Translational Medicine: Bench Research & Baby Brain Development to Clinical Care

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AAAS Vancouver
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To promote human health by providing a forum for communication and cross-fertilization among basic, translational, and clinical research.
Full-term 37-41 weeks gestation

Neonatal Intensive Care Unit (NICU)
Neonatal Intensive Care

- Mechanical ventilation
- Infections
- Illness
- Medications
- Surgery
- 10 invasive procedures per day
NEURODEVELOPMENT in Children Born Very Preterm

- Poorer attention, cognition, memory, executive functions, motor, academics, behavior
- Little knowledge of *mechanisms*
Fetal Brain Development

(Cunningham FG, Leveno KL, Bloom SL, et al Williams Obstetrics, 22nd Ed)
Brain Development Differs in Infants/Children Born Preterm


- **Smaller brain volumes in multiple regions** (e.g. Nosarti et al 1999, Peterson et al 2003)

- **Thinner cortex** (e.g. Ranger et al 2013)

- **Altered connectivity & networks** (e.g. Kostovic & Jovanov-Milosevic 2006, Uhlhaas et al 2009, Doesburg et al 2011)
Slower Postnatal Growth Is Associated with Delayed Cerebral Cortical Maturation in Preterm Newborns

Jillian Vinall, Ruth E. Grunau, Rollin Brant, Vann Chau, Kenneth J. Poskitt, Anne R. Synnes, Steven P. Miller
Preterm Neonatal MRI Brain Imaging

- Diffusion tensor imaging (DTI)
- Fractional Anisotropy (FA)
- MR spectroscopy imaging
- N-acetylaspartate (NAA)/choline

Scan 1: Shortly after birth

Birth – Scan 1

Scan 1 – Scan 2

Number of invasive procedures & multiple clinical confounders

Scan 2: Term-equivalent age

Number of invasive procedures & multiple clinical confounders
Growth (weight) change from early MRI to term equivalent is associated with maturation of cortical gray matter

<table>
<thead>
<tr>
<th>Effect size</th>
<th>SE</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Gestational age</td>
<td>-0.038</td>
<td>0.011</td>
</tr>
<tr>
<td>Birth weight</td>
<td>&lt;-0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.031</td>
<td>0.023</td>
</tr>
<tr>
<td>Weight change</td>
<td>-0.410</td>
<td>0.089</td>
</tr>
<tr>
<td>White matter injury</td>
<td>-0.009</td>
<td>0.012</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>-0.004</td>
<td>0.010</td>
</tr>
<tr>
<td>Cerebellar hemorrhage</td>
<td>0.004</td>
<td>0.034</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>-0.036</td>
<td>0.030</td>
</tr>
<tr>
<td>Days intubated</td>
<td>-0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>-0.047</td>
<td>0.029</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>0.040</td>
<td>0.046</td>
</tr>
</tbody>
</table>

(Vinall et al *Sci Transl Med* 2013)
Prenatal Cerebral Ischemia Disrupts MRI-Defined Cortical Microstructure Through Disturbances in Neuronal Arborization

Justin M. Dean,† Evelyn McClendon,† Kelly Hansen, Aryan Azimi-Zonooz, Kevin Chen, Art Riddle, Xi Gong, Elica Sharifnia, Matthew Hagen, Tahir Ahmad, Lindsey A. Leigland, A. Roger Hohimer, Christopher D. Kroenke, Stephen A. Back
The normal maturational decrease in cortical FA that occurs in several species is anisotropic because of the predominant alignment of cellular processes perpendicular to the pial surface. With neuronal enucleation in neonatal ferrets (18–21), we recently quantified the orientation distributions of phospholipid bilayer structures that restrict water diffusion in a direction parallel to the pial surface. With neuronal enucleation, water diffusion is highly restricted in the immature cortex, water diffusion is highly restricted. The normal maturational decrease in cortical FA that occurs in several species is anisotropic because of the predominant alignment of cellular processes perpendicular to the pial surface. 

It has been proposed that in the supragranular or infragranular location, the structural explanation for the decrease in FA appears to relate to morphological differentiation and elaboration of the dendritic arbor. Similarly, neurons in the prefrontal cortex of preterm infants can exhibit dysmorphic dendrites that are similar in magnitude in the cortex and white matter (16, 17). Thus, an ischemia-reperfusion insult that we have shown to be effective in human cerebral white matter (16, 17) is also effective in the ovine cerebral cortex, with the restriction of water diffusion being highly anisotropic because of the predominant alignment of cellular processes perpendicular to the pial surface.

Abnormal development of basal dendritic arborization and retraction of dendrites in the neonatal ferret following ischemic injury (22) and in the human (23) have been described. In vivo, we examined the distribution of orientational anisotropy (21), thus demonstrating a progressive developmental decrease in FA, which was preserved in the cortex of ferrets that had undergone enucleation (18–21). Interestingly, the observed decrease in FA was not uniform throughout the cortex, but rather was present in the supragranular or infragranular location, where the structural changes were most pronounced.

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Sheep brain development

- Reduced
  - total dendritic length
  - number of branches
  - branch endings
- Notably, the dendritic arbor was most simplified closer to the cell body, where synaptic integration occurs
NEUROLOGY

Brain Maturation After Preterm Birth

Zoltán Molnár¹* and Mary Rutherford²,³
The editors suggest the following Related Resources
Science Translational Medicine

- INTRACRANIAL HEMORRHAGE Overexpression of Vascular Endothelial Growth Factor in the Germinal Matrix Induces Neurovascular Proteases and Intraventricular Hemorrhage

- BRAIN DEVELOPMENT Cross-Hemispheric Functional Connectivity in the Human Fetal Brain

- PRETERM BIRTH A Small-Molecule Smoothened Agonist Prevents Glucocorticoid-Induced Neonatal Cerebellar Injury

- PRETERM BIRTH Preterm Cerebellar Growth Impairment After Postnatal Exposure to Glucocorticoids

- PREMATURE INFANTS Integration of Early Physiological Responses Predicts Later Illness Severity in Preterm Infants
  Suchi Saria, Anand K. Rajani, Jeffrey Gould, Daphne Koller, and Anna A. Penn Sci Transl Med 8 September 2010 2:48ra65
ALTered BrAIN dEVELOPMENT IN PReterm NeONates

• Human preterm neonates (Vinall et al)
• Newborn lambs (Dean et al)
• Editor’s Summary (Hammond)
• Perspective Commentary (Molnar & Rutherford)
Animal Studies of Fetal Stress

(Figures and text adapted from Matthews 2002, Trends in Endocrinology & Metabolism)
Neonatal pain in relation to postnatal growth in infants born very preterm

Jillian Vinall a,b, Steven P. Miller b,c, Vann Chau b,c, Susanne Brummelte b,c, Anne R. Synnes b,c, Ruth E. Grunau a,b,*

a Department of Neuroscience, University of British Columbia, Vancouver, BC, Canada
b Developmental Neurosciences & Child Health, Child & Family Research Institute, Vancouver, BC, Canada
c Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
Pain/stress is associated with early growth (weight) in the neonatal intensive care unit

<table>
<thead>
<tr>
<th>Early neonatal variables</th>
<th>Weight percentile at 32 weeks PCA&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Wald $\chi^2$</td>
</tr>
<tr>
<td>Birth weight percentile</td>
<td>124.45</td>
</tr>
<tr>
<td>Birth HC percentile</td>
<td>-</td>
</tr>
<tr>
<td>Neonatal pain (number of skin-breaking procedures)</td>
<td>7.36</td>
</tr>
<tr>
<td>Days of mechanical ventilation</td>
<td>0.38</td>
</tr>
<tr>
<td>Morphine exposure</td>
<td>0.39</td>
</tr>
<tr>
<td>Hydrocortisone exposure</td>
<td>0.01</td>
</tr>
<tr>
<td>Dexamethasone exposure</td>
<td>4.83</td>
</tr>
<tr>
<td>Postnatal infection</td>
<td>0.43</td>
</tr>
<tr>
<td>Illness severity SNAP-II day 1</td>
<td>2.06</td>
</tr>
<tr>
<td>PCA at 32-week weigh-in</td>
<td>0.38</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values (not shown).

(Vinall et al Pain 2013)
Original Article

Score for Neonatal Acute Physiology–II and Neonatal Pain Predict Corticospinal Tract Development in Premature Newborns

Jill G. Zwicker PhD, OT(C)\textsuperscript{a,b}, Ruth E. Grunau PhD\textsuperscript{a,b,c}, Elysia Adams MSc\textsuperscript{a}, Vann Chau MD\textsuperscript{a,b,c}, Rollin Brant PhD\textsuperscript{b,d}, Kenneth J. Poskitt MDCM\textsuperscript{a,b,c}, Anne Synnes MHSc, MDCM\textsuperscript{a,b,e}, Steven P. Miller MDCM\textsuperscript{a,b,c,f,∗}

\textsuperscript{a} Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada
\textsuperscript{b} Child and Family Research Institute, Vancouver, British Columbia, Canada
\textsuperscript{c} British Columbia Children's Hospital, Vancouver, British Columbia Canada
\textsuperscript{d} Department of Statistics, University of British Columbia, Vancouver, British Columbia, Canada
\textsuperscript{e} British Columbia Women's Hospital, Vancouver, British Columbia, Canada
\textsuperscript{f} Department of Pediatrics, University of Toronto and The Hospital for Sick Children, Toronto, Ontario, Canada
Neonatal Pain-Related Stress Predicts Cortical Thickness at Age 7 Years in Children Born Very Preterm

Manon Ranger¹,², Cecil M. Y. Chau²,³, Amanmeet Garg⁴, Todd S. Woodward³,⁵, Mirza Faisal Beg⁴, Bruce Bjornson¹,², Kenneth Poskitt²,⁶, Kevin Fitzpatrick², Anne R. Synnes¹,²,⁷, Steven P. Miller¹,²,⁸, Ruth E. Grunau¹,²,⁷,*
Structural changes in mouse brain following neonatal pain

(Simon Beggs in preparation)
Sensitive parent interaction may protect the developing brain

(Milgrom et al *Pediatric Research* 2010)
Mission: To promote human health by providing a forum for communication and cross-fertilization among basic, translational, and clinical research.

BASIC RESEARCH  CLINICAL RESEARCH  HEALTH CARE
Thank you to the families who participate

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