Interaction of Neonatal Pain-Related Stress and Regional Brain Cortical Thickness Associated With Executive Function in Children Born Very Preterm At 8 Years.

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INTRODUCTION

- In infants born very preterm, neonatal procedural pain-related stress during a period of very rapid brain development, is associated with:
  1) atypical brain development from birth to term-equivalent age[1]
  2) more problems in executive functions (EFs) at school-age[2]
- Cortex thickness differs (thinner or thicker) in children to young adults born very preterm compared to full-term[3,4, 5]
- Among preterms, neonatal pain-related stress is associated with altered cortical thickness in 21/66 specific brain regions[5]
- EF performance is related to cortical thickness in preterm[4] and full-term children[6]
- Relationships between neonatal pain-related stress, cortical thickness and EFs in children born very preterm has not been examined

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

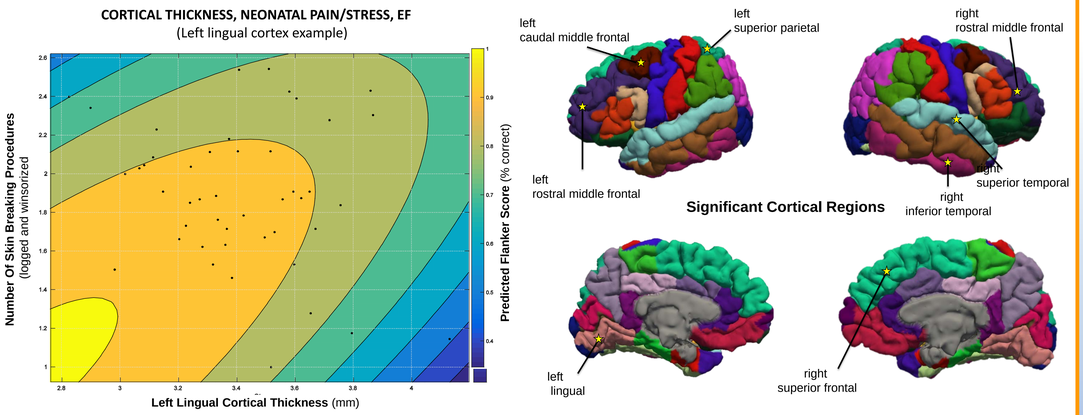
- N=46 children born very preterm 25-32 weeks gestational age (GA) followed longitudinally from birth underwent MR imaging on a Siemans 1.5 Tesla Avanto system at median age 7.8 years
- Children with severe brain injury and/or major motor/sensory/cognitive impairment were excluded
- Chart review from birth to term was carried out by a neonatal research nurse (e.g. invasive procedures [pain-related stress], early illness severity [SNAP-II], surgeries, infections, morphine exposure)
- Cortical thickness in 21 brain regions previously associated with levels of neonatal pain–related stress[5], measured using custom software based on FreeSurfer
- EF assessed using a Flanker paradigm (% correct)
- Data Analysis: Generalized linear modeling; multiple comparisons were compensated for using the false discovery rate adjustment method (α = .05)

DESCRIPTIVE STATISTICS

Characteristics	N = 46 (18 boys, 28 girls)
Neonatal characteristics	
GA at birth (wks)	29.4 (27.21-31.46)
Birth Weight (g)	1202 (892-1509)
Severity of illness day 1 (SNAP-II)	9.0 (0.0-17.5)
Skin-breaking procedures (number)	76 (47-136)
Culture proven infection (number, %)	12 (26)
Surgery ≥ 1 (number, %)	8 (17)
Morphine (cumulative daily µg adjusted for weight)	43 (0-771)
Flanker task (% correct)	94 (88-94)
WISC IV Verbal Comprehension Composite score	98 (93-105)
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)

Median and interquartile range
SNAP-II, score for neonatal acute physiology; WISK-IV, Wechsler Intelligence Scale for Children –4th Ed

Figures



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

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**

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