Cognitive Development in Infants Born Moderate-to-Late Preterm: Role of Iron Deficiency and Maternal Risk Factors

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Introduction

Do postnatal iron deficiency or maternal risk factors affect cognitive development in infants born moderate-to-late preterm?

Infants born moderate-to-late preterm (32-36 weeks gestation) are not closely followed after hospital discharge and have a greater risk for developing iron deficiency and neurodevelopmental delays. Individual differences in prenatal risk and neonatal risk factors may impact long-term cognitive outcomes in these children.

One individual difference that likely impacts cognitive development in infants born moderate-to-late preterm is postnatal iron levels. **Iron deficiency is a common micronutrient deficiency that can cause altered cognitive development in children if not treated** (Thorisdottir, Gunnarsdottir, Palsson, Gretarsson, Thorsdotti, 2013). Iron is essential for neurodevelopmental processes such as myelination, neurotransmitter production, and development of the hippocampus; thus infants could suffer from memory problems as a result of low iron levels (Georgieff, 2011). **Maternal risk factors during pregnancy**, such as pre-eclampsia and HELLP syndrome, both characterized by hypertension, **have also been associated with lower performance by infants in various cognitive tasks** (Kronenberg, Raz, and Sander, 2006).

Few studies have been done specifically with moderate-to-late preterm infants and risk factors that could affect their cognitive development. Based on previous studies, we hypothesized that infants born moderate-to-late preterm would perform more poorly on measures of infant memory and general cognitive development, and that individual differences in maternal risk factor history (presence of hypertension) and postnatal iron levels (hemoglobin) would also predict infant's performance.

Participants

	Full-Term Children (n=74)	Preterm Children (n=70)
Age at Test	*M* = 9.10 months	*M* = 10.21 months (9.00 months adjusted age)
Sex	36 female, 38 male	33 female, 37 male
Gestational Age	*M* = 39.84 weeks *range* = 37.43 – 42.71 weeks	*M* = 35.34 weeks *range* = 32.00 – 36.86 weeks
NICU/SCN stay?	9.5% of sample (< 24 hours)	68.6% of sample
9-12 Month Hemoglobin	*M* = 11.77 mg/dL *range* = 10.1 - 13.9 mg/dL	*M* = 11.78 mg/dL *range* = 8.7 - 13.5 mg/dL
Maternal Hypertension	0%	11.4%

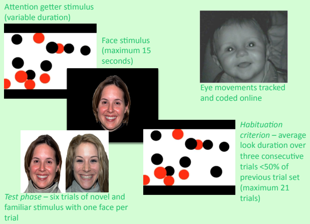
Methods

Battery of prefrontal-dependent tasks for 9-month old infants

BAYLEY SCALES OF INFANT DEVELOPMENT
(Bayley, 2006)

- *Cognition* is assessed by examining how infants react and learn about their surroundings
- *Language* is assessed by measuring the recognition of sounds and objects and production of speech sounds and gestures
- *Motor* skills measured include both fine (e.g. infant's grasp) and gross skills (e.g. crawling)

Working Memory HABITUATION TASK



- Infant driven, sliding window design using NimStim facial stimuli (based on Markant et al., 2014)
- Novelty detection and dishabituation are prefrontal dependent in young infants (Nakano et al., 2008)

MEDICAL RECORD ABSTRACTION

- Parents consented to release their child's birth hospitalization, well-baby check records, and any iron-related labs
- All records were abstracted for *gestational age and pregnancy and birth-related risk factors; hemoglobin labs* at birth and between 9-12 months of age were collected

ADDITIONAL MEASURES

- *Complete infant task battery* also includes eye-tracking measures of reversal learning, processing speed, and behavioral measures of inhibitory control (A not B task) and problem solving
- *Complete parent questionnaire battery* also includes parent-report measures of parental depression and life stress, parenting styles, infant temperament, and infant sleep and feeding patterns

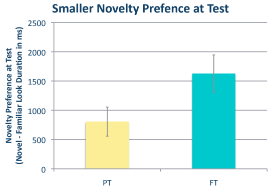
Prematurity & Cognitive Development Results

Iron Levels: PT and FT infants did not differ in HgB levels between 9-12 months of age.

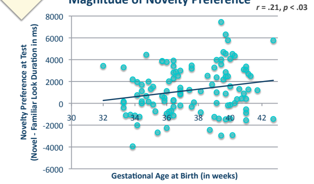
Bayley: PT and FT infants did not differ on any of the Bayley subscales.

Habituation Task: Of those who successfully habituated, **both PT and FT groups showed a novelty preference at test** ($p < .01$), **although this effect was reduced in PT children** ($p < .04$) and was related to gestational age at birth across the entire sample.

Preterm Infants Demonstrated a Smaller Novelty Prefence at Test



Gestational Age at Birth Predicts Magnitude of Novelty Preference

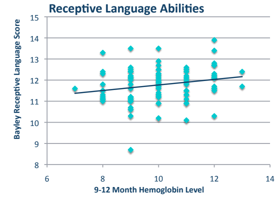


Iron & Cognitive Development Results

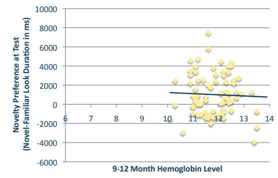
Bayley: Infants with higher HgB levels had **higher receptive language scores** ($r = .22$, $p < .03$).

Habituation Task: Iron levels were **not related** to novelty preference scores ($r = -.04$, $p < .71$).

Higher Iron Levels Predict Better Receptive Language Abilities



Iron Levels Were Unrelated to Infant Working Memory

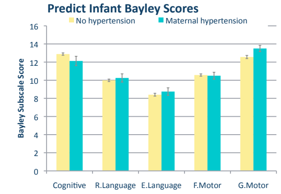


Maternal Risk Factors & Cognitive Development Results

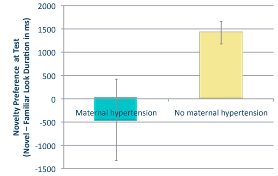
Bayley: Infants did not differ on any of the Bayley scales. There was a trend ($p < .12$) toward lower cognitive scores in the risk group.

Habituation: The risk group failed to show a novelty preference at test ($p < .62$) and significantly differed from the non-risk group in novelty preference magnitude ($p < .03$).

Maternal Hypertension Does Not Predict Infant Bayley Scores



Maternal Hypertension Predicts Poorer Infant Working Memory Performance



Discussion

Moderate-to-late preterm infants exhibited **poorer working memory development** at 9 months of age. Additionally, there was evidence that **iron deficiency and maternal risk factors** such as hypertension affect infant's **memory and cognitive development**.

Limitations: *Many of the preterm infants in this study were supplemented with iron which likely contributed to their normal iron levels at 9-12 months of age. Additionally, the lack of relationship between iron levels and memory performance may be specific to the task used. The habituation task measures working memory, which relies on the prefrontal cortex. Iron deficiency has been most strongly associated with hippocampal development, so other memory tasks could have yielded different results. Last, infants born to mothers with hypertension could have other risk factors driving their poorer performance.*

Future studies should continue to investigate the effects of iron deficiency on cognitive outcomes in infants, including those born moderate-to-late preterm. Moreover, these studies should investigate which pregnancy-related risk factors predict children's outcomes in order to ensure appropriate interventions take place to prevent cognitive developmental delays.

Conclusion

Infants born moderate-to-late preterm show subtle alterations in working memory at 9-months corrected age. Both prenatal (maternal hypertension) and postnatal (low iron) risk factors also influence infants' early cognitive development.

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