

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 age¹
 - 2) more problems in executive functions (EFs) at school-age²
- 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 regions⁵
- EF performance is related to cortical thickness in preterm⁴ and full-term children⁶
- 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 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 illness severity [SNAP-II], surgeries, infections, morphine exposure)
- Cortical thickness in 21 brain regions previously associated with levels of neonatal pain-related stress⁵, 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 ($\alpha = .05$)

DESCRIPTIVE STATISTICS

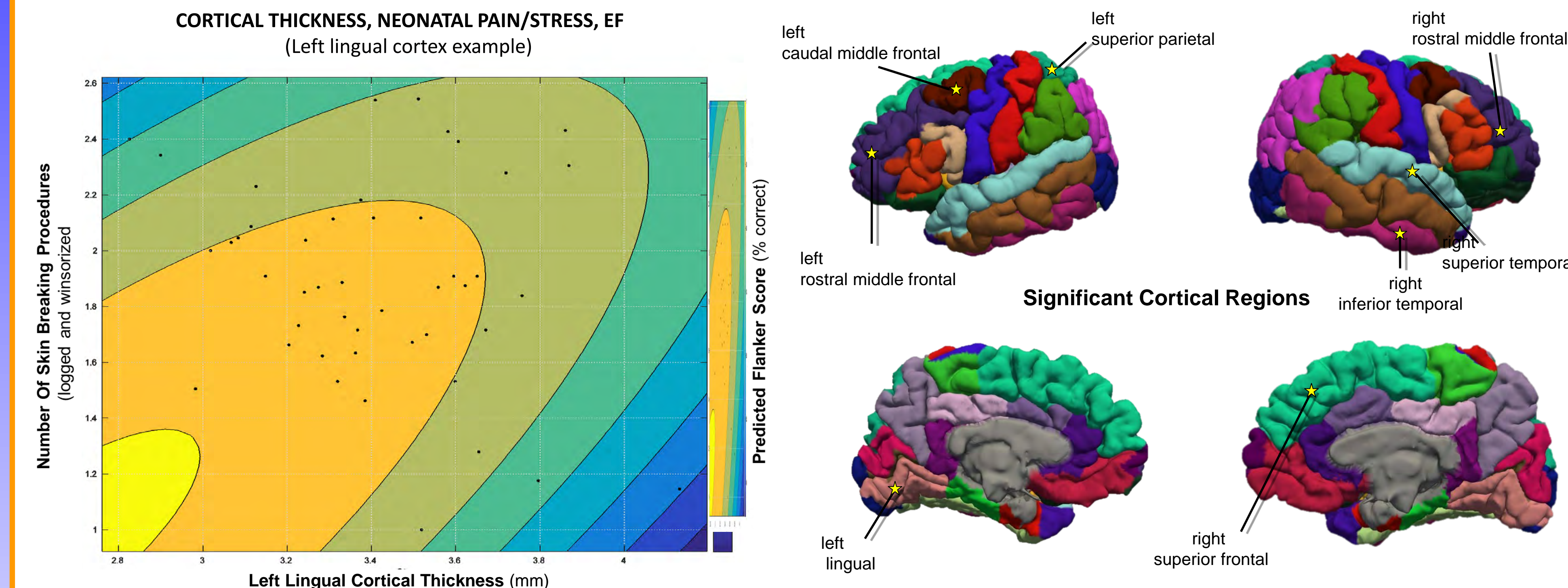
Characteristics	N = 46 (18 boys, 28 girls)
Neonatal characteristics	
GA at birth (wks)	29.4 (27.21-31.46)
Birth Weight (g)	1202 (892-1509)
Severity of illness day 1 (SNAP-II)	9.0 (0.0-17.5)
Skin-breaking procedures (number)	76 (47-136)
Culture proven infection (number, %)	12 (26)
Surgery ≥ 1 (number, %)	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; WISC-IV, Wechsler Intelligence Scale for Children -4th Ed

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)

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

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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