Epilepsy and early brain development

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4 months before birth
- cells are generated and dying,
- neurons migrate and differentiate,
- connections are made and removed,
- networks are formed and reorganized,
- neurotransmitters change their function.

birth
1. Birth of neurons - regulated by neurotransmitter GABA (neurogenesis, stem cell therapy)
2. Neuronal migration

Wonders & Anderson (2006)

Cell migration may be disturbed not only in epilepsy, but also in other neurological and neuropsychiatric disorders (from P. Rakic, Yale University)
Cell migration is controlled by many factors
Cell migration is regulated by neurotransmitters as GABA

GABA modulation

Luhmann & coworkers (2005, 2007)

Virchow (1867)
Cell migration is regulated by neurotransmitters as GABA

GABA modulation

Luhmann & coworkers (2005, 2007)

Virchow (1867)
3. Network activity

- **Prenatal**
  - Activity-independent
    - Genetic information (e.g. transcription factors)
  - Activity-dependent
    - Experience-independent ('precritical period')
      - Electrical activity (e.g. Ca\(^{2+}\) waves, GDPs)

- **Postnatal**
  - Activity-dependent
    - Experience-dependent ('critical period')
      - Synaptic plasticity (e.g. Hebbian learning)
  - Adult learning

*TRENDS in Neurosciences*

Khazipov & Luhmann (2006)
The very immature brain is very active!

age: ca. 6 months postconceptional
Animal models are most valuable, important and necessary!

age: ca. 6 months postconceptional

Milh, ..., Ben-Ari, Khazipov (2009) *Cerebral Cortex*

3 days old rat

Luhmann and coworkers, unpublished
Current view and knowledge
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- The young brain is NOT a small adult brain!
- By studying epilepsy we get further insights into normal brain development and into other brain disorders (e.g. autism).
- We constantly develop new methods and improve existing techniques in basic and clinical research to understand developmental processes in the brain, both at the genetic / molecular level as well as at the network / whole brain level.
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Future and open questions

- Why is the immature brain more vulnerable to develop epilepsy?
- What are the causes of early and late-onset epilepsy?
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Future and open questions

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EU-wide interdisciplinary interactions and cooperations in basic and clinical research and translational approach between both fields.
"That’s our job to bridge that gap."
Nikki Saarsteiner, Dublin, 25th May 2013

Thank you for your interest, your attention and your support!
Development of cortical layers during prenatal human development

- 6th week
- 3rd mon
- 4th mon
- 5th mon
- 8th mon
- Birth

MZ  IZ  SVZ  VZ  

CP  SP  IZ  SVZ  VZ

IV  V  VI  SP  VZ

III  IV  V  VI  SVZ  VZ

WS

WS

Images of human brain at different stages of development.
Development of rat cerebral cortex
(modified from Kageyama & Robertson, 1993)
neurogenesis, axonal "path finding", neuronal migration, apoptosis, cell differentiation, synaptogenesis

Luhmann et al. (2003)
Developmental disorders of the cerebral cortex

- MZ
- CP
- SP
- IZ
- VZ
- RG
- WM
- THALAMUS

Exogenous, endogenous & genetic factors
Cell migration is also regulated by neurotransmitters
Change in GABA function during early development!

**A**

- Extracellular
- Membrane
- Intracellular

**B**

- Depolarization & Excitation of immature neurons: $[Cl^-]_i = 25mM$
- Hyperpolarization & inhibition of adult neurons: $[Cl^-]_i = 7mM$

Ben-Ari et al. (2007)
Spontaneous Epileptic Manifestations in a DCX Knockdown Model of Human Double Cortex

Damien Lapray\textsuperscript{1}, Irina Y. Popova\textsuperscript{2}, Jennifer Kindler\textsuperscript{1}, Isabel Jorquera\textsuperscript{2}, Hélène Becq\textsuperscript{2}, Jean-Bernard Manent\textsuperscript{2}, Heiko J. Luhmann\textsuperscript{1} and Alfonso Represa\textsuperscript{2}