Early Pain Exposure and Region Specific Brain Cortical Thickness Interact to Predict Executive Function at 8 yrs in Children Born Very Preterm

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OBJECTIVE

To evaluate whether neonatal pain-related stress and cortical thickness together predict performance in executive functions at school-age in children born very preterm

METHODS

• N=46 children born very preterm 25-32 gestational age (GA) followed longitudinally from birth underwent MRI imaging on a Siemens 1.5 Tesla Avanto system at median age 7.8 years
• Children with severe brain injury and/or major motor/sensory/cognitive impairment were excluded
• Chart review from birth to term was carried out by a neonatal research nurse (e.g. invasive procedures [pain-related stress], early infection, morphine exposure)

RESULTS

After adjusting for neonatal clinical factors (GA, SNAP-II day 1, infection, number of surgeries, cumulative morphine exposure) and WISC IV Verbal Comprehension Composite score (Verbal IQ):

• In 8/21 brain regions, the interaction between neonatal pain/stress and cortical thickness predicted Flanker % correct (p < .001 to p = .003)
• The relationship is shown for the left lingual cortex, and was the same for:
  - left & right rostral middle frontal, right inferior temporal, left caudal middle frontal, left superior parietal, right superior frontal, right superior temporal (after adjustment for multiple comparisons)

CONCLUSIONS

• Our findings suggest that executive function performance in very preterm children is dependent on both neonatal pain/stress exposure and cortical thickness
• The relationship these factors have to executive function performance cannot be understood by examining them individually

REFERENCES


FUNDING

Eunice Kennedy Shriver Institute of Child Health and Human Development (NICHD/NIH) grant R01 HD039783 [REG]. Canadian Institutes for Health Research (CIHR) grants MOP146904 [REG] and MOP139952 [SPN], Senior Scientific award; Child & Family Research Institute [REG]. Bloorview Children’s Hospital in Paediatric Neuroscience [SPN]. Post-doctoral Fellowship CIHR [MB] Paediatric Health Research [MB] Eunice Kennedy Shriver Institute of Child Health and Human Development [MB]. Four Year Doctoral Fellowship, University of British Columbia [MB]. Faculty of Medicine Graduate Award [MB]

INTRODUCTION

• In infants born very preterm, neonatal procedural pain-related stress during a period of very rapid brain development, is associated with:
  - Cortical thickness differs (thinner or thicker) in children to young adults born very preterm compared to full-term1,2,3
  - Among preterms, neonatal pain-related stress is associated with altered cortical thickness in 21/66 specific brain regions4,5
  - EF performance is related to cortical thickness in preterm and full-term children4
  - Relationships between neonatal pain-related stress, cortical thickness and EFs in children born very preterm have not been examined

DESCRIPTIVE STATISTICS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 46 (18 boys, 28 girls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal characteristics</td>
<td></td>
</tr>
<tr>
<td>GA at birth (wks)</td>
<td>29.4 (27.21-31.46)</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>1202 (892-1509)</td>
</tr>
<tr>
<td>Severity of illness day 1 (SNAP-II)</td>
<td>9.0 (0.0-17.5)</td>
</tr>
<tr>
<td>Skin-breaking procedures (number)</td>
<td>76 (44-137)</td>
</tr>
<tr>
<td>Culture proven infection (number, %)</td>
<td>12 (26)</td>
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<tr>
<td>Surgery ≥ 1 (number, %)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Morphine (cumulative daily µg adjusted for weight)</td>
<td>43 (0-771)</td>
</tr>
<tr>
<td>Flanker task (% correct)</td>
<td>94 (88-94)</td>
</tr>
<tr>
<td>WISC IV Verbal Comprehension Composite score</td>
<td>98 (93-105)</td>
</tr>
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</table>

School-Age characteristics at scan

- Chronological Age (yrs): 7.78 (7.69-8.03)
- Weight (kg): 23.2 (21.2-26.7)
- Height (cm): 123.9 (120.8-126.5)
- Head circumference (cm): 51.5 (50.0-53.0)

DESCRIPTIVE STATISTICS

• Data Analysis: Generalized linear modeling; multiple comparisons

CONCLUSIONS

In very preterm children with no severe neonatal brain injury and/or major sensory/motor/developmental impairments, after adjusting for clinical confounders and Verbal IQ:

• Combination of fewer skin breaking procedures and thinner cortex predicted better Flanker % correct

In children with thicker cortex, exposure to more skin breaking procedures predicted poorer Flanker % correct

• Same relationship was found in eight brain regions related to EFs

RESULTS

In infants born very preterm, neonatal procedural pain-related stress and cortical thickness interact to predict performance in executive functions during a period of very rapid brain development, is associated with:

• Cortical thickness differs (thinner or thicker) in children to young adults born very preterm compared to full-term1,2,3
• Among preterms, neonatal pain-related stress is associated with altered cortical thickness in 21/66 specific brain regions4,5
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