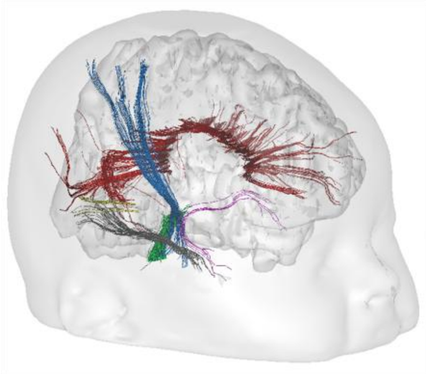


Diffusion tensor imaging of the infant brain: From technical problems to neuroscientific breakthroughs

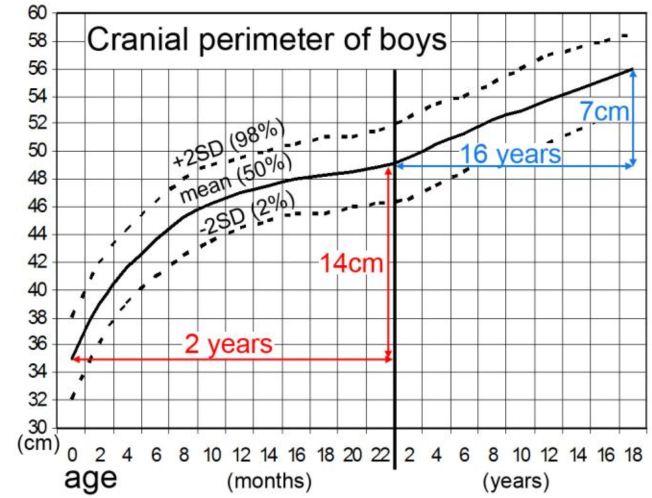
Jessica Dubois

L. Hertz-Pannier, G. Dehaene-Lambertz, J.F. Mangin, D. Le Bihan
Inserm U562, U663; NeuroSpin (CEA); Hôpital Necker-Enfants malades
Saclay, Paris (France)

Brain development during infancy

Sensori-motor and cognitive advances

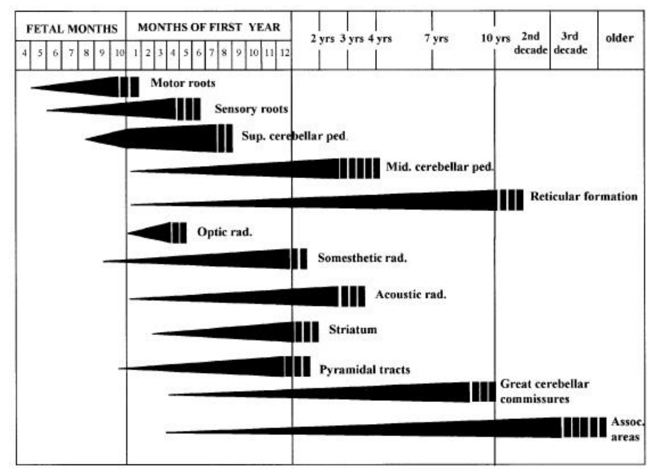
Birth 3 months 6 months 1 year



Post-mortem myelin staining

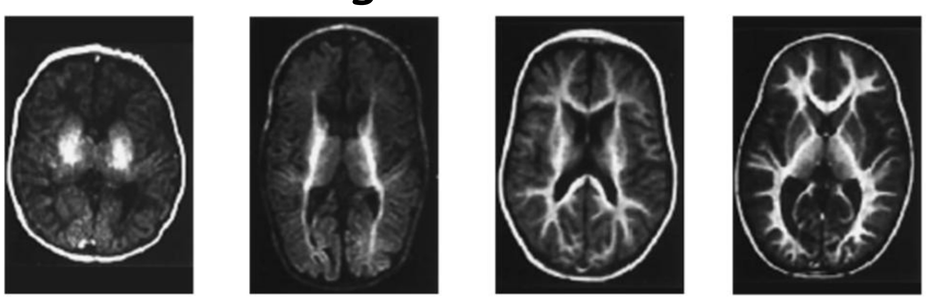
Cycles of myelination

Fleschig, 1920



Baumann and Pham-Dinh, 2001
From Yakovlev and Lecours, 1967

In vivo MRI: T1-w images



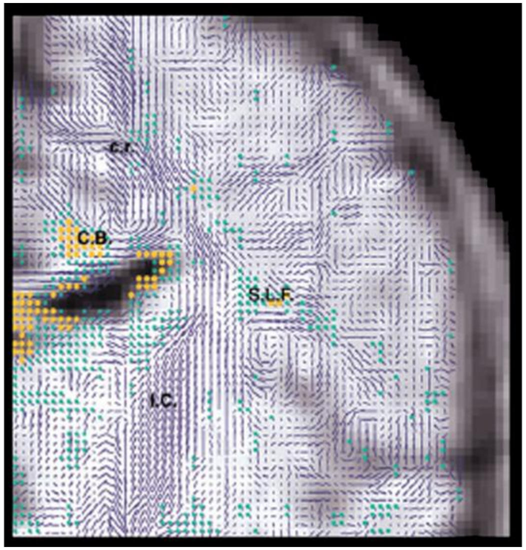
Paus *et al*, 2001

Brain development and diffusion MRI

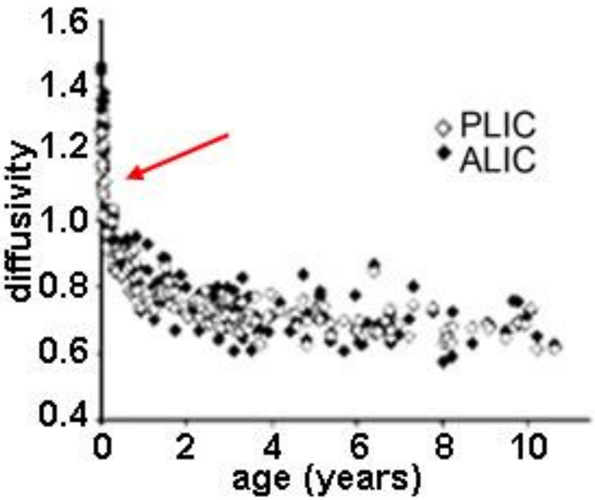
Potential of diffusion MRI and diffusion tensor imaging (DTI) to study the infant white matter development:

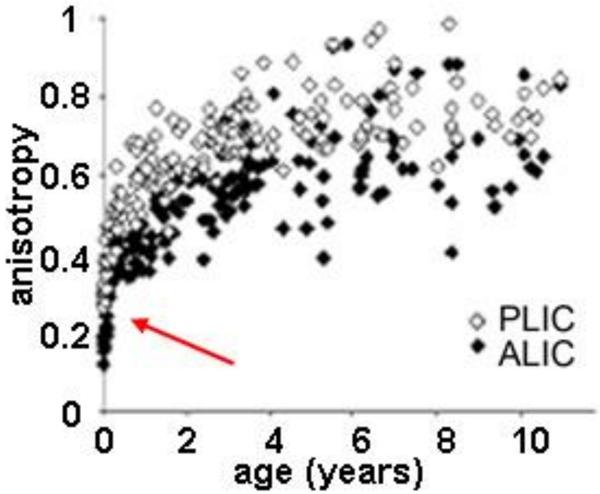
• spatial organization of fiber fascicles

• fascicles' maturation



Hüppi *et al*, 2001

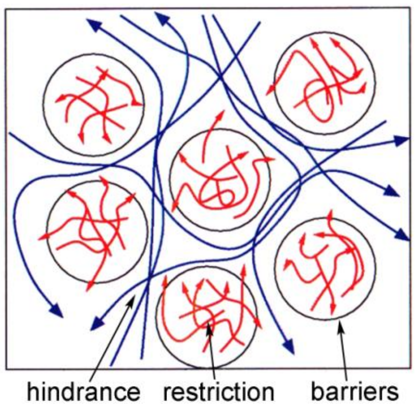




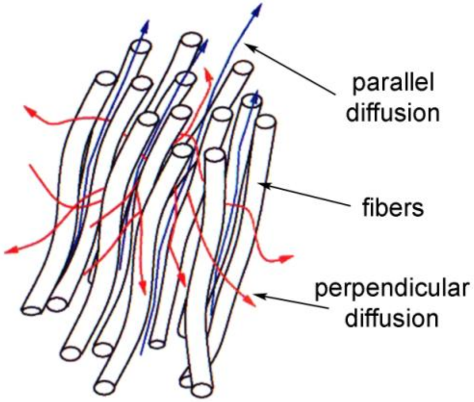
Neil *et al*, 1998, 2002; Mukherjee *et al*, 2001

Diffusion tensor imaging (DTI)

Diffusion of water molecules



Oriented organization



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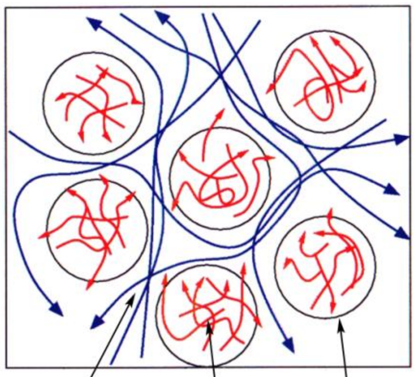

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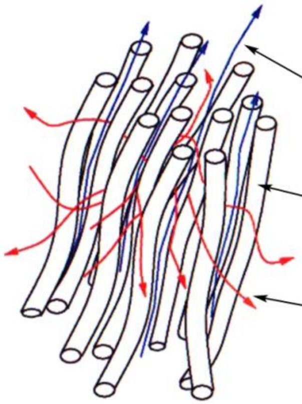
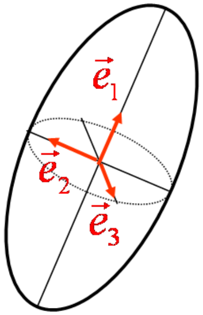


Diffusion tensor



$$\overline{\overline{D}} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$$

$$\lambda_{//} = \lambda_1$$

$$\lambda_{\perp} = \frac{\lambda_2 + \lambda_3}{2}$$

DTI indices

Mean diffusivity

$$\langle D \rangle = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Fractional anisotropy

$$FA = \left(\frac{3}{2} \frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right)^{1/2}$$

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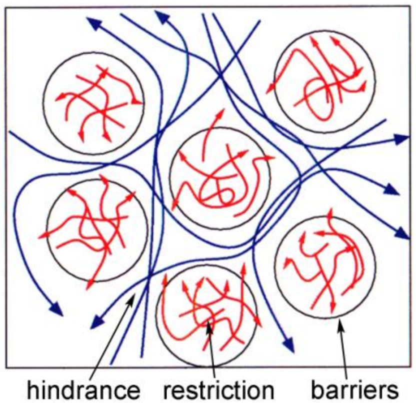

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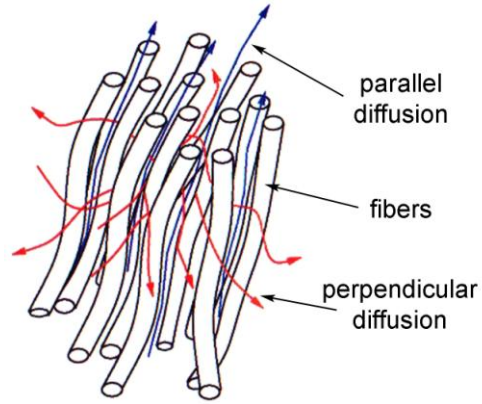

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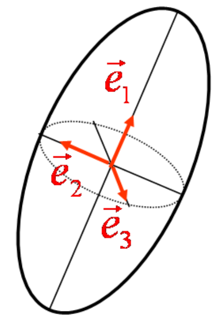

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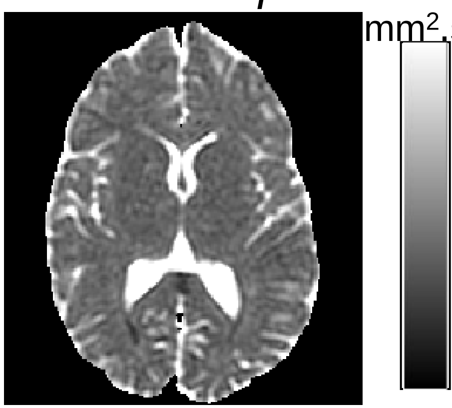
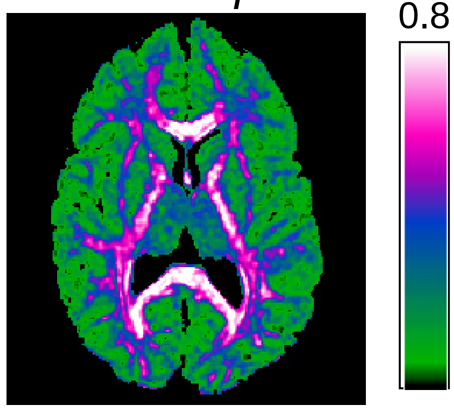
White matter fibers

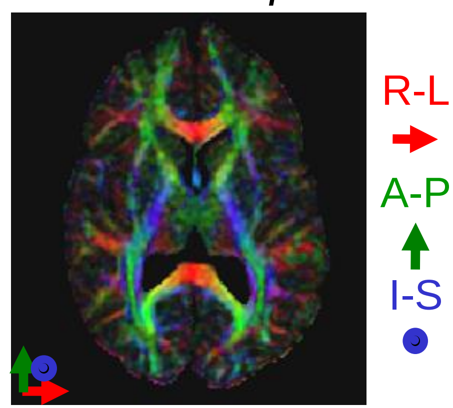
<D> map



FA map



RGB map



Objectives

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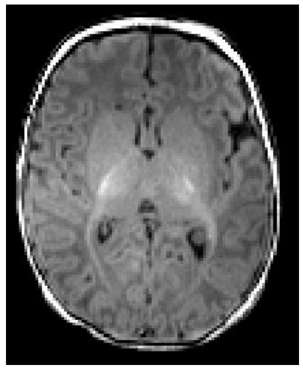
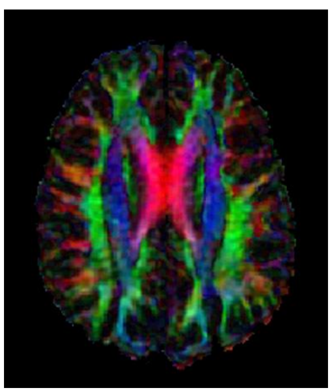
Difficulties in imaging infants' brain

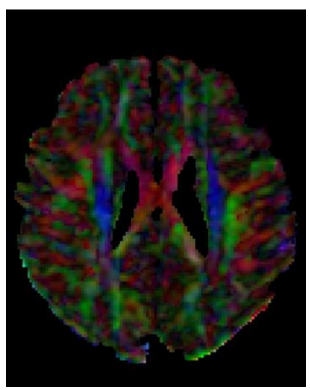
T1-w MRI adult

2-m old infant



DTI-RGB map





Constraints in MR images:

- contrast: high water content, tissues immaturity
- spatial resolution: structures' size, partial volume effects

Constraints in MR acquisition:

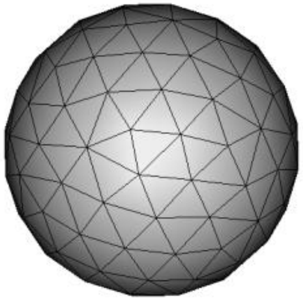
- time
- scanner noise
- wake up
- motion

→ Only a few MRI studies in healthy infants without sedation

Optimization of diffusion orientations sets

Methodological objective:

Optimize DTI acquisitions in function of the possible babies' wakening



↑ Orientation number → ↑ SNR + spatial estimation
BUT → ↑ acquisition time
Compromise between orientation number and acquisition time?
OR Outsmart temporal order of orientations within a set

Electrostatical model

$$E = \sum_{i \neq j} E_{ij}^{0} \qquad E_{ij}^{0} = \frac{1}{\vec{r}_i - \vec{r}_j} + \frac{1}{\vec{r}_i + \vec{r}_j}$$

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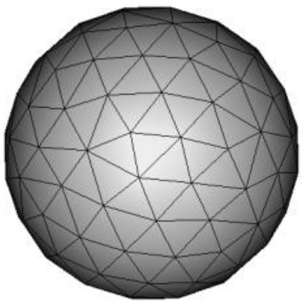

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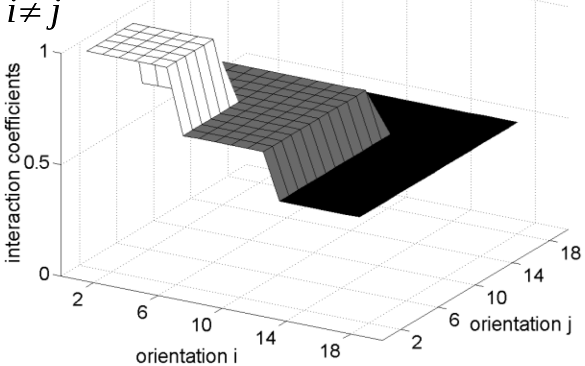
$$E = \sum_{i \neq j} \alpha_{ij} E_{ij}^0$$



(Dubois *et al*, MAGMA 2006)

Optimization of diffusion orientations sets

Methodological objective:

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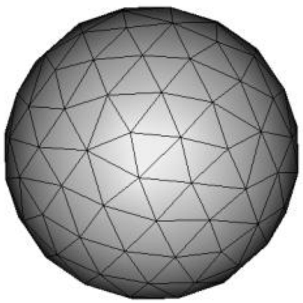

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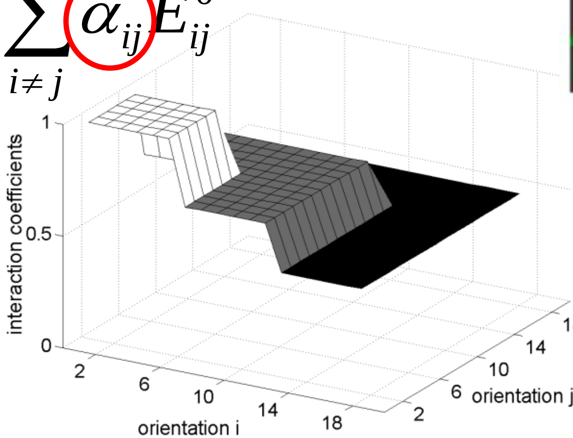
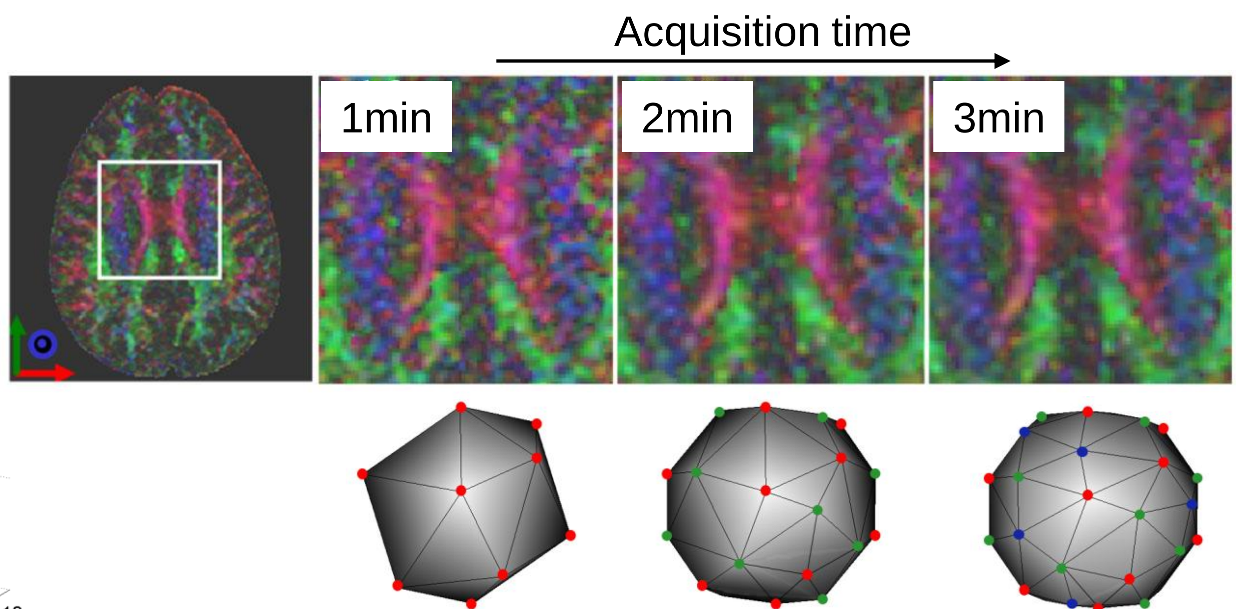




(Dubois *et al*, MAGMA 2006)

Subjects and DTI acquisition

- Subjects

  23 healhty infants (age : 10.3 ± 3.8 weeks, [3.9 - 18.4] w)
  6 healhty adults (age : 25.7 ± 1.4 years)

- Acquisition

  1.5T Signa LX GEMS
  Birdcage head coil
  Protection against noise, no sedation

- DTI imaging

  b = 700s.mm^{-2}
  15 orientations of diffusion gradients
  Spatial resolution 1.9 x 1.9 x 2.5mm^3
  30 axial slices covering the whole brain
  Acquisition time 3min40s

Data post-processing

- Softwares: Anatomist (Rivière *et al*, 2000)
  BrainVISA (Cointepas *et al*, 2003)
  SPM2 (*Functional Imaging Laboratory*, Londres)

- Estimation of diffusion tensor parameters

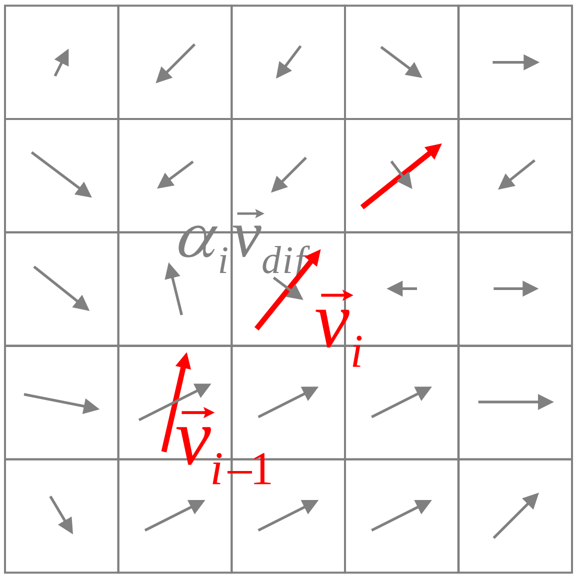
- Reconstruction of fiber fascicles by tractography

Reconstruction of fiber fascicles

Non linear tractography

Regularization of the *particles' trajectory* (Perrin, Mangin *et al*, 2005)

Local diffusion field



Particles' speed

$$\vec{v}_i = (1-\alpha_i)\vec{v}_{i-1} + \alpha_i \vec{v}_{dif}$$

α_i index of anisotropy

Reconstruction of fiber fascicles

Non linear tractography

Regularization of the *particles' trajectory* (Perrin, Mangin *et al*, 2005)

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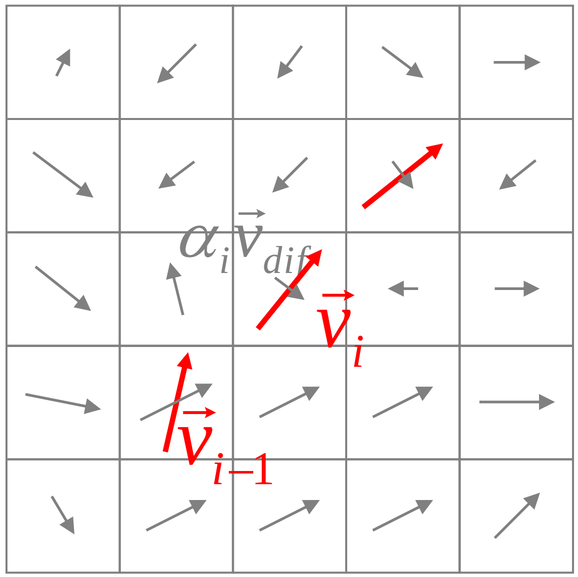

Particles' speed

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α_i index of anisotropy

Infants' white matter

$\langle D \rangle < 2.10^{-3} mm^2.s^{-1}$; $FA > 0.15$

15° < maximal curvature angle < 45°

a priori hypothesis on the fasciculus trajectory (Catani *et al*, 2002)

Data post-processing

- Softwares: Anatomist (Rivière *et al*, 2000)
  BrainVISA (Cointepas *et al*, 2003)
  SPM2 (*Functional Imaging Laboratory*, Londres)

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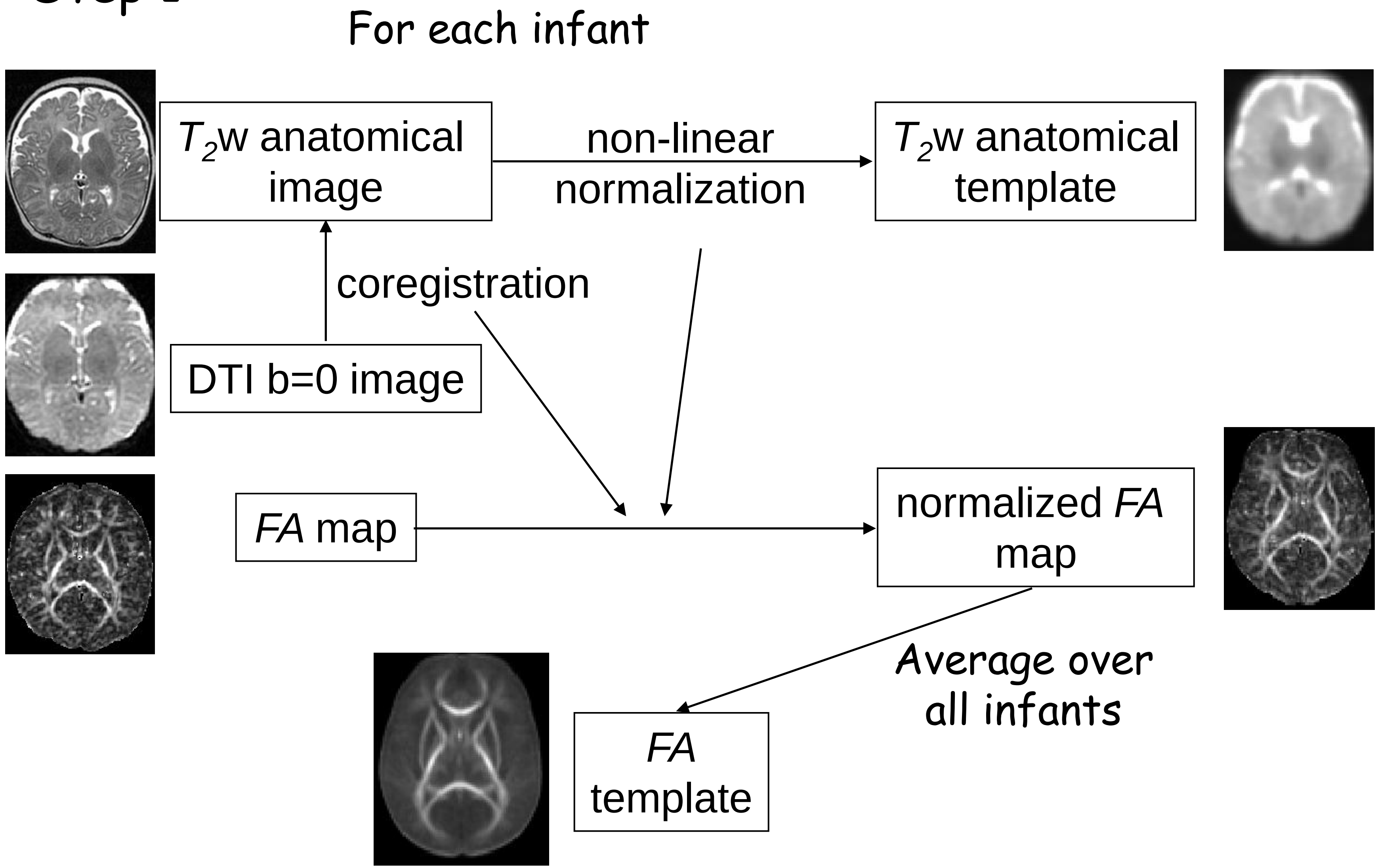
- Normalization of DTI maps through a FA template

Normalization of DTI maps

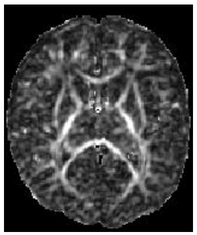
- Step 1



Normalization of DTI maps

- Step 2

For each infant

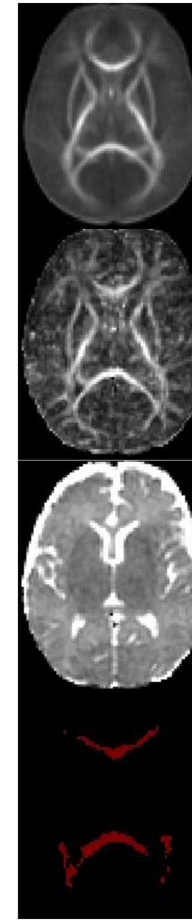


FA map → non-linear normalization → *FA* template

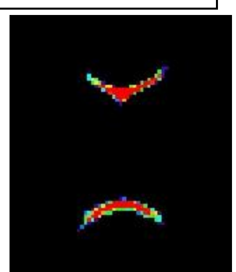
→ Normalized *FA* map

<*D*> map → Normalized <*D*> map

Fasciculus mask → Normalized fasciculus mask



Average over all infants → Fasciculus probability map



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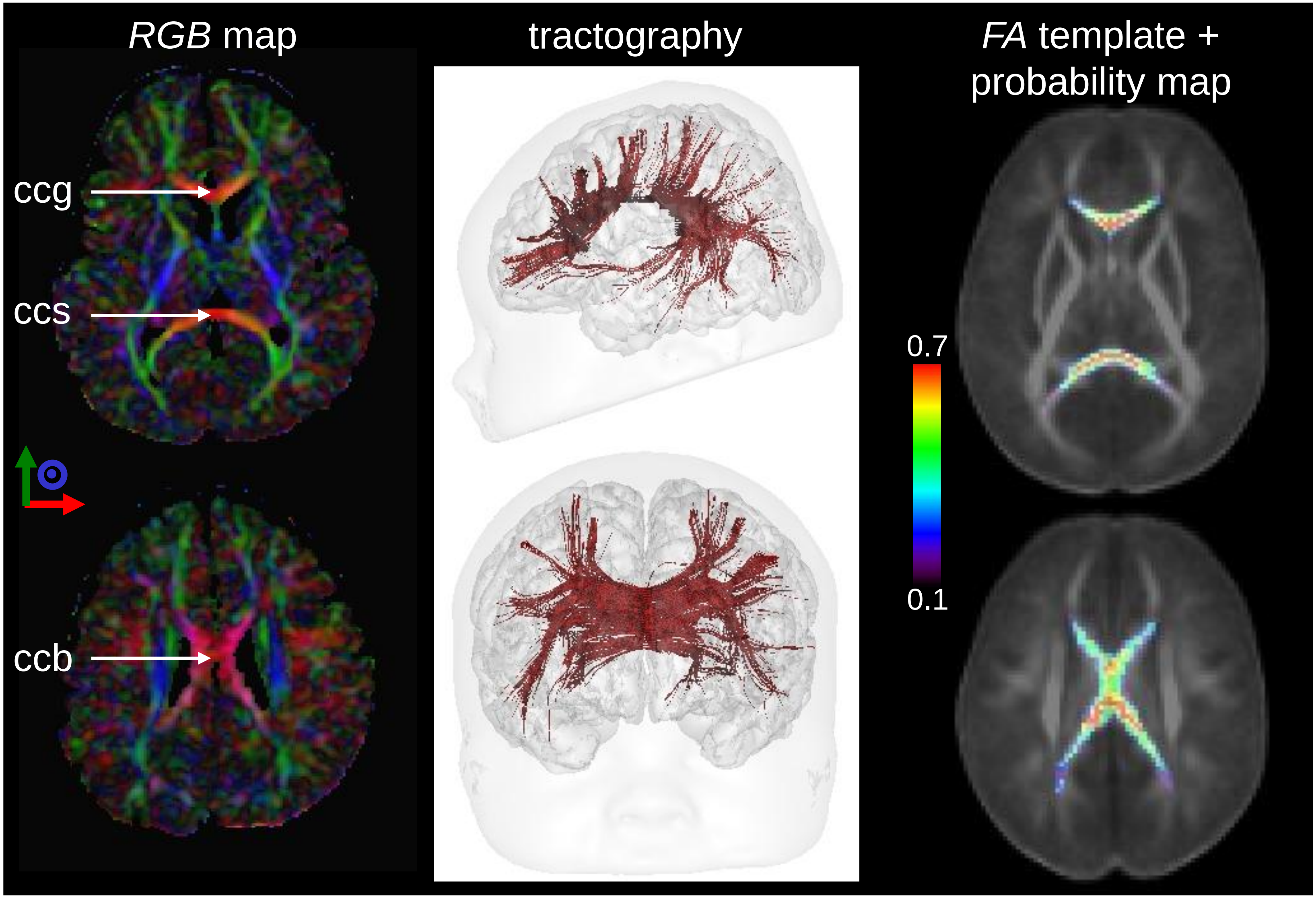
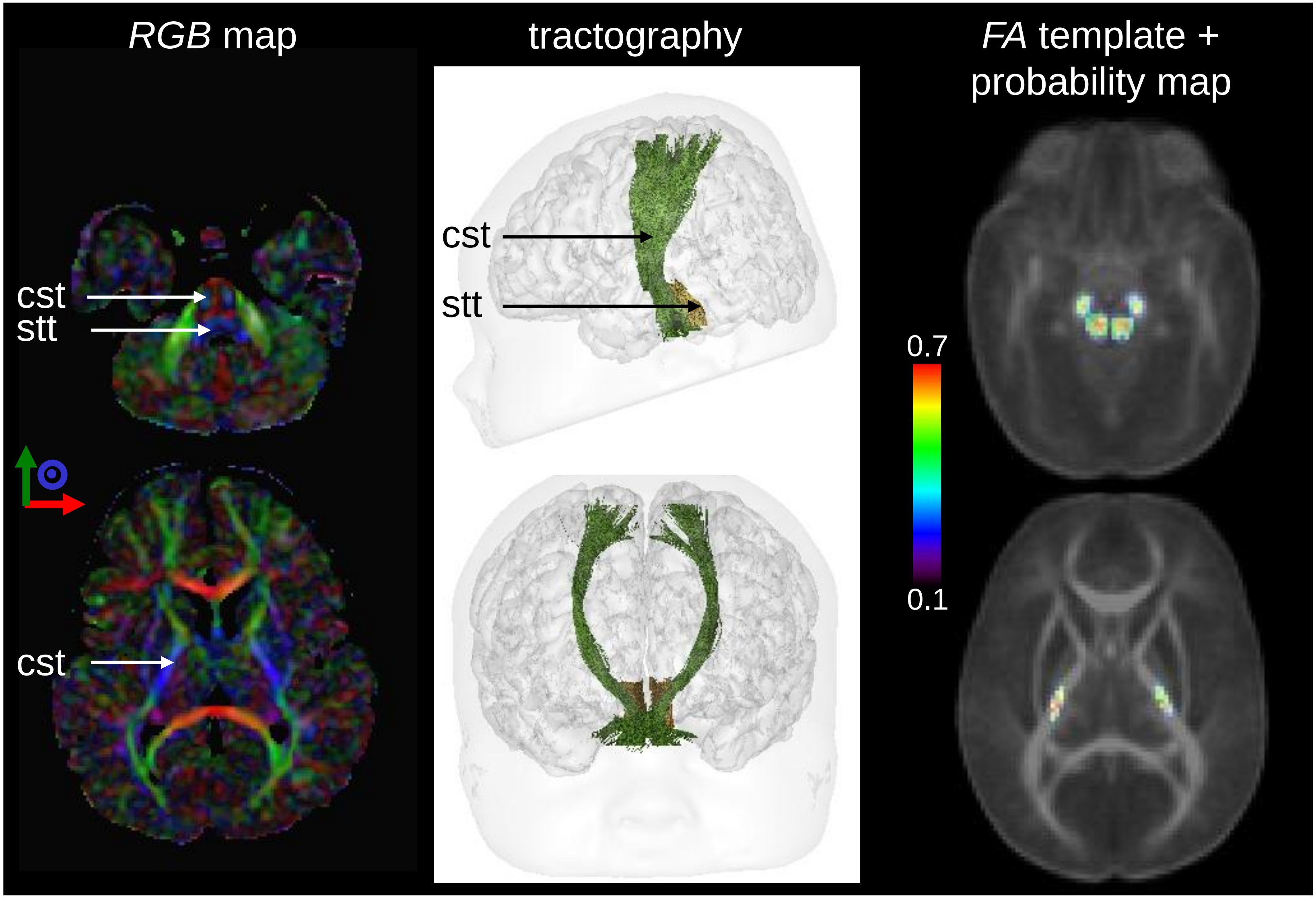
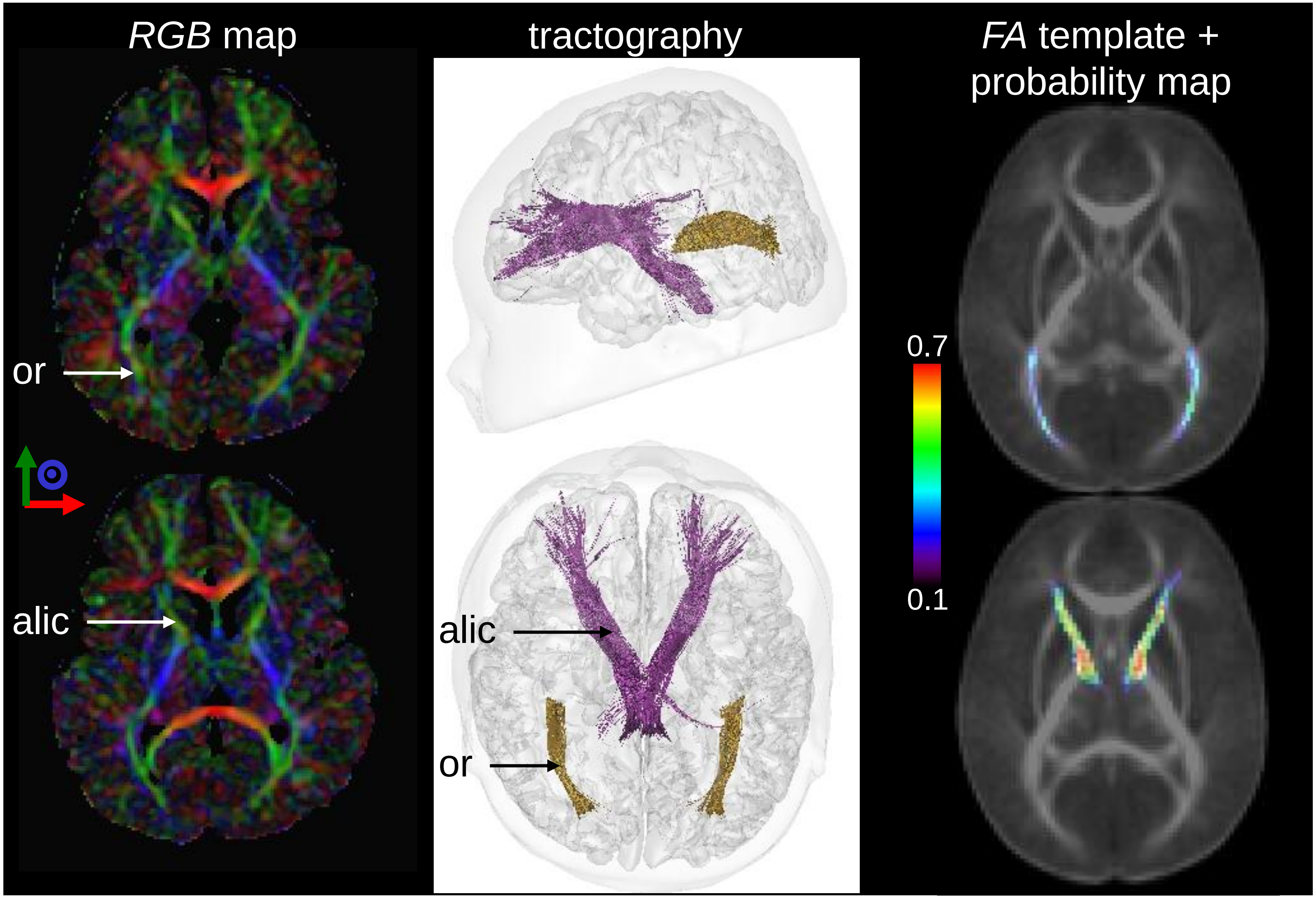
Corpus callosum



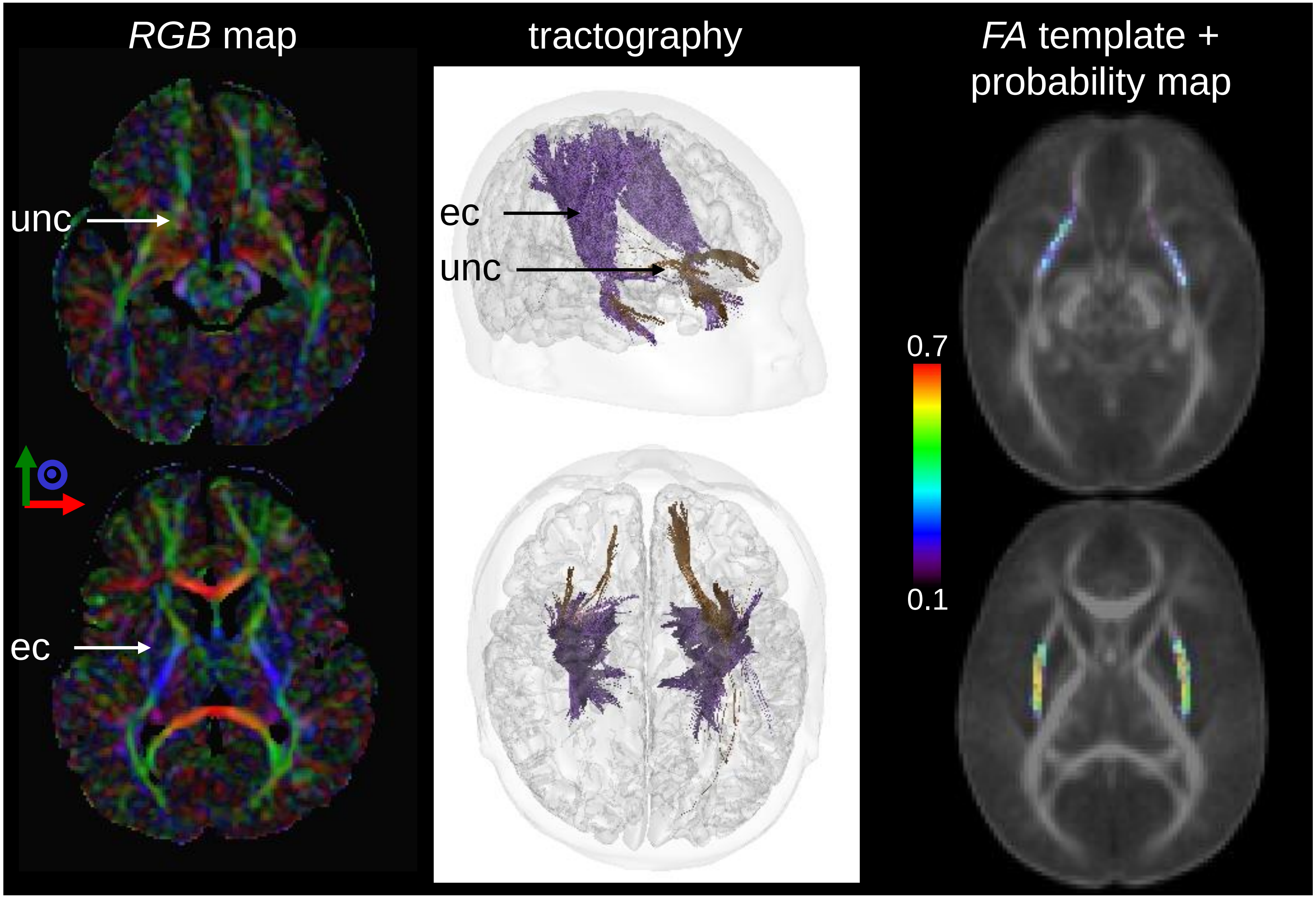
Cortico-spinal and spino-thalamic tracts



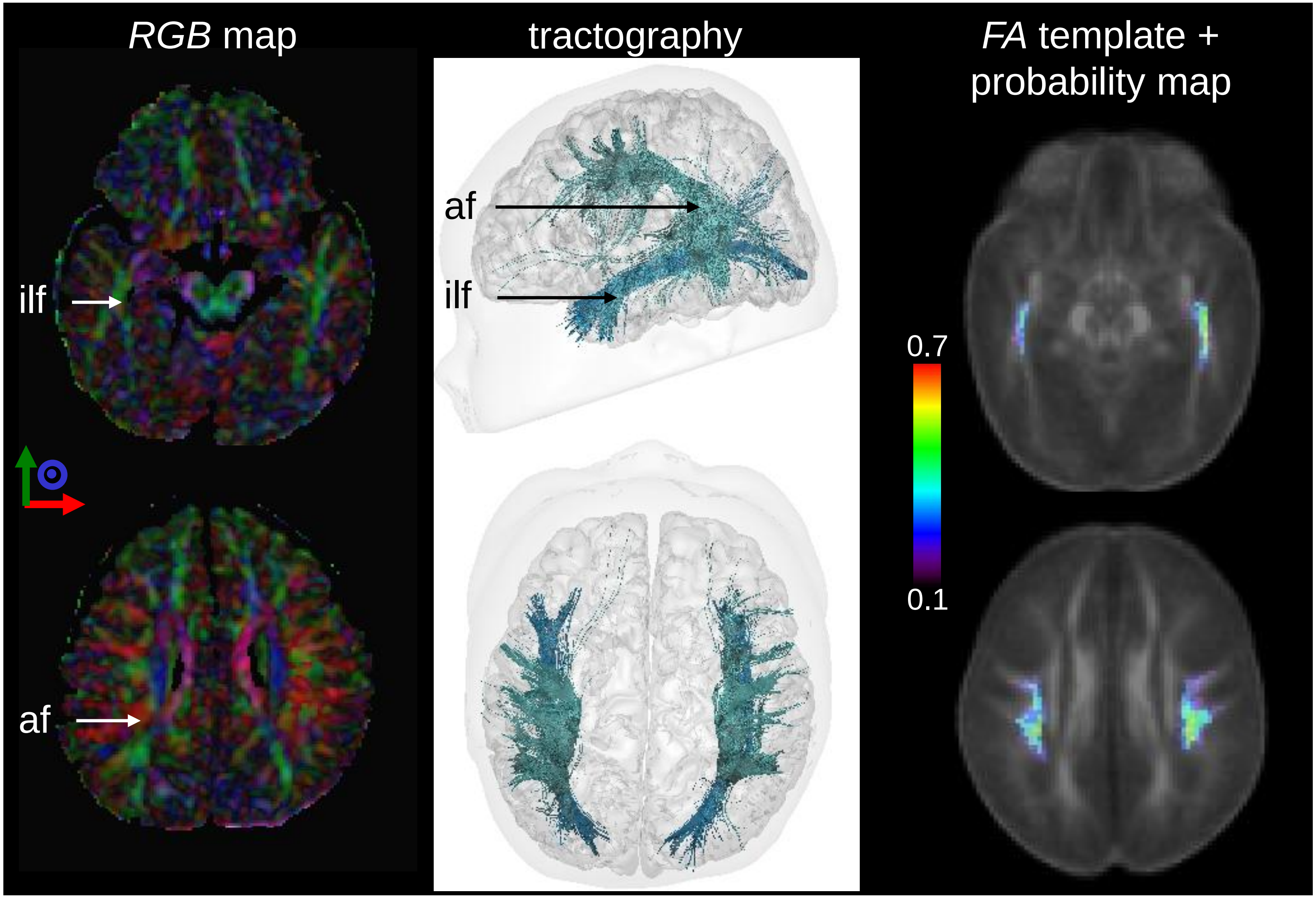
Optic radiations and internal capsule (anterior limb)



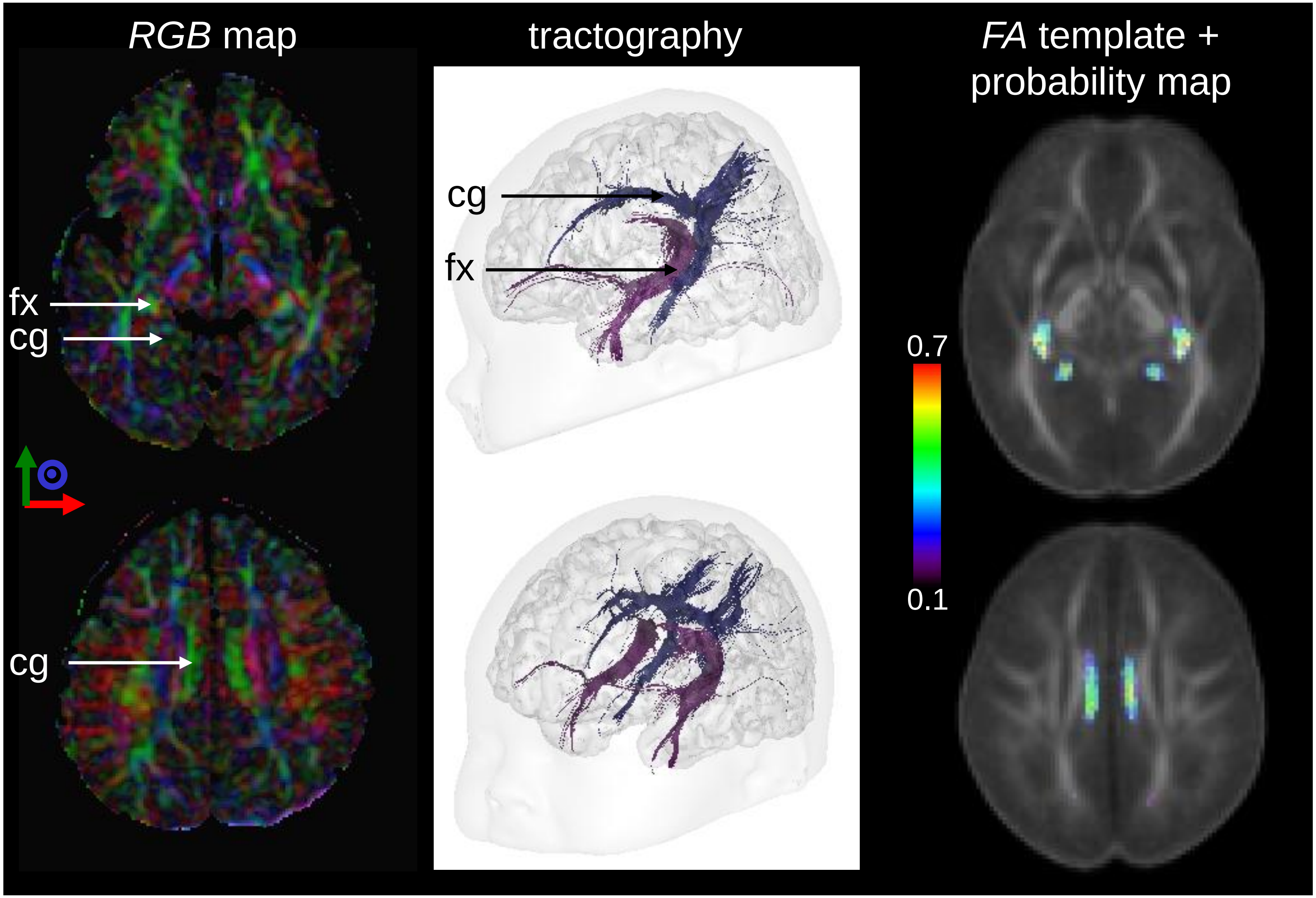
Uncinate fasciculus and external capsule



Inferior longitudinal and arcuate fascicles



Fornix and cingulum



Organization of infants' fascicles

- Early identification of white matter fascicles despite immaturity

- All kinds of fascicles: commissures, projection, association and limbic fascicles

- Methodological limitations:
  - spatial resolution / partial volume
  - tensor model / fiber crossings
  - tractography / anatomical hypotheses

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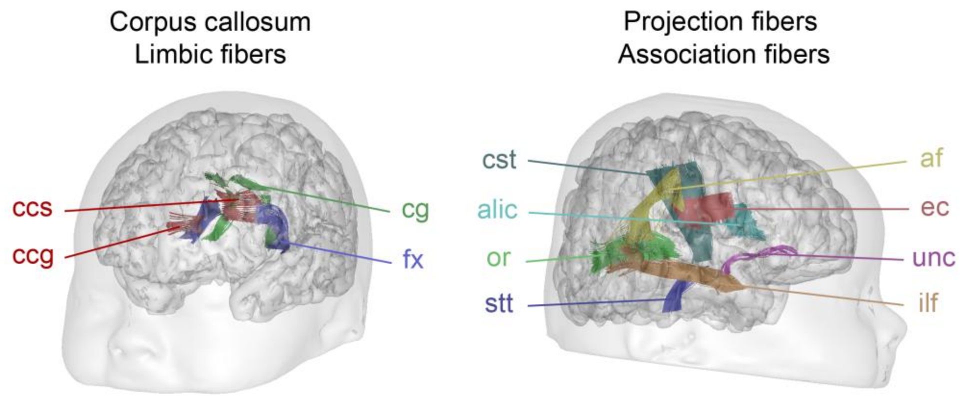
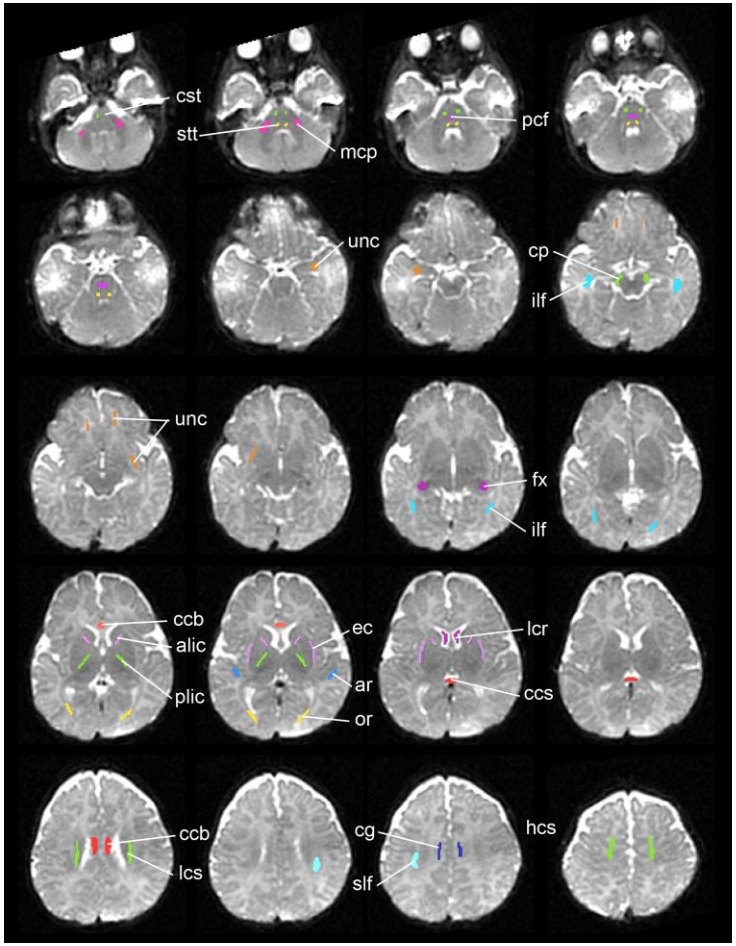
Quantification of DTI indices

- Averaging approach over *volumes of interest*
  - sections of tracts >> regions of interest



(Dubois *et al*, NeuroImage 2006)

- individual volumes >> group volumes



- *Voxel-by-voxel* approch

- Approach *along the tract*

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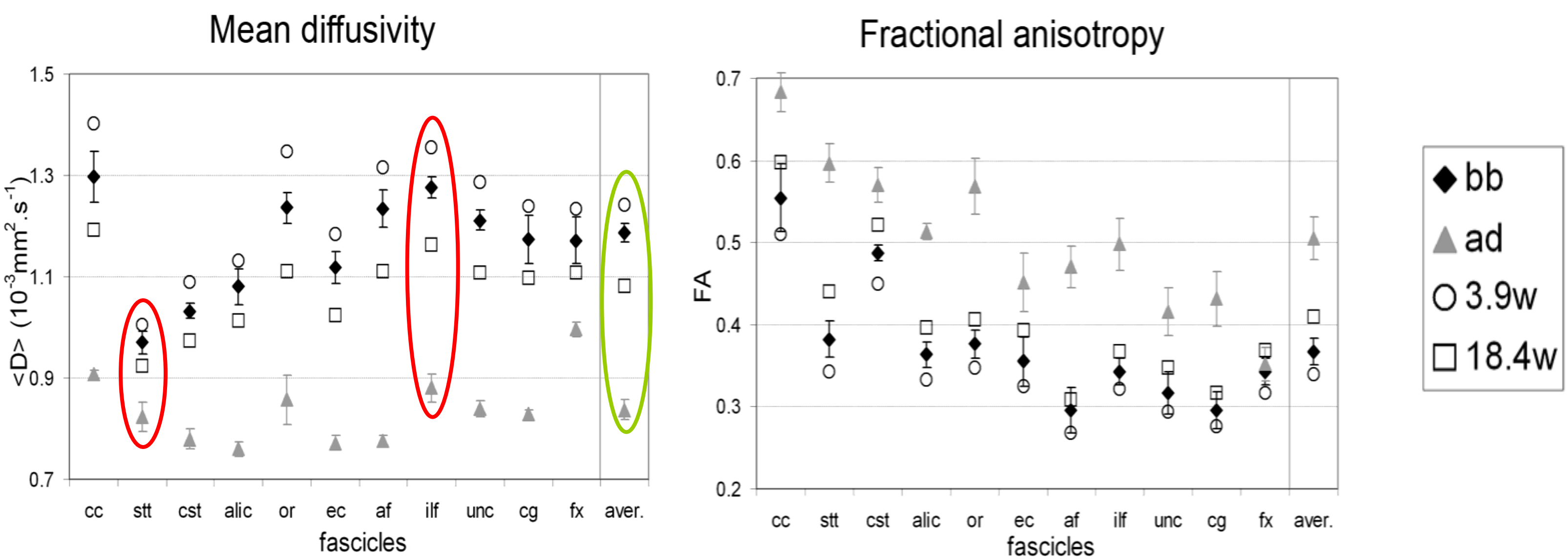
Differential maturation of fascicles

- Spatio-temporal pattern of maturation across the brain, according to the development of functional systems

- Focus on eleven fascicles of interest

- Relevance of DTI indices



(Dubois *et al*, Hum Brain Map 2008)

Classification model of fascicles' maturation

For each fasciculus (*f*) and each DTI index (*I*)

- Maturation *state* and *speed*

- State: median over babies % median over adults + fasciculus % "average"

$$state(f,I)=\left|\frac{M_I^{bb}(f)/M_I^{ad}(f)}{M_I^{bb}(aver)/M_I^{ad}(aver)}-1\right|$$

- Speed: age-related change over babies % adults and "average"

$$speed(f,I)=\frac{\Delta I^{bb}(f)/M_I^{ad}(f)}{\Delta I^{bb}(aver)/M_I^{ad}(aver)}-1$$

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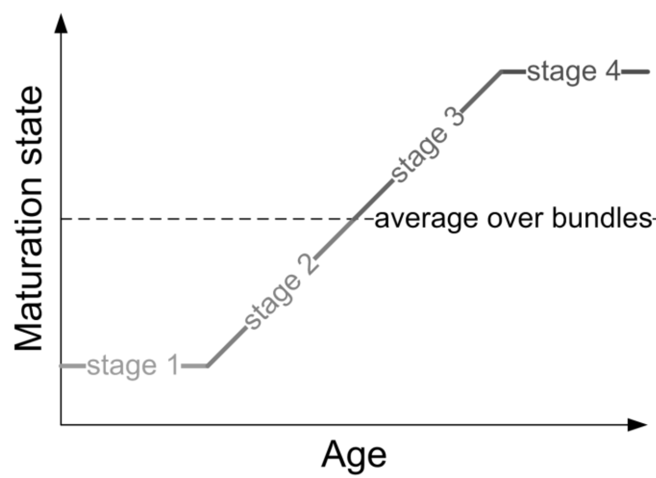
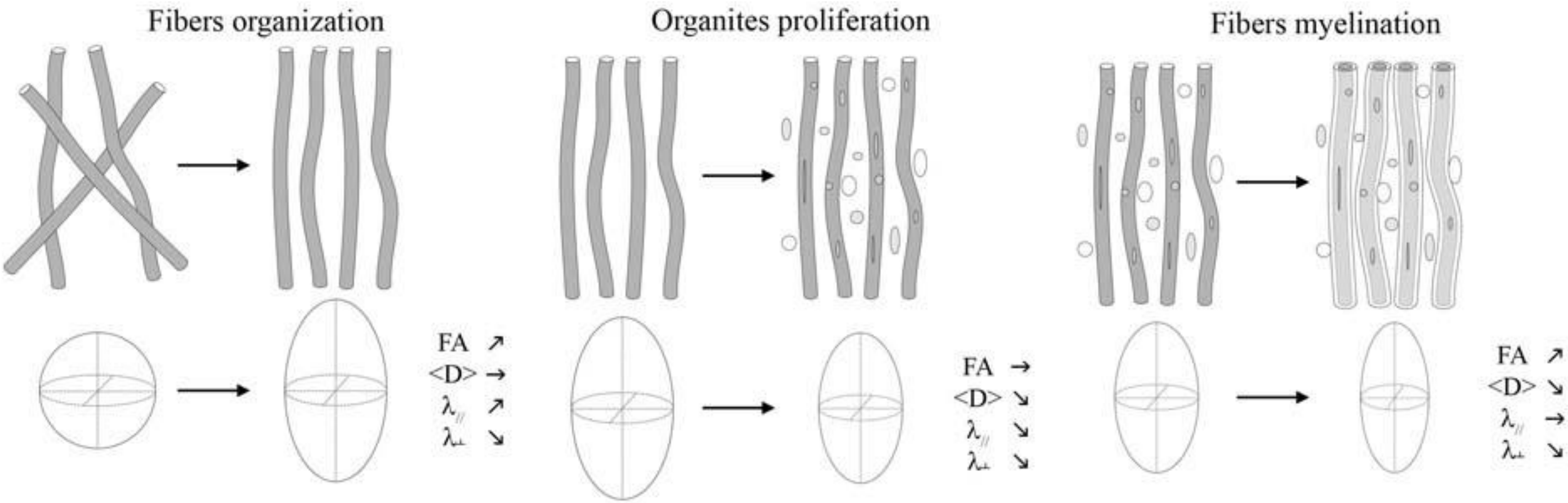
- Maturation *stage*

		Maturation speed	
		<0	>0
Maturation state	<0	Stage 1: delay in maturation low speed	Stage 2: delay in maturation high speed
	>0	Stage 4: advance in maturation low speed	Stage 3: advance in maturation high speed



Maturation processes and DTI indices

- Complementarity of DTI indices in white matter



1- to 4-months old infants

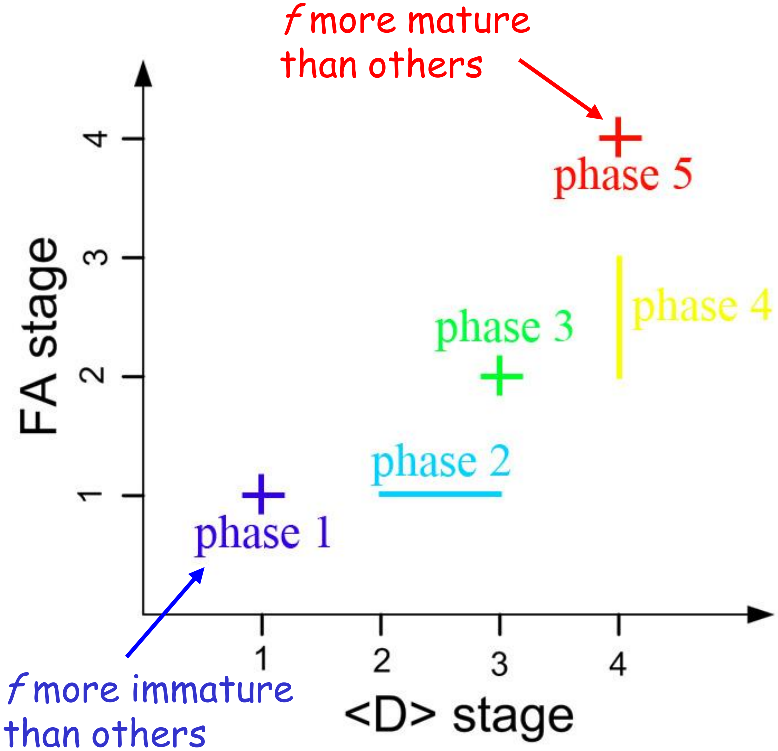
- Possibility to detect maturation earlier with <D> than with FA?

Classification model of fascicles' maturation

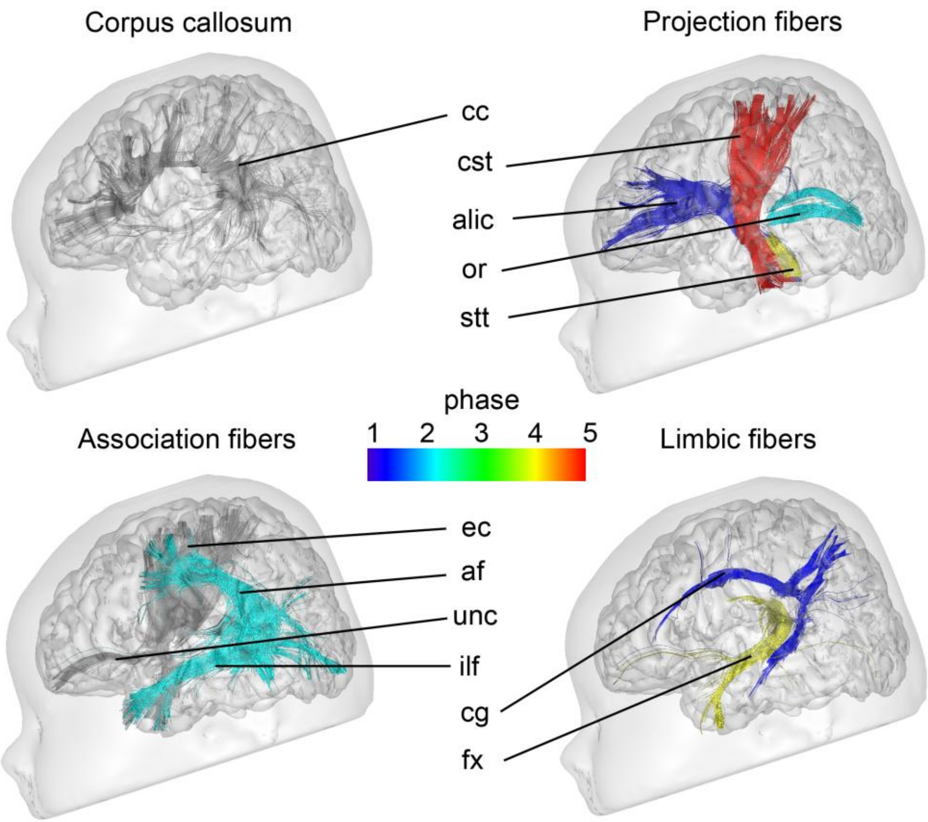
For each fasciculus (*f*)

- Maturation *phase*

<D> stage % FA stage



In vivo validation: infants' DTI data



(Dubois *et al*, Hum Brain Map 2008)

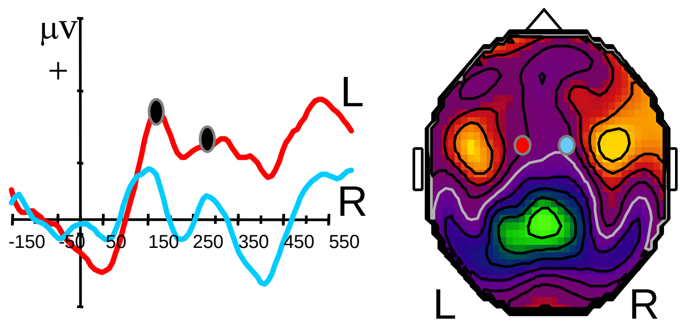
Objectives

- Methodological objectives:
  - Develop a *DTI methodology* dedicated to the infant brain
  - Evaluate the *spatial organization* of immature white matter fascicles
  - *Quantify the fascicles' maturation* with DTI indices

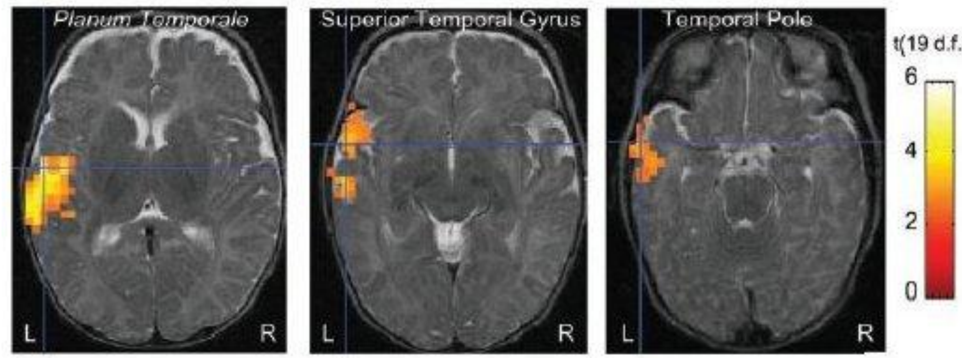
- Neuroscientific objectives:
  - *Classify* the differential maturation of fascicles
  - Evaluate inter-hemispherical *asymmetries* of the developing white matter
  - Correlate structural maturation with *functional maturation* for the developing visual system

Functional asymmetries during development

- **Language:** left hemispherical predominance in the infant brain

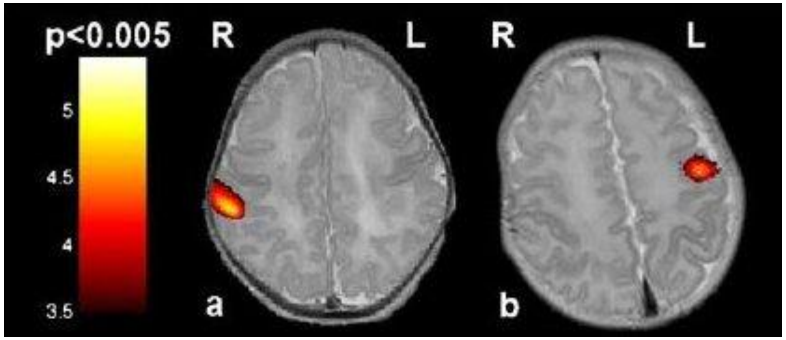


Dehaene-Lambertz, 2000



Dehaene-Lambertz *et al*, 2002

- **Somato-sensorial response:** lateralization in the newborn brain



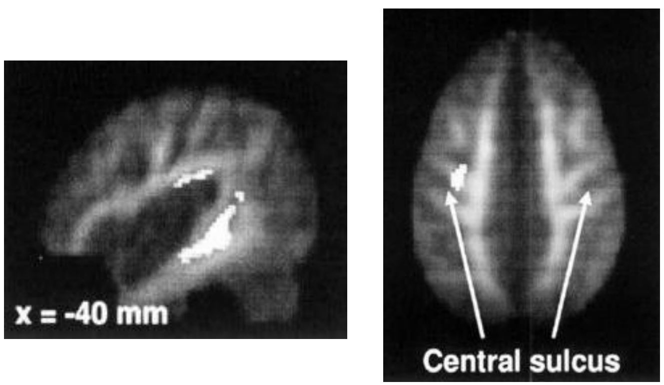
Erberich *et al*, 2005

Anatomical asymmetries during development

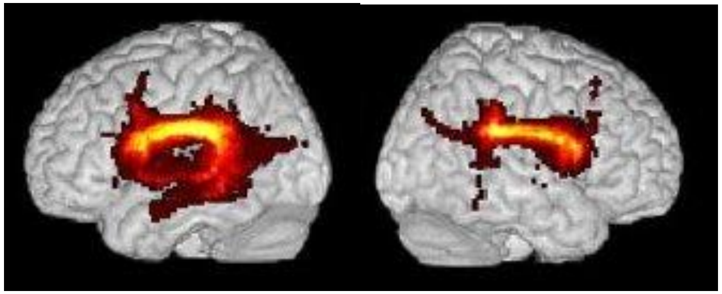
- *Planum temporale* (left), Heschl gyrus (left), superior temporal sulcus (right): asymmetries in the fœtal, newborn and child brain (Witelson *et al*, 1973; Chi *et al*, 1977)

- What about white matter?

- DTI in the adult brain



Buchel *et al*, 2004

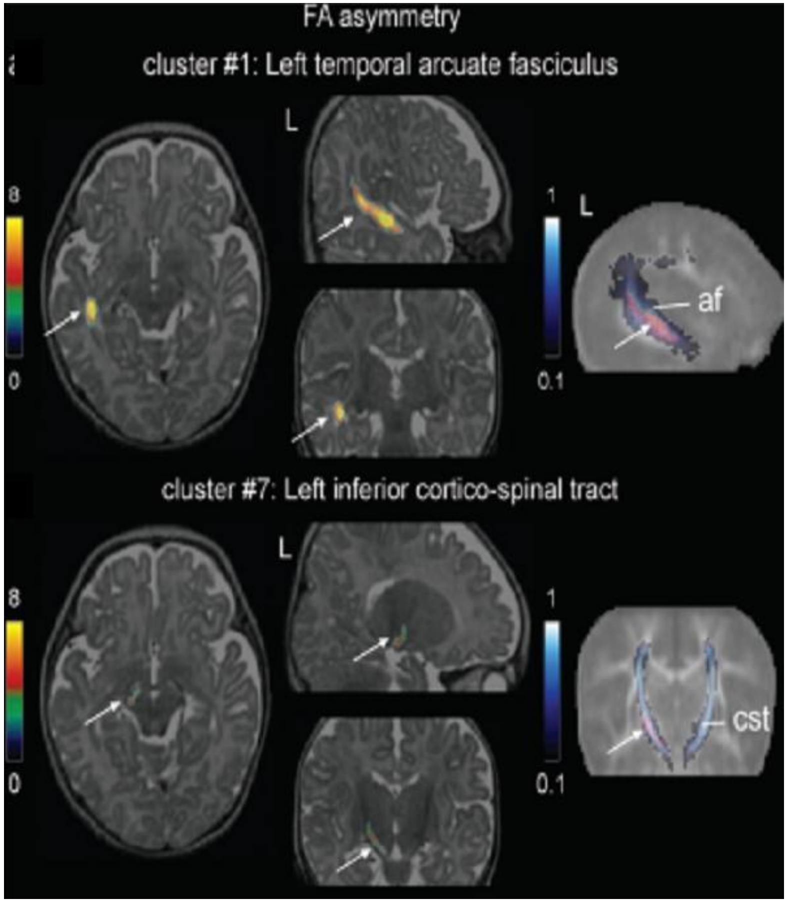


Parker *et al*, 2005

White matter asymmetries in infants

- Voxel-by-voxel analysis of FA map

Asymmetries of the temporal arcuate fasciculus and the inferior cortico-spinal tract favouring the left hemisphere

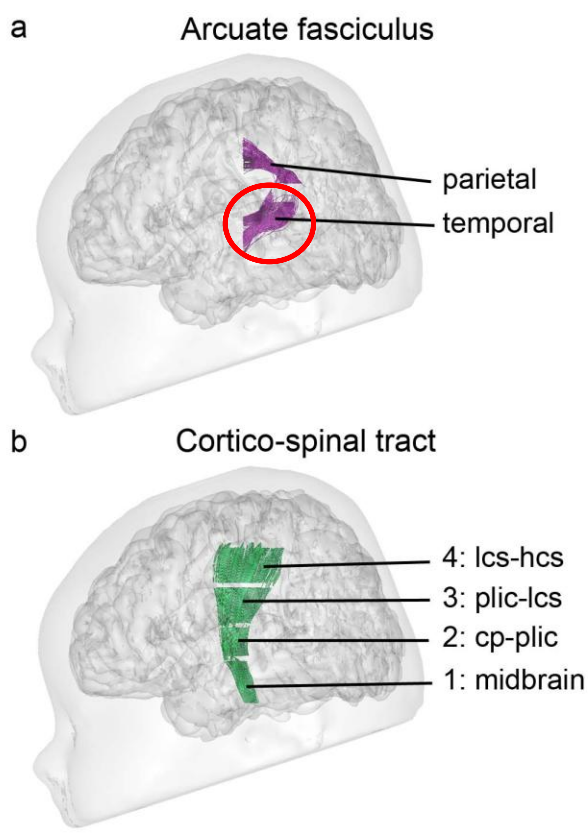


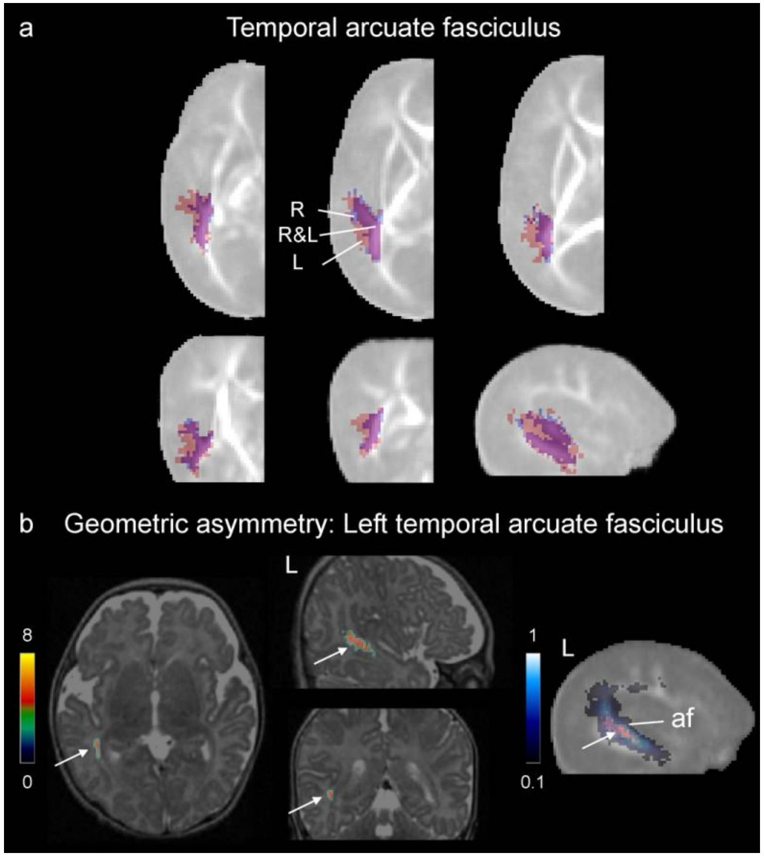
(Dubois *et al*, Cereb Cortex 2009)

White matter asymmetries in infants

- Analysis of the fascicles' macroscopic geometry

The temporal arcuate fasciculus is larger and more posterior on the left side



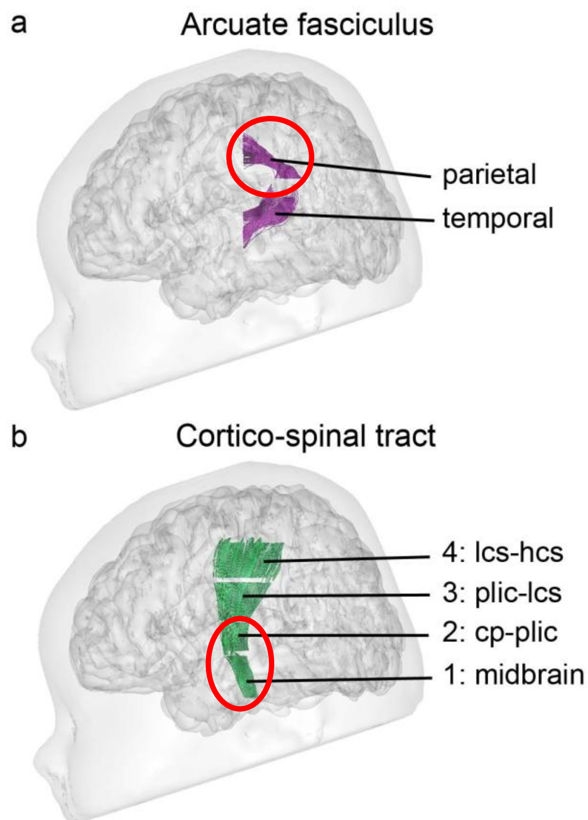


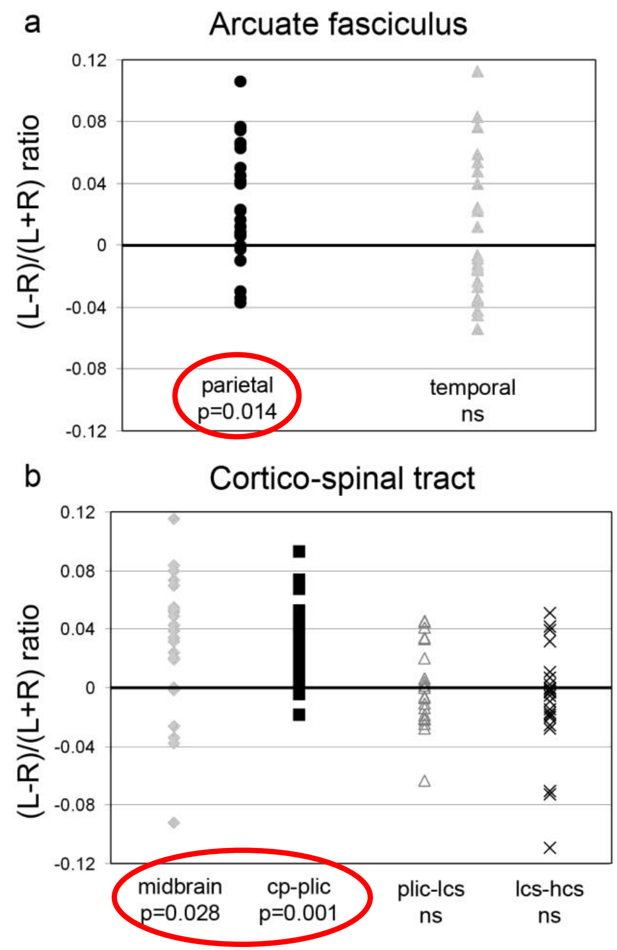
(Dubois *et al*, Cereb Cortex 2009)

White matter asymmetries in infants

- Analysis of DTI indices over the tracts' sections

FA is higher on the left side in the parietal arcuate fasciculus and the inferior cortico-spinal tract





(Dubois *et al*, Cereb Cortex 2009)

White matter asymmetries in infants

- Arcuate fasciculus

  temporal: asymmetry in macroscopic geometry (larger volume on the left side)

  parietal: asymmetry in microscopic organization (higher compacity on the left side)

- Cortico-spinal tract

  inferior: asymmetry in maturation (advance on the left side)

→ Structural asymmetries are observed early on in the infant brain, in immature white matter networks implicated in *language perception* and *manuality*.

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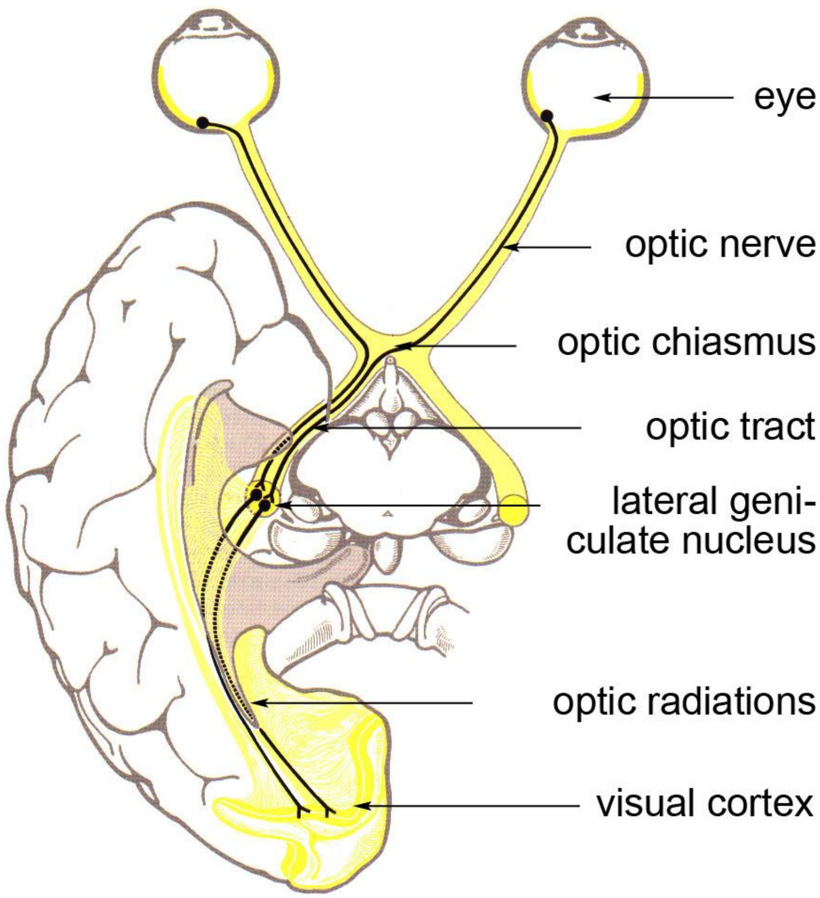
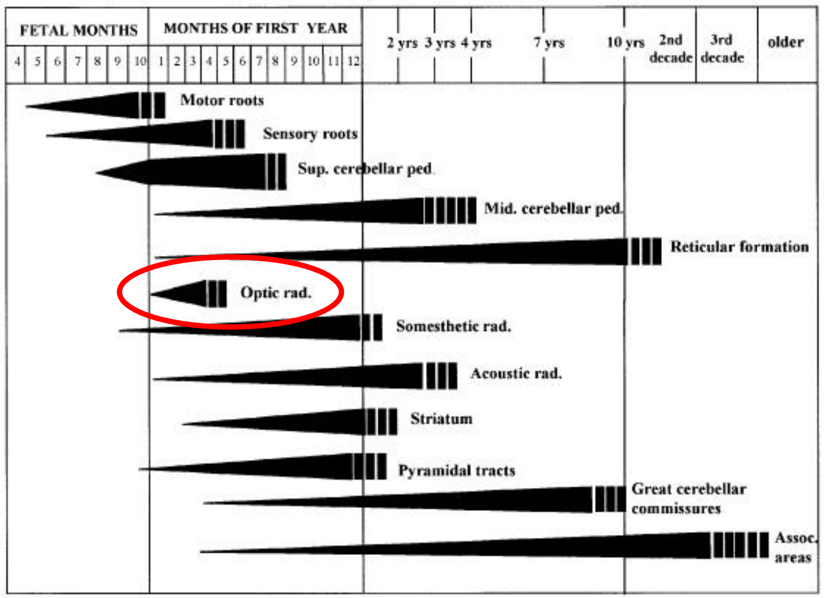
Visual system development

- Visual pathways: early anatomical maturation
- Vision: one of the first developing functions after birth



Cycles of myelination



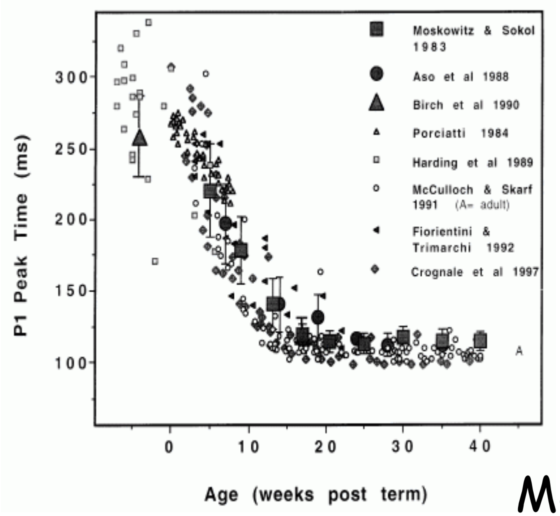
Baumann and Pham-Dinh, 2001
From Yakovlev and Lecours, 1967

Visual system development

- Visual pathways: early anatomical maturation
- Vision: one of the first developing functions after birth

- Correlations?
- *Structural* maturation of visual pathways: DTI imaging
- *Functional* development of vision: event-related potentials (ERP)

Decrease of P_1 latency with age



McCulloch *et al*, 1999

- Subjects: 16 / 23 infants (age: [3.9 – 15.7] w.)

Functional maturation of the visual system

- Visual ERP

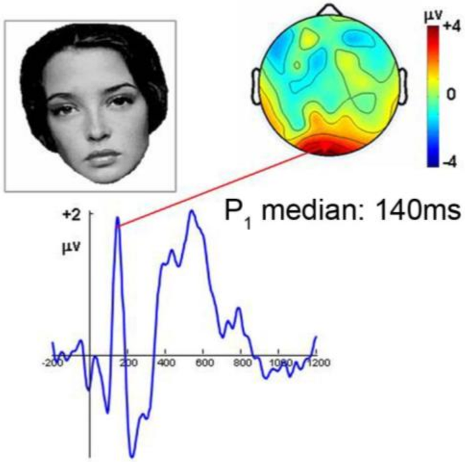
  Recording system: 64 electrodes, 4ms

  Visual stimulations (faces): 1.5s

  Averaging of events' signals

  → latency of P1

  → conduction speed of visual information



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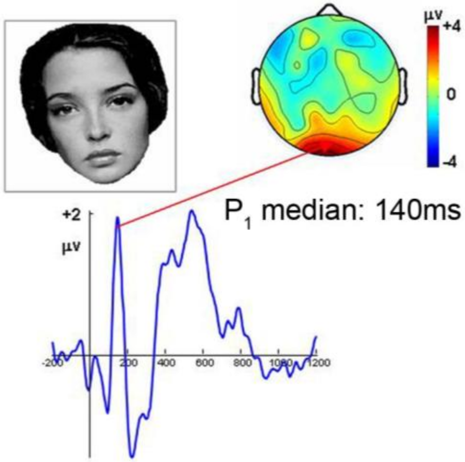


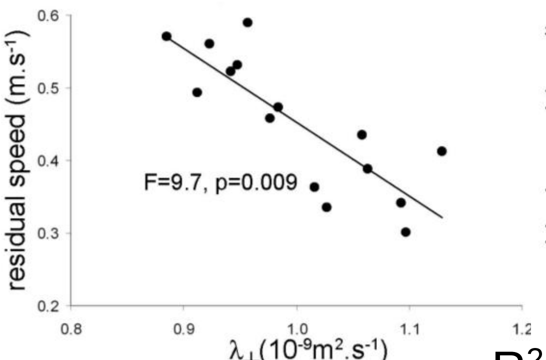
- Model ERP / DTI

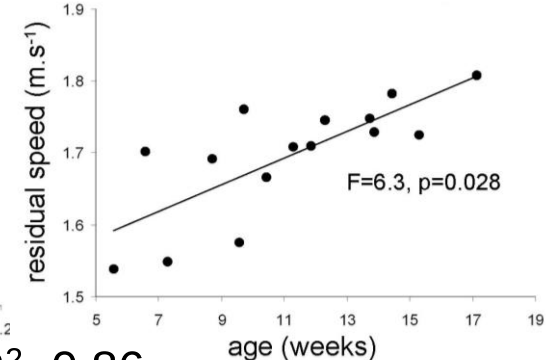
  Speed depends on DTI indices (FA, $\lambda_\perp$) and age in the optic radiations

  → Fibers myelination

  → *First correlation between structural and functional brain maturations in infants*

$$speed_{visual\,ERP} = \frac{distance}{P1} = \alpha \cdot index_{DTI} + \beta \cdot age + \gamma$$



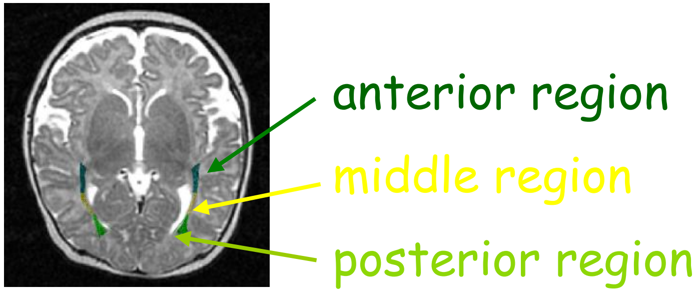


R^2=0.86

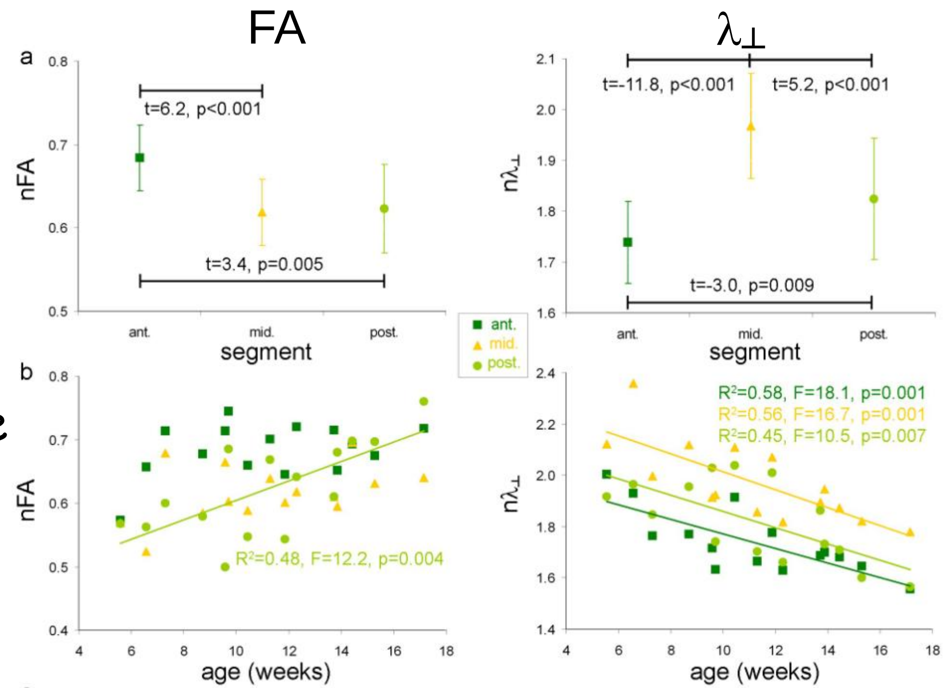
(Dubois *et al*, J Neurosci 2008)

Structural maturation of the optic radiations

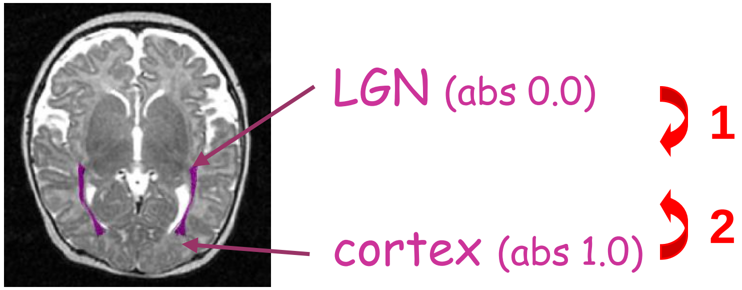
- 3 sections of the tract



Anterior region: maturation advance
Posterior region: acute changes



- Along the tract



- Myelination of geniculo-cortical (1) (Dubois *et al*, J Neurosci 2008) and cortico-geniculate (2) fibers? (McCart et al, 1994)

Conclusion

- DTI study of the organization and maturation of white matter fiber fascicles in healthy infants
  - Dedicated methodology % technical problems
  - Potential of tractography with DTI indices quantification
  - Neuroscientific breakthroughs

- Future directions
  - Subjects: developmental period (preterm newborns, infants > 4-m old), pathological development (epilepsies, etc.)
  - Acquisition: 3T + parallel imaging (spatial resolution, time), orientation number
  - Post-processing: diffusion model, tracts clustering, TBSS registration, etc.
  - Analyses: diffusion indices % relaxation times (T1, T2), white matter % cortex
  - Anatomo-functional applications: auditory / tactile stimulations

Many thanks!

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F. Lethimonnier
F. Leroy
V. Santoro
C. Chiron
F. Brunelle
C. Soarès
T. Gliga
etc.

All the babies and parents…

And thank you for your attention!