A Novel Glucocorticoid Score Predicts Behavior Problems in Children Born Very Preterm

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Background

Children born < 30 weeks gestational age (GA) are at ↑ risk for negative downstream effects on neurodevelopment and neurobehavior relative to full-term infants.

Methylation of HPA Axis genes may change gene expression in response to adverse intrauterine conditions leading to altered stress response set points.

We have shown associations between

Adverse intrauterine environments[1]

AND

Neonatal epigenetic dysregulation[2]

& neurobehavior at 2 years old.

However, it is unknown whether DNA methylation of specific HPA-related genes is associated with neurobehavioral outcomes in very preterm infants.

[1]Camerota et al. (2023) *J Peds*
[2]Camerota et al. (2024) *Transl Psych*

Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) Study

704 infants & caregivers
542 with DNAm data

439 with 2-year outcome data

9 NICUs / 6 research sites across United States

2014-2016 recruitment

Measures

DNA Methylation at ~450K CpG sites

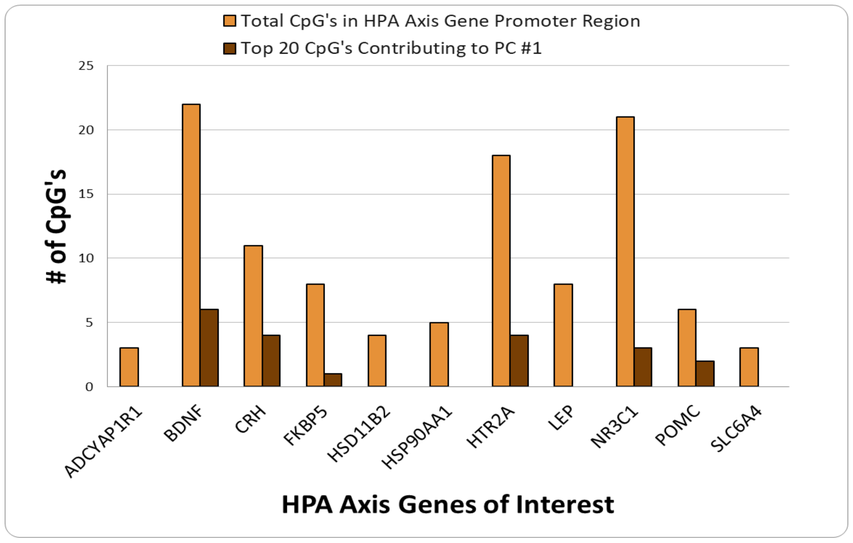
- From neonatal buccal swabs
- Assayed on Illumina MethylationEPIC Array
- identified 109 CpG's in 11 HPA-related genes of interest (Fig. 1)

Child Behavior Checklist

- 113 item parent-rated assessment
- Internalizing, Externalizing Behaviors, and Total Behaviors

OBJECTIVE: (1) To develop a novel Glucocorticoid Score utilizing a weighted approach to summarize methylation levels within promoter regions of HPA-related genes **(2)** To determine the associations between the Glucocorticoid Score and neurobehavioral outcomes at **age 2** in children born < 30 weeks gestational age.

Figure 1. CpGs and Genes Included in Glucocorticoid Score



Of the top 20 CpGs contributing to the first Principal Component, the genes most represented were BDNF (6), HTR2A (4), NR3C1 (3), POMC (2), FKBP5 (1).

Figure 2. Association Between Glucocorticoid Score and Child Outcomes

There was a significant negative association between our Glucocorticoid Score and child internalizing problems (b = -2.67, p = .03) and a marginal association with total problems (b = -2.17, p = .07).

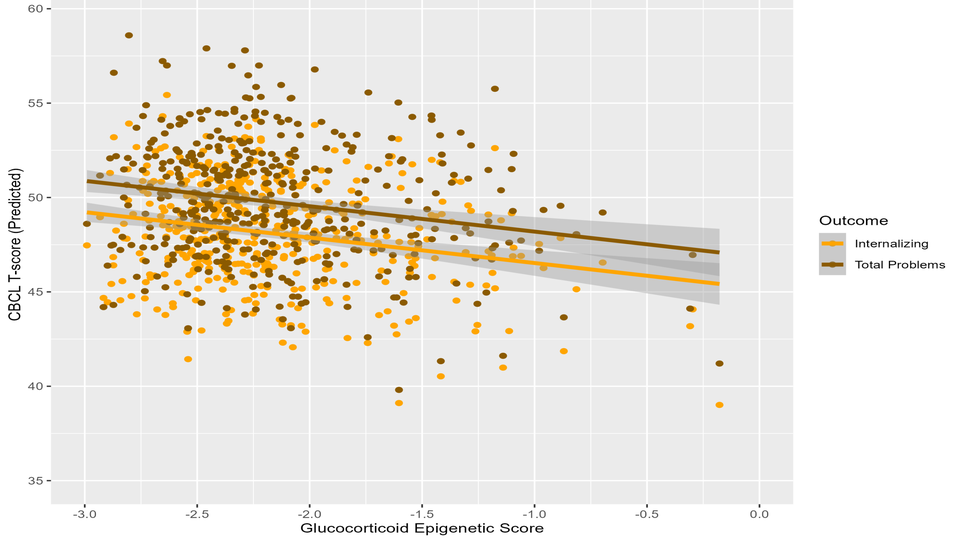


Table 1. Demographic Characteristics of the Study Sample.

Maternal characteristics (N = 482)	**M (SD) or % (n)**
Minority race or ethnicity	55% (261/478)
American Indian / Alaska Native race	0.21% (1/482)
Asian race	3.7% (18/482)
Native Hawaiian/Other Pacific Islander race	1.7% (8/482)
Black or African American race	21% (99/482)
White race	44% (214/482)
More than one race	21% (100/482)
Unknown/Race not reported	8.7% (42/482)
Hispanic/Latino ethnicity	21% (103/482)
Low SES: Hollingshead level 5	8.4% (40/478)
Maternal education: < HS/GED	14% (68/477)
No partner	26% (124/478)
Neonatal characteristics (N = 542)	**M (SD) or % (n)**
Multiple gestation	27% (145/539)
Vaginal delivery	29% (157/539)
Severe retinopathy of prematurity	6.3% (34/539)
Necrotizing enterocolitis/sepsis	19% (103/539)
Bronchopulmonary dysplasia	51% (277/539)
Serious brain injury	13% (69/539)
Sex = Male	56% (301/542)
GA at birth (weeks)	27 (1.91)
Head circumference (cm)	24.48 (2.48)
GA at NICU discharge (weeks)	40.32 (5.2)
Length of NICU stay (days)	92.77 (42.7)
Birth weight (g)	951.1 (282)
Weight at discharge (g)	3001 (861)

Analysis

- **Principal Components (PC) Analysis** to reduce the dimensionality of CpG's associated with HPA Axis while accounting for a significant degree of the variance
  - The first PC explained 94% of the variance and was retained as our HPA/Glucocorticoid Score
- Generalized Estimating Equation (GEE) models to test **prediction** of neonatal Glucocorticoid Score to 2-year Child Behavior Checklist scores

Covariates of GEE Model: site, infant GA at birth, GA at buccal swab, neonatal morbidities, sex assigned at birth, sample batch, cellular heterogeneity

Conclusion

We developed a **novel Glucocorticoid Score** using 109 CpG's from 11 HPA-Related Genes

Our PC Score accounted for **94% of the variance across all CpGs**

Our novel Glucocorticoid Score displayed associations with:

Increased risk for internalizing behavior problems

Marginal risk for total behavioral problems

Implications

Regulation of HPA-Axis genes have potential to predict long-term behavioral outcomes in infants born very preterm.

Thank you!

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Let's Connect!

Thank you for visiting my poster!

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