Advanced magnetic resonance imaging for monitoring brain development and injury

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Vulnerability of the developing brain: prematurity-growth restriction

- Preterms <1500g and IUGR
- 5-15% major neurological deficits
  - Cerebral palsy, hemiplegia, diplegia, quadriplegia.
- 25-50% neurodevelopmental deficits
  - Cognitives deficits, attention, learning disabilities, behavioural difficulties
  - ADHD
- Risk factor for adult psychiatric diseases

Laroque B EPIPAGE Studygroup Lancet 2008; 371: 813–20
The making of the brain

- Migration
- Proliferation
- Subplate
- Radial Glia
- Organisation: Orientation of neurons, interconnections, synapses
- Glial cell differentiation
- Cortical folding
- Myelination
- Prematurity

<table>
<thead>
<tr>
<th>Weeks gestation</th>
</tr>
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<tbody>
<tr>
<td>10</td>
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<tr>
<td>15</td>
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<tr>
<td>20</td>
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<td>25</td>
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<td>30</td>
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<td>35</td>
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<td>40</td>
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</table>
Encephalopathy of Prematurity

- Vulnerability of the SVZ vs stimulation of stem cells of the SVZ
- Focal & diffuse lesion of the white matter
- Necrosis, apoptosis of OL progenitors
- Arrest of maturation of OL lineage
- Myelination deficit
- Astrogliosis / microglia activation
- Neuro-axonal damage
- Cortical and subcortical grey matter damage
- Cortical lamination alteration
- Subplate neuronal damage
- Connectivity alteration

Volpe JJ Lancet Neurol 2009;8:110-24
Advanced MR imaging: Multimodal tool to study brain development and injury

- **T1-T2, 3D MRI**: Macrostructure
- **DWI-DTI**: Microstructure
- **1H-MRS**: Metabolism
- **f-MRI**: Function

**Human**

**Rodent**

**Sheep**
Gyrification index: internal cortical surface

Cortical maturation: effect of twinning and IUGR in preterm

Cortical grey matter development

Hüppi, PS et al Ann Neurol 1998 43(2) 224-235
Long term alteration of grey matter development at 8 years in preterms

3D-MRI at 8 years
WISC score of development

Cortical Thickness at adolescence

Cortical alteration after HI injury

To define mechanisms of impaired growth of the preterm cerebral cortex, we determined the effect of in utero global cerebral ischemia in our fetal sheep model of WMI. Ex vivo high-field diffusion MRI identifies alterations in cortical microstructure consistent with a progressive disturbance in cortical microstructure observed between 1 and 2 weeks after the insult.

Cortical neuronal density did not contribute to cortical volume loss. However, the ischemia group and their twin controls, who had been subjected to global cerebral ischemia, showed a significant decrease in cortical volume compared to age-matched controls. Further analysis according to centrifugal nomenclature suggested that this increase in dendritic complexity was a response to a progressive disturbance in cortical microstructure caused by a loss of cortical neurons.

Supplementary tables and figures are available as 

Cortical alteration after HI injury

Prematurity and basal ganglia development

27 wks at term

Basal ganglia volume and WM injury

Srinivasan L et al, 2007, Pediatrics

Hypocampus

Image analysis by Group comparison, voxel-based-morphometry: Bilateral Hippocampus

Cerbellum development and WMI

Regional volume quantification: Reduction of white matter in preterms

1 precentral Sulcus
2 central sulcus
3 postcentral sulcus
4 sylvian fissure

<table>
<thead>
<tr>
<th>Volume, ml, Mean±SD</th>
<th>Preterm</th>
<th>term</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central unmyelinated WM</strong></td>
<td>36.1±6.0</td>
<td>40.2±5.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Right inferior central UMWM</strong></td>
<td>6.8±1.1</td>
<td>8.0±1.1</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td><strong>Myelinated WM</strong></td>
<td>7.3±2.4</td>
<td>9.8±3.8</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>Central myelinated WM</strong></td>
<td>3.7±1.2</td>
<td>4.8±1.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Occipital myelinated WM</strong></td>
<td>3.1±1.4</td>
<td>4.4±1.9</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Change in cerebral growth during early adolescence in preterm

Percentage of total cerebral volume change, of grey matter and cerebellum between 8 and 12 in preterm (PT) and term (T)

*Ment L et al, Pediatrics, 2009*
Diffusion imaging of microstructure

- **Parallel diffusion**
- **Perpendicular diffusion**
- **Fibres**

Le Bihan D, Breton E. *CR Acad Sci Paris* 1985; 301: 1109-1112

Tissue characteristics during early cortical development

Neill JJ, Miller J, Hüppi PS NMR in Biomedicine 2002;15:543-552
Sizomenko et al, Cerebral Cortex, 2007; 17(11): 2609-2617
Apparent coefficient diffusion (ADC) and anisotropy (RA) in WM

ADC

RA

Maturation along WM tract and effect of prematurity

Indices quantification along the cortico-spinal tract, between the internal capsule (abscissa=0) and the high centrum semiovale (abscissa=1)

J. Dubois et al. 2007, Cerebral Cortex
J. Dubois, et al. 2014, Neuroscience
### Alteration of white matter microstructure in preterm with injury

<table>
<thead>
<tr>
<th>Diffusion MRI</th>
<th>PT with WMI mean±SD (n=10)</th>
<th>PT at T mean±SD (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FA (%)</strong></td>
<td>9.5±1.7</td>
<td>12.9±3.3</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>FA (%)</strong></td>
<td>17.2±3.9</td>
<td>22.8±4.7</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ADC (µm²/ms)</strong> Central WM</td>
<td>1.5±0.2</td>
<td>1.5±0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>ADC (µm²/ms)</strong> Int. Capsule</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Myelinated WM (cc)</strong></td>
<td>14.5±4.5</td>
<td>23.1±6.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

White matter tractography in injury

Twin 1: WM injury and severe neurodevelopmental delay
Twin 2: no damage and normal neurodevelopment

(courtesy of Simon Warfield and Terrie Inder, Boston)
Long-term alteration of white matter microstructure

Reduction of FA at 11 years in WM tracts

Inflammation: white matter alteration

IL-1β injection in newborn mice

Inflammation: white matter alteration

IL-1β injection in newborn mice

Connectivity assessment by MRI

With tractography and cortex parcellation, we can depict the fibers that link determined areas in the brain and compare them between different groups.
Connectivity matrix
Inter-hemispheric connectivity

Cingulate
Thalamocortical connectivity

G. Ball et al. Cortex 10, 2012
Connectivity at 6 years

Preterm > Controls
- Short Cortico-cortical

Preterm < Controls
- Cortico Basal ganglia Thalamo Cortical Loop
- Short Cortico-cortical Brain Stem
- Subthalamic Commisural

Gomez E.F., Vasung L., et al. 2014. Cerebral Cortex
Summary

CONSEQUENCES OF PREMATURE BIRTH ON BRAIN STRUCTURE AND FUNCTION

Altered microstructure

Smaller volumes of the cerebral cortex and white matter

Reduced sulcal complexity

Altered thickness of cerebral cortex

Altered activation of cortical areas during resting state

Thank you for your attention