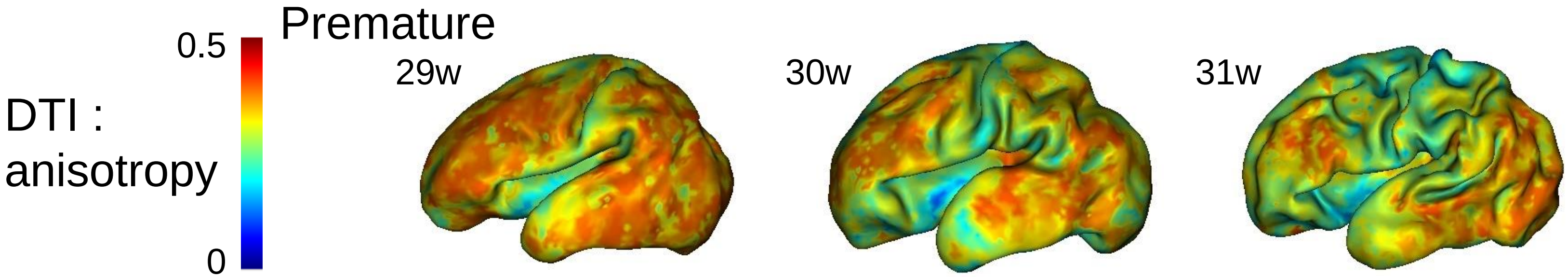




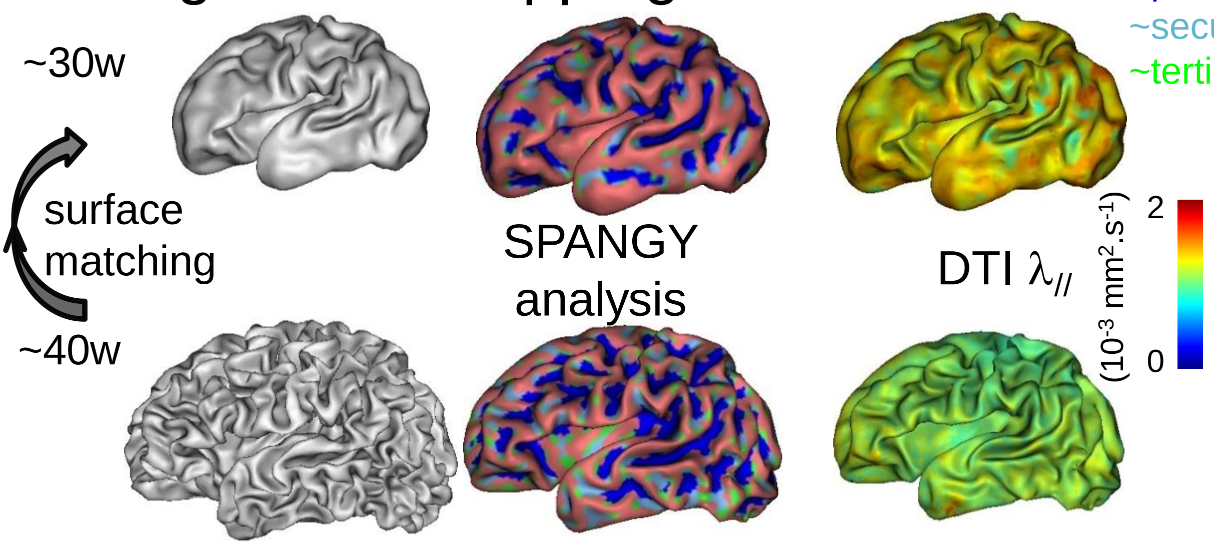
McKinstry *et al*, Cerebral Cortex 2002; Ball *et al*, PNAS 2013
Zomeno *et al*, OHBM 2016; Hertz *et al*, ISMRM 2018

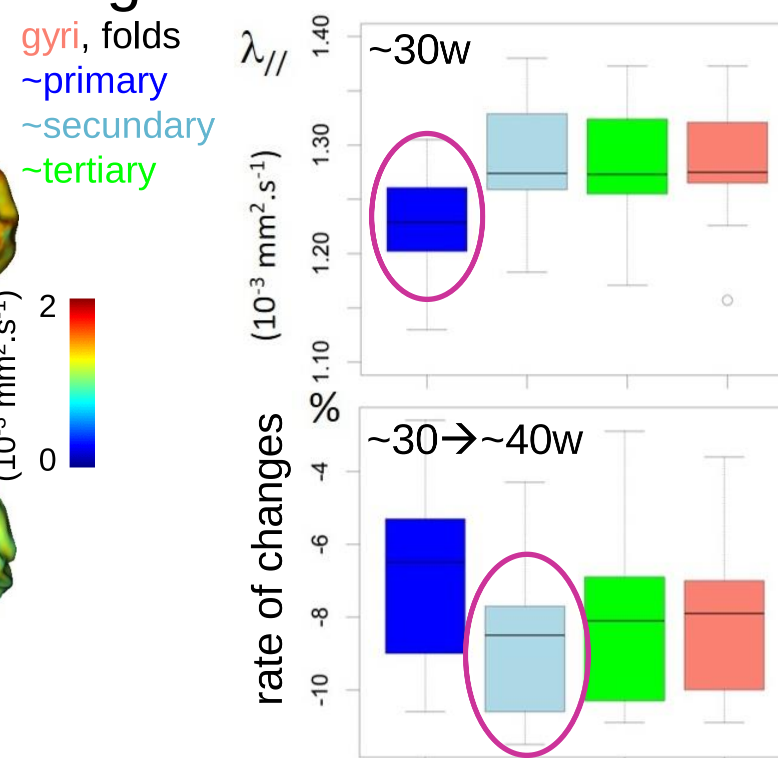
Microstructure and folding of the cortex

- Differences between cerebral regions



- Relationships between changes in folding and microstructure?
- Longitudinal mapping:

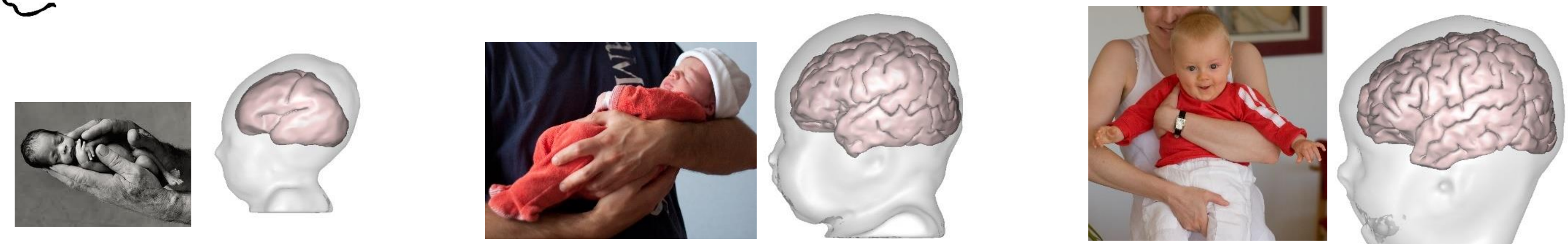




→ Folding regions show different age-related changes in microstructure.

Zomeno *et al*, OHBM 2016; Hertz *et al*, ISMRM 2018

MRI of early brain development



6 months — Birth at term — 6 months

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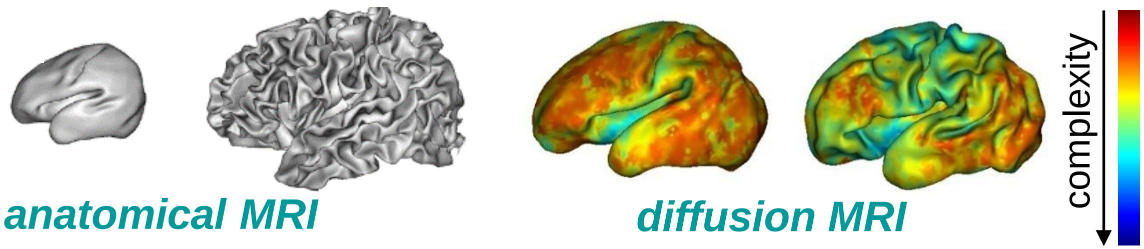
CORTEX

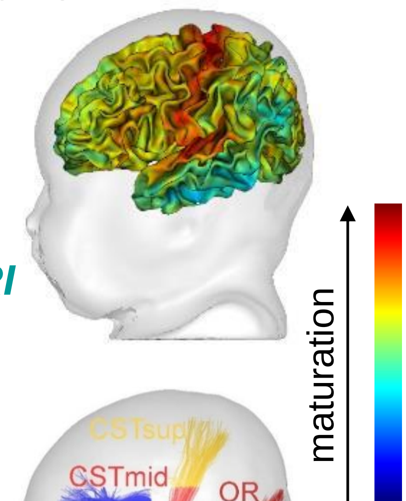
Growth and folding

Microstructure / Maturation



anatomical MRI

diffusion MRI

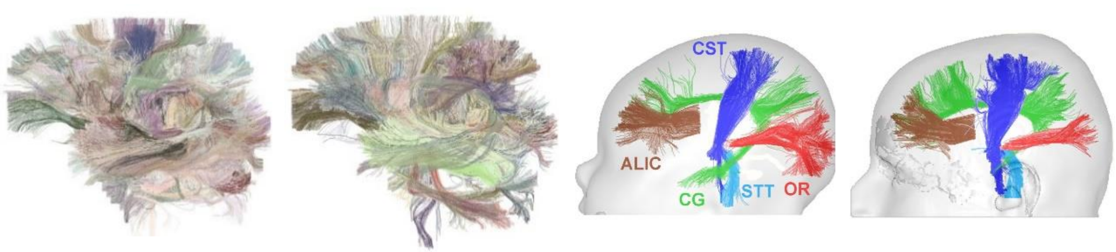


quantitative T1 and T2 MRI

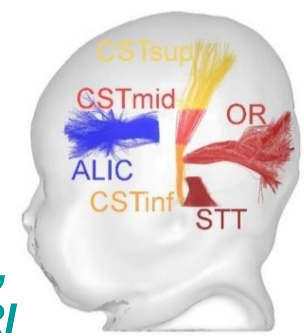
WHITE MATTER

Development of connectivity

Myelination



diffusion MRI and tractography

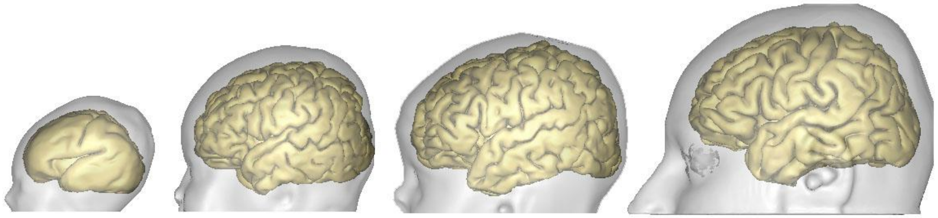


diffusion MRI, T1 and T2 MRI

Perspectives

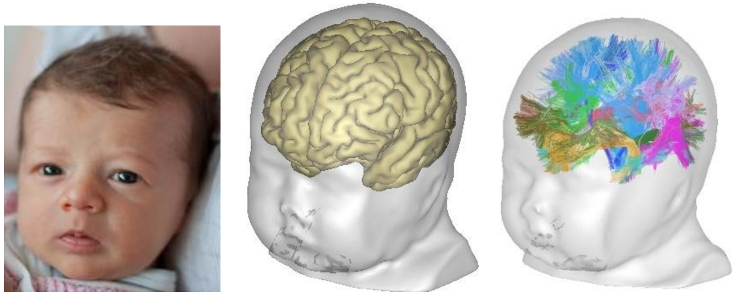
The developing brain:

- Intensity of the folding process
- Early architecture in networks



- Post-natal maturation and plasticity (role of the environment)

- Stability and variability among infants
- Potential of longitudinal studies



- Links with functional and behavioral development
- Understanding of neurodevelopmental disorders

Thank you!

Questions? jessica.dubois@cea.fr

NeuroSpin (Saclay)

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Robert Debré Hospital (Paris)

D. Germanaud…

Institut des Neurosciences de la Timone, Marseille Hospital

J. Lefèvre, N. Girard…

Geneva and Utrecht Hospitals

P. Hüppi, F. Lazeyras…
M. Benders, L. de Vries, F. Groenendaal…

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