Role of Neuroplasticity in Perinatal Brain Injuries

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Learning Objectives

- Understand the major types of brain plasticity during development and recognize their role in the outcome of a variety of insults to the fetal or neonatal brain.
- Recognize the major cognitive and behavioral outcomes of injuries to the fetal or neonatal brain as assessed by brain magnetic resonance imaging and ultrasound brain imaging as well as standardized behavioral and neurological testing in the newborn intensive care unit (NICU).
- Recognize the major cognitive and behavioral outcomes of injuries to the fetal or neonatal brain as assessed by brain imaging and neuropsychological testing in toddlers who have graduated from the NICU.
Perinatal Brain Injury & Plasticity: Major Themes

- Injury to a fetal or neonatal brain does not manifest as it would in a more developed or fully developed brain.
  - Injuries and neurobehavioral outcomes are complex and multifaceted injuries
  - Research involving preemies is the most robust, but still limited as it pertains to quantifying impairments under increased and multifaceted cognitive demands
  - Overall, efficiency of thinking and performing is compromised
  - Recruitment of small versus large neural networks/brain regions
  - Use of basic strategies versus complex strategies in problem-solving
- How do we identify the children who will need additional support?
  - Empirical research in infants and toddlers is primarily focused on motor skills
  - Most empirical research regarding cognitive outcomes is in school-age formerly preterm infants

Individual, Family, and Injury-related Factors In Perinatal Brain Injury

Prenatal Factors:
- There are a number of prenatal factors that have or may have a negative impact neurodevelopmental, neuropsychological, and neuropsychiatric outcomes.

  - Some of the more common factors include exposure to maternal hypertension, diabetes, and thyroid dysfunction, as well as infection and exposure to toxins, substances, and drugs.

  - Fetal therapy/surgical interventions are becoming more widely used and the impact of these procedures on neurodevelopmental and neuropsychological outcomes is widely unknown at this time.

Neuroplasticity

- Long-term Outcomes
  - Neuroplasticity
  - Long-term Outcomes
  - Neuroplasticity

Interventions

Adapted from Waters, 2010 model of concussion
**Very Early Environmental Factors**

- The typically developing fetus is exposed to a unique multisensory environment that supports overall growth and development (including the CNS).
- Premature birth or hospitalization after birth requires adaptation to a less than ideal environment.
  - Hypo stimulation:
    - Rhythmic and kinesthetic stimulation changes
    - Lack of continuous maternal contact
    - Different body posture within the incubator
  - Hyper stimulation:
    - Continuous light and different noises
    - Invasive and painful medical procedures

**Psychosocial Factors & Outcomes**

- Low SES is a risk factor for delay across all domains of neurodevelopmental and neuropsychological function (Potijik et al., 2013)
  - Independent of gestational age at birth or perinatal brain injury at term
- Specific maternal characteristics negatively impact mother-child interactions and child development:
  - Trait anxiety (Zelkowitz et al., 2009)
  - Depressive symptoms (McManus & Poehlmann, 2011)
- Maternal use of complex scaffolding methods in play and daily activities improve outcomes (Lowe et al., 2013)
  - Complexity of scaffolding increases with maternal level of education

**Perinatal Brain Injury Recovery and Outcome**
Identification of Ongoing Need

- Developmental Disabilities are often identified through
  - Developmental Failure
    - Delays diagnosis and therapeutic intervention
      - Potentially missing critical windows of neuroplasticity
    - Increases the incidence of secondary consequences
      - Contractures in children with late identification of cerebral palsy
      - Language delay in late identification of hearing impairment
      - Behavioral problems in school in late identification of learning problems
  - Routine Screening and Surveillance of High Risk Infants
    - Allows families the opportunity to develop appropriate expectations
    - Allows institution of therapeutic services or accommodations to maximize achievement by taking advantage of critical periods of neuroplasticity

Role of Early Intervention

- Cochrane Review (2012)
  - “Early intervention programs for preterm infants have a positive influence on cognitive and motor outcomes during infancy, with the cognitive benefits persisting into preschool”
  - Following development as early as possible allows us to identify concerns and take advantage of plasticity.

Perinatal Brain Injury in the Neonatal Period:
Characterization & Course
Neurodevelopmental Evaluation in NICU and Infancy

- Amiel-Tison
  - A qualitative infant neurological exam
- NICU Network Neurobehavioral Scale (NNNS)
  - Quantitative neurological exam and evaluation of infant neurobehavioral function in first 6 months of life.
  - Sleep Protection
  - State Regulation
  - Orientation
- Prechtl’s General Movement Assessment (GMA)
  - A semi-quantitative observation of the presence/absence and quality of motor movements in the first 3 months of life.

Premature Birth

- Approximately 12% of U.S. births are premature, defined as younger than 37 weeks gestation.

Proterm Birth, by Completed Weeks of Gestation, 1990–2012

- Data for 2012 are preliminary
Premature Birth Definitions

- Low Gestational Age/Low Birth Weight
  - Children born extremely preterm (≤28 weeks gestation)
  - Children born very preterm (<28 and ≤32 weeks)
  - Children born moderate to late preterm (>32 weeks and ≤36 weeks)

Vignette: Premature Birth

- Davidson was the product of a twin gestation (twin B) and a pregnancy complicated by pre-eclampsia treated with magnesium sulfate. He was born at 26 weeks gestation via vaginal delivery in breech presentation due to spontaneous rupture of membranes for Twin A. Davidson’s birth weight was 890 grams.
  - Mother received betamethasone X 2 prior to delivery
  - APGAR scores were 1, 4 and 8 at one, five
  - Intubated in the delivery room and received surfactant

Premature Birth Neurodevelopmental Risk Factors

- Brain Injury
  - Encephalopathy of Prematurity
  - Intraventricular Hemorrhage
    - Hydrocephalus
    - Periventricular Leukomalacia
- Medical Complications
  - Chronic Lung Disease
  - Surgical Necrotizing Enterocolitis
  - Retinopathy of Prematurity
2 Do we include any info on family, SES, parental education?
Gwendolyn Gerner, 1/20/2018
Vignette: Premature Birth

- Davidson had a 233 day NICU course
  - Ventilation for over a month in total and discharged on oxygen.
  - G-tube and Nissen
  - PDA s/p ligation.
  - Retinopathy of Prematurity Zone III, Stage 0 bilaterally.
  - Brain Injury
    - Bilateral intraventricular hemorrhage left > right
    - Post-hemorrhagic hydrocephalus initially treated with a ventriculostomy and subsequently with subsequent right frontal endoscopic third ventriculostomy which was converted to a right frontal ventriculoperitoneal shunt
    - Periventricular leukomalacia and a large porencephalic cyst
    - Seizures that were treated with Keppra and Trileptal.

Vignette: Premature Birth & Neonatal Exam

- Cranial Nerves:
  - Pupils equal, round, reactive to light.
  - Symmetric face at rest and with activation.
  - Intact burst and pause suck with swallow pattern.
  - Tongue is midline.

- Motor:
  - Good muscle bulk.
  - Moves all extremities spontaneously.
  - Hands are open more than half the time, with mobile thumbs.
  - Near constant high frequency, low amplitude tremors in all extremities.

- Tone:
  - No head preference, but has difficulty maintaining head in midline due to significant neck extensor tone.
  - Extensor tone is greater than flexor tone.
  - Hypotonic ataxically with significant head lag with pull to sit, some shoulder activation, and brief attempts in right head but not maintained for more than a second.
  - Grasp present, but not significant.
  - Rests with legs in extension and with strong flexor resistance and delayed and incomplete recoil.
  - Flexed angles are less than 90 degrees on the left, 90-110 on the right.
  - Akle dorsiflex past neutral with a catch during flex phase and 6-7 bends of dorsiflexion on the left.
  - Anterior neck sign out to the midline bilaterally.
  - Upper extremities with moderate resistance and complete and fast recoil.
  - In neutral suspension demonstrates minimal neck extension and some hip flexion.
  - In prone, does not appear to activate neck flexors but uses extensor tone to turn his head to the side.

- Reflexes:
  - Babinski: spontaneously present bilaterally.
  - Palmar: present bilaterally.
  - Plantar: absent bilaterally.
  - Demonstrated brief positive support, but no steps.
  - Upper extremity group: present, lower extremity group is exaggerated bilaterally.
  - Ataxia complete bilaterally.
  - More present, but incomplete bilaterally.
Do we include any info on family, SES, parental education?
Vignette: Premature Birth & Neonatal Exam

- **Sleep Protection**: Not assessed as infant was awake.
- **State Regulation**:
  - Was in a quiet or active awake state for most of the exam; did shift to drowsy during orientation.
  - Demonstrated very brief periods of irritability that were not sustained.
  - Did show subtle signs of stress during the exam including rapid breathing, yawning, and sneezing.
  - He was physiologically stable.
- **Orientation**:
  - Responded best to animate objects compared to inanimate objects.
  - Demonstrated very brief periods of irritability that were not sustained.
  - Did show subtle signs of stress during the exam including rapid breathing, yawning, and sneezing.
  - Physiologically stable.
- **General Movements Assessment at 39 weeks post-menstrual age was abnormal**: For the majority of the time observed movements were cramped synchronized.

Vignette: Premature Birth & Early Intervention

- Received physical therapy and occupational therapy through Infants and Toddlers.
- Received vision intervention through the Maryland School for the Blind.
- Participated in 30 days Specialized Transition Program intensive therapy program focusing on left hand function.
- Continues with additional private weekly therapies.

Vignette: Premature Birth and Early Outcome

- Davidson had a neurodevelopmental evaluation at age 17 months.
- Best Motor Performance: Sitting independently; diagnosed with quadriplegic cerebral palsy (CP).
- Diagnosis of cortical visual impairment (CVI).

<table>
<thead>
<tr>
<th>Scale</th>
<th>DQ adjusted</th>
<th>DQ chronological</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLAMS</td>
<td>96.7</td>
<td>77.1</td>
</tr>
<tr>
<td>CAT</td>
<td>77.1</td>
<td>61.4</td>
</tr>
</tbody>
</table>

DQ = Developmental Quotient  
CLAMS = Clinical Linguistic & Auditory Milestone Scale  
CAT = Cognitive Adaptive Test
Neonatal Hypoxic Ischemic Encephalopathy (HIE)

- Loss of blood and oxygen to the brain
- Most common cause of perinatal brain injury in full-term neonates
  - One of the leading causes of neonatal death
  - Affects approximately 1-3 in 1000 births in US
- Range of Neurodevelopmental Disabilities
  - Severe cerebral palsy and profound intellectual disability to unperceivable limitations
- Long-term severe sequelae include
  - Intellectual Disability
  - Cerebral Palsy
  - Epilepsy
  - Sensorineural Hearing Loss and Visual Impairment

Traditional Patterns of Injury after Neonatal HIE

<table>
<thead>
<tr>
<th>Brain Structure Involved</th>
<th>Severity and Timing of Analogous Lesion(s) in Animal Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral = deep nuclear, thalamus</td>
<td>Severe, prolonged</td>
</tr>
<tr>
<td>Cerebral or deep nuclear or most caudally, thalamus</td>
<td>Moderate, prolonged, and/or inconstant</td>
</tr>
<tr>
<td>Deep nuclear = thalamus</td>
<td>Severe, relatively brief</td>
</tr>
<tr>
<td>Cortical white matter</td>
<td>Mild/hemorrhage, gradual/prolonged (? hypoglycemia, infection)</td>
</tr>
</tbody>
</table>

*Composite = involvement of corticomedullary white matter, often with periventricular (presumed) perifocal edema and necrosis. Deep nuclear = thalamus, head, and thalamus (medial dorsal). Bitemporal = especially inferior colliculus, tegmentum, central white matter is periventricular/cortical white matter at a dominant brain.

Principal animal models are non-traditional monkey and tree that are described in text.
**Vignette: Neonatal HIE**

- Lucas was born at 41 weeks and weighed 4.23 kg via emergency C-section due to non-reassuring fetal tracing to a 26 year old G1P1 woman.
  - Bloody fluid at rupture of membranes, found to have a placental abruption.
  - Apgars scores were 2, 4, 6 and 9.
- Arterial Cord gas pH 6.9/92/14
- Modified Sarnat Score consistent with moderate encephalopathy:

<table>
<thead>
<tr>
<th>Level of consciousness</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous activity</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Tone</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>Abnormal</td>
<td>Absent</td>
</tr>
<tr>
<td>Suck</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic reflexes</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Pupils</td>
<td>Constricted</td>
<td>Severe</td>
</tr>
<tr>
<td>Respiration</td>
<td>Periodic</td>
<td>Mechanical ventilation</td>
</tr>
</tbody>
</table>

**Neonatal HIE: Johns Hopkins Hospital Criteria**

- Born at ≥35 weeks gestation
- Evidence of moderate or severe hypoxic-ischemic encephalopathy
  - Cord Blood
    - pH ≤ 7.15
    - Base Deficit ≥ 10
- AND
  - Encephalopathy on exam
    - Neurologic examination abnormality consistent with Stage 2 or 3 Sarnat criteria
    - Seizure
- Able to start hypothermia within 6 hours
- Exclusion criteria include severe hemodynamic compromise, coagulopathy, congenital anomalies, injury felt to be so severe that the patient is likely to die or less than 1800 grams.
Therapeutic Hypothermia: Reduces Secondary Energy Failure and Cell Death

Johnston, Fatemi, Wilson, & Northington 2011

Clinical Trials For Therapeutic Hypothermia
Treatment of HIE

Cochrane Review 2013

Number needed to treat:
- 7 (95% CI 5 to 10)

Primary Composite Outcome
- Death and/or Disability at 18 months

In children who received therapeutic hypothermia:
- Incidence of cerebral palsy is approximately 17% with a cost to the US exceeding $1.9 billion per year
- Incidence of IQ<70 is approximately 27% with a cost to the US exceeding $3.4 billion per year
Neonatal HIE Survival and Outcomes: Post-hypothermia

- Estimates after HIE treated with hypothermia:
  - 30% mortality
  - 17% with cerebral palsy
  - 27% of children with intellectual disability
  - 7% with visual impairment
  - 4% with hearing impairment

- Total Body Hypothermia for Neonatal Encephalopathy Trial
  - 55% of HIE survivors who received hypothermia had persistent neurologic abnormalities at age 6–7 years

- The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network
  - 35% of survivors who received hypothermia had moderate or severe disabilities at 6–7 years of age

Azzopardi et al, 2009; Gluckman et al., 2005; Shankaran et al., 2005

Johns Hopkins Hospital NICN Clinical Protocol for Neonatal HIE

- Follow the NICHD Protocol
  - Hypothermia
    - 32–34 degrees Celsius
    - 72 hours
  - Monitoring
    - Continuous EEG
      - cooled, rewarmed
      - aEEG
    - NIRS
    - HUS
      - Before and after cooling
    - MRI
      - 4–7 days

- Blood Biomarkers:
  - GFAP
  - NRGN
  - BDNF
  - IL6
  - VEGF

Vignette: Neonatal HIE

- Lucas was passively cooled and transferred for evaluation and initiation of therapeutic hypothermia

- Initial HUS at 6 hours of life showed global cerebral edema
  - Increased prominence of the gray-white matter differentiation, suggestive of cerebral edema.
  - Slit-like appearance of the ventricles, suggestive effacement.
  - Full term gyration/sulci/cification is noted.
  - No intra-axial or extra-axial hemorrhage identified.
  - No midline anomalies or focal lesions identified.
  - No ventriculomegaly
  - Normal response of resistive index values, measuring 0.69 without transducer pressure and 0.67 with transducer pressure.
  - The superior sagittal sinus is patent.
**Vignette: Neonatal HIE**

- Continuous EEG results for Lucas:
  - There was overall medium voltage record with good spontaneous variability and reactivity.
  - There was both continuous periods with periods of discontinuity that are longer than expected for gestational age that decreased over the 3 days.
  - There were occasional sharp transients but no seizure activity.

**Vignette: Neonatal HIE**

- Lucas’ follow-up radiology exam results:
  - HUS showed improvement in global cerebral edema.
    - Decrease in prominence of grey-white matter differentiation
    - Improvement in slit-like appearance of the lateral ventricles
    - Increase in RI values, compatible with improvement in global cerebral edema.
  - Brain MRI at 7 days of life read with no abnormal restricted diffusion or T2 hyperintensity

**Neonatal HIE: Detection of Neurologic Injury**

- Children with impairments at 2 had higher MAP\textsubscript{per} during rewarming.
- Greater blood pressure deviation below MAP\textsubscript{per} during rewarming was associated with greater disability at age 2.
- Neither rSO\textsubscript{2} (p>0.10) nor blood pressure below ga+5 (p>0.10) was associated with outcome.

*Burton et al, BMC Neurology, 2015*
**Neonatal HIE Treated with Therapeutic Hypothermia: Autoregulation and Outcome**

- The mean pre-hypothermia RRI values for the entire clinical sample fell within the lower limits of the normal range (M = 0.65, SD = 0.12), as did the mean post-cooling RRI value (M = 0.65, SD = 0.09).

_Gerner et al., Journal of Perinatology, 2015_

**Neonatal HIE: Trans Doppler Head Ultrasound (HUS) Resistive Indices (RI) and Outcomes**

- Neonates with RRI values <0.60 prior to and following cooling were more likely to die or have severe neurodevelopmental disability by ages 20-32 months than those with RRI >0.60.

- Lower RRI values were associated with specific neurodevelopmental deficits in motor development.

_Gerner et al., Journal of Perinatology, 2015_

**Neonatal HIE: Prediction of Outcome Using HUS RI**
5 Should we put this slide with the other slide about the RI paper?
Gwendolyn Gerner, 1/20/2018
Neonatal HIE: Neuroimaging after Therapeutic Hypothermia

- Between January 1, 2010 and December 31, 2014, 125 neonates with HIE underwent therapeutic whole-body hypothermia treatment
- N=57 included in a neuroimaging study:
  - Normal MRI = 11 (19%)
  - Periventricular white matter changes only = 38 (67%)
  - Deep gray matter nuclei or cortex = 3 (5%)
  - Deep gray matter nuclei and cortex = 5 (9%)  

Poretti, unpublished data

Neonatal HIE: Other Predictors of Neurologic Injury

- Cooled neonates with hypoxic birth injury. Relationship of daily GFAP to (A) an abnormal brain MRI and (B) time to oral feeding


Vignette: Neonatal HIE Neurodevelopmental NICU Exam

- Cranial Nerves: Pupils equal, round, react to light. Symmetric face at rest and with activation. Intact swallow with brief burst and suck pattern. Tongue is midline.
- Motor: Good muscle bulk. Right-sided head preference. Moves all extremities spontaneously. Hands are open more than half the time, with mobile thumbs.
- Tone:
  - Hypotonic axially.
  - Significant head lag with pull to sit and brief attempts to right head.
  - Extension in vertical suspension with moderate slip through.
  - Rests with legs in flexion and has appropriate flexion resistance and recal.
  - Pupillary angles at 90-110 on the right and 120-130 degrees on the left.
  - Ankle flexion past neutral and no clonus present.
  - Anterior scapull sign to the midline bilaterally.
  - Upper extremities with moderate resistance and delayed but complete.
  - Demonstrates some activation of neck and hip flexion in vertical suspension.
  - Activates neck flexors and turns head to the side prone.
Vignette: Neonatal HIE Neurodevelopmental NICU Exam

- Reflexes:
  - Babinski present bilaterally.
  - Gallant present bilaterally.
  - Placing present bilaterally.
  - Demonstrated brief positive support and no steps.
  - Upper extremity grasp present, though delayed.
  - Lower extremity grasp present.
  - ATNR incomplete bilaterally.
  - Moro present bilaterally.

Vignette: Neonatal HIE Neurodevelopmental NICU Exam

- Sleep Protection: Demonstrated adequate sleep protection for visual and auditory stimuli.
- State Regulation:
  - Shifted appropriately from sleep to a quiet and then active awake state.
  - Demonstrated very brief periods of irritability that were generally not sustained.
  - When actively crying, soothed to voice and resting a hand on her chest.
  - Did show subtle signs of stress during the exam including hiccupping, yawning and brief high frequency low amplitude tremors.
  - He was physiologically stable.
- Orientation:
  - Fixed and followed visual stimuli horizontally.
  - Turned and localized voice.
  - Stilled but did not turn to sound.
  - Demonstrated some signs of overstimulation including startle, gaze aversion and closing eyes when presented with more than one stimulus at a time.
- General Movements Assessment at 42 weeks post-menstrual age:
  - Normal writhing was observed for the majority of the time

Vignette: Neonatal HIE Early Intervention

- Lucas was evaluated by Infants and Toddlers following NICU discharge.
- He qualified for physical therapy services through Infants and Toddlers for 6 months.
- An educator monitored Lucas’ development until age 12 months and then he was discharged from Infants and Toddlers Early Intervention Services.
Lucas had a comprehensive neuropsychological evaluation at age 31 months:

<table>
<thead>
<tr>
<th>Median Scales of Early Learning Skill Domain</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross Motor</td>
<td>46</td>
</tr>
<tr>
<td>Visual Reception</td>
<td>20</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>36</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>49</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>39</td>
</tr>
</tbody>
</table>

Occupational therapy services were recommended and initiated.

Continued neurodevelopmental and neuropsychological follow-up was recommended.

Some results of Lucas' Neuropsychological Evaluation at age 6 years of age:

- Receptive Language Index: 77
- Expressive Language Index: 89
- Full Scale: 87

- Some selected subtests scores:
  - Object-Perceptual: 85
  - Comprehension: 87
  - Verbal Expression: 91

- Summary: Overall outcomes were within the high average range with some areas of concern in memory and attention.

- Recommendations: Continued support in academic areas and strategies for improved executive function and attention.
Vignette: Neonatal HIE School-Age Neuropsychological Evaluation

- Lucas was diagnosed with Developmental Coordination Disorder and continued participation in Occupational Therapy was recommended.
- Lucas was diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), Combined Type
  - Recommendations for both participation in behavioral therapy and consultation for medication were made.

Perinatal Brain Injury

- Incidences of childhood and perinatal ischemic strokes are 2-3 per 100,000 and 40 per 100,000 respectively [Felling et al., Cells Mol Dis 2017]
- Focal vascular injury: “A group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, and confirmed by neuroimaging or neuropathological studies (Raju et al, Pediatrics; 2007)”
  - Perinatal arterial ischemic stroke
  - Cerebral sinovenous thrombosis
  - Hemorrhagic stroke
Perinatal Stroke

A. Symptomatic neonatal arterial ischemic stroke
   • Most common is Left MCA

B. Presumed perinatal ischemic stroke
   A. Periventricular venous infarction
      • Germinal Matrix hemorrhage

Neuroimaging of Acute Presentations of Perinatal Stroke

A) Acute axial diffusion weighted magnetic resonance image (DWI) indicating bilateral restricted diffusion typical of acute bilateral middle cerebral artery (MCA) infarcts in neonatal arterial ischemic stroke (NAIS)

A) Acute axial diffusion weighted MRI with restricted diffusion in the left MCA territory indicating acute arterial ischemia

A) Sagittal computed tomography (CT) angiogram with filling defect in the superior sagittal and straight sinus in a neonatal cerebral sinus venous thrombosis (CSVT)

A) Axial unenhanced CT with acute blood bilaterally into the lateral ventricles, commonly seen in acute CSVT

A) Axial gradient echo MRI of an acute intraparenchymal hemorrhage appearing as a dark "blooming" artifact in the right parietal-occipital area.

A) Axial CT of the same patient with hyperdensity suggestive of acute blood in the occipital parietal.

Perinatal Stroke

• Presentation
  – Symptomatic
    • Seizures
      – 16.4% of the patients developed post neonatal epilepsy (Suppiej et al, Brain Dev, 2016)
    • Encephalopathy
      – Feeding difficulties
      – Apnea
  – Non-symptomatic
    • Delays diagnosis, usually due to more focal delays
Vignette: Perinatal Stroke

• Jane was born full term via cesarean section after failure to progress. There were no prenatal complications.
  - At 4 hours of life, episodes of apnea with accompanying left-sided nystagmus, deviation of the tongue, and increased right lower extremity tone were noted.
  - A brain MRI revealed a large left middle cerebral artery hemorrhagic infarction with mild mass effect.
  - An EEG revealed bilateral epileptiform activity, which was treated with phenobarbital and Keppra.
  - A follow-up brain MRI revealed no further progression of the hemorrhage, but there was evidence of early Wallerian degeneration.

• Jane has been participating in neurodevelopmental follow-up since age 2 months.

Outcomes following Perinatal Stroke

• 60% with cerebral palsy
  - Usually spastic hemiplegia
• 30–60% with epilepsy
• 25% with language delay
• Up to 22% behavioral difficulties

Recovery Following Perinatal Stroke

• In adults, longitudinal recovery has been well characterized in several studies:
  - For instance, the majority of recovery of motor deficits occur within the first 3 months after a stroke (Jorgensen et al., The Copenhagen Stroke Study. Archives of physical medicine and rehabilitation 1997).
• It is reasonable to assume a similar phenomenon occurs after injury to the pediatric brain, but ongoing developmental processes likely influence this extensively.
I need to add a second slide about her neurodevelopmental course.

Gwendolyn Gerner, 1/20/2018
Recovery Following Perinatal Stroke

- The concept of a "sensitive period" for stroke recovery during which specific processes of neuroplasticity are uniquely upregulated (Zeiler & Krakauer. Current opinion in neurology 2013; Murphy et al, Nature reviews Neuroscience 2009)

- In animal models, recovery after stroke is thought to be mediated by neuroplasticity (Carmichael, Annals of neurology 2006)
  - A complex combination of cellular phenomena including neurogenesis, axon growth, and synaptic remodeling.

Vignette: Perinatal Stroke

- Jane had a neuropsychological evaluation at age 16 months:
  - She has a diagnosis of a Right Hemiplegic Cerebral Palsy and she had no use of her right hand.
  - Average visual perceptual and expressive language skill development
  - Below average receptive language, as well as fine and gross motor skills development
  - A speech and language evaluation at age 25 months revealed average expressive and receptive language skills, but oral motor weaknesses placing her at risk for the development of dysarthria.
  - She participated in one month of Constraint Induced Movement Therapy at age 27 months. At the end of the therapy:
    - When her left hand was casted, she began grasping and releasing with her right hand.
    - After the left hand cast was removed, Jane was able to use her right hand 50% of the time during tasks requiring bimanual coordination.
    - She continues to have left hand dominance.
    - She continues to require verbal prompting to use her right hand.
- Jane returned for neurodevelopmental follow-up at age 3½ years due to emerging concerns about a high level of activity and difficulty sustaining her attention:
  - She was referred for a neuropsychological evaluation
Famous Preemies: Adaptive Plasticity at Work

- Johannes Keppler
- Napoleon Bonaparte
- Sir Isaac Newton
- Sir Winston Churchill
- Pierre-Auguste Renoir
- Anna Pavlova
- Stevie Wonder
- Albert Einstein
- Charles Darwin
- John Keats
- Mark Twain
- Victor Hugo
- Jean-Jacques Rousseau
- Sidney Poitier

Perinatal Brain Injury

Motor Outcomes

Preterm Birth: Cerebral Palsy

- Cerebral Palsy (CP) is a severe neuromotor disorder that is more common among survivors of preterm birth.
- A recent meta analysis reported prevalence rates of CP among children born preterm (Himpens et al., 2008):
  - ~14.6% of those born < 28 weeks gestation
  - ~6.2% of those born between 28 and 32 weeks
  - ~0.7% of those born between 32 and 36 weeks
- Bilateral spastic CP (spastic diplegia) is the most common form of CP (66% of cases) in children born preterm.
- PVL, especially Cystic PVL, is a risk factor.
- Reduction in gray matter volume bilaterally in sensorimotor areas is also a risk factor (Limperopoulos et al., 2014).
Predicting Cerebral Palsy in After Premature Birth in NICU Follow-up Clinics

• In a cohort of 39 children born preterm (22/39 with longitudinal data)
  – 3 have cerebral palsy, 1 has a probable diagnosis
  – 10.3% rate of CP

  1. Placement of shunt for hydrocephalus
  2. Structural Brain Injury
  3. Sepsis in the neonatal period

DQ < Chronological age on the Cognitive Adaptive Subtest (CAT) from the Capute Scales at 3-5 months

DQ < Chronological age on the Cognitive Adaptive Subtest (CAT) from the Capute Scales at 6-9 months

Model 1 predicts 100% of CP diagnoses
Model 2 predicts 67% of CP diagnoses

Preterm Birth Trajectory of Visual-Motor Skills Development on the Capute Scales

• The space between the red lines is performance in an age appropriate range.

Preterm Birth: Trajectory of Visual-Motor Skills Development on the Capute Scales

• The space between the red lines is performance in an age appropriate range.
Preterm Birth: Motor & Visuomotor Outcomes

- Evidence of moderate to mild neuromotor impairments are high, including Developmental Coordination Disorder.
- Estimates of the prevalence of DCD in those born preterm ranges from 9.5% to 72.2% (Edwards et al., 2011).
- Neuromotor impairment appears to persist at least into early adulthood, but potentially beyond (Zwicker et al., 2013; Edwards et al., 2011; Husby et al., 2013).
- Visuomotor differences between preterm and term groups at age 8-10 years (Newsham et al., 2007):
  - Variability of saccades is higher in the preterm group.
  - The preterm group has more anti-saccade errors and corrects anti-saccades less.
  - Smooth pursuits start slower and is somewhat faster at the end of tracking.

Perinatal HIE: Cerebral Palsy

- Reduced rates of death (28% vs. 44%) and cerebral palsy (17% vs. 29%) with therapeutic hypothermia versus no hypothermia (Shankaran et al., 2012).
- HIE is traditionally thought to most significantly result in basal ganglia and thalamic injury leading to dystonic or atethoid CP.
- Some studies have found that only 46% of patients who develop CP have a dystonic/atethoid CP (Martinez-Biarge et al., 2011).
- The remaining 54% of patients have a spastic pattern of CP (Martinez-Biarge et al., 2011).
  - This suggests likely concurrent white matter and cortical injury (Spittle et al., 2011).

Hypoxic-ischemic Encephalopathy (HIE) Cohort

- In a sample of 50 children born at term with HIE:
  - 6 have diagnoses of Cerebral Palsy, and 1 has a probable diagnosis.

  1. Clinical Severity of brain injury on MRI
  2. Highest Glial Fibrillary Acidic Protein (GFAP) blood level between birth – 7 days

Model 1 predicts 85.7% of CP diagnoses

Gross Motor Function Measure (GMFM) Total Score between ages 18 – 24 months

Model 2 predicts 100% of CP diagnoses
HIE: Additional Factors for Neurologic Injury

- There are differences in white matter development in the posterior centrum semiovale and the splenium of the corpus callosum between children with HIE and controls on DTI.

- Abnormalities in white matter in the posterior centrum semiovale are associated with:
  - How a child learns and problem-solves visually between ages 18 and 30 months (p ≤ .05 for FA, MD, AD, and RD).
  - Development of fine motor skills between ages 18 and 30 months (p ≤ .05 for RD).

Cognitive Outcomes

- "It's got what you want, first create a list of everything that you want. Then, draft a dynamic plan of action, then follow through with actions to maximize effort. If it doesn't work, just try and plan.

Preterm Birth: General Outcome Findings

- The prevalence of intellectual disability is 10 to 15% in this clinical population (Brosco et al., 2013).

- Full Scale IQ is typically 8 to 10 points below that of healthy, typically developing peers born at term (Hutchinson et al., 2013).

- Based on imaging, alterations in neural connectivity and more recruitment of additional brain regions (Constable et al., 2012; Mullen et al., 2011; Salvan et al., 2014).

- Altered resting state connectivity (Smyser et al., 2013).
HIE: Neuropsychological Outcomes prior to Therapeutic Hypothermia

- Neuropsychological outcomes based on HIE severity and prior to therapeutic hypothermia were collected at school age using the British Ability Scale and NEPSY (Marlow et al., 2005):
  - No difference between controls and those with moderate HIE on Full Scale IQ, but those with severe HIE had significantly lower Full Scale IQ
    - Not a consistent finding across all studies (van Handel et al., 2013)
  - This finding was consistent across other domains including:
    - Nonverbal reasoning
    - Verbal skills
    - Visuospatial skills
    - Attention and Executive Function

- van Handel et al. (2013) examined results of parent and teacher behavioral questionnaires (i.e., CBCL, CSBQ) and the results of the DSM-IV (all translated into Dutch) among children with histories of mild and moderate HIE:
  - Parents endorsed more “thought problems” on the CBCL if their child had mild HIE
  - Parents endorsed more total social difficulties on the CSBQ for both mild and moderate HIE
  - Teachers endorsed more total behavioral problems, attention problems, and symptoms of anxiety/depression on CBCL in children with moderate HIE
  - Teachers also endorsed more social problems on the CBCL for both mild and moderate HIE
**HIE: General Outcome Findings Following Therapeutic Hypothermia for Neuro-protection**

- Mean IQ is higher but not significantly higher in group receiving therapeutic hypothermia (82 vs. 75) at 6-7 years
- No significant group differences in visual or hearing impairments
- No observed differences in visuospatial skills, attention, or executive function by ages 6-7 years
  - Authors acknowledged that appropriate power to closely examine specific neuropsychological deficits was limited

  Shankaran et al. (2012)

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**Perinatal Stroke Outcomes**

- 1/3 neurologically normal/unperceivable limitations
- 2/3 motor and cognitive impairment
- 3% death

  Lynch et al., 2001; Curr Opin Pediatr

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**Perinatal Stroke: General Neuropsychological Outcomes**

- IQ scores remain broadly in the average range overall (e.g., Carlsson, 1997; Gonzalez-Monge et al., 2009; Ricci et al., 2008).
  - Compared to age matched controls, IQ scores are somewhat lower or shifted down in the lower part of the average range (Talib et al., 2008; Trauer et al., 2001).
  - Some studies have found verbal abilities are more preserved than perceptual abilities (e.g., Carlsson et al., 1994; Muter et al., 1997; Kolk et al., 2011).
    - This occurs despite the fact that majority of perinatal strokes are left sided and is believed to be related to developmental plasticity.
Perinatal Brain Injury

Attention and Inhibition

Preterm Birth: Selective Visual Attention
- At 7 months, infants born very preterm compared to full-term controls demonstrate (Rose et al., 2001):
  - Less orientation to novelty
  - More time looking at stimuli once oriented
  - Slower shifting when visually scanning
- At age 5 years, children born very preterm perform worse on visual search tasks (Geldof et al. 2013):
  - Slower speed of visual search
  - More difficulty with increased stimulus density
  - More difficulty with random organization of stimuli
  - Higher rate of false positive errors

Preterm Birth: Selective Auditory Attention
- Preterm infants are able to detect novel tones and discriminate between frequent and infrequent speech sounds similar to full-term controls (Therien et al., 2004).
- Differences include (Therien et al., 2004):
  - Lower amplitude EEG response (N250 wave) in the frontal-central electrodes for standard tones.
  - ERPs during infrequent speech sound presentation were observed in frontal and temporal regions compared to just frontal regions in full-term controls.
  - Did not differentiate between mother’s voice and strangers voice.
Preterm Birth: Executive Function & Working Memory

- There is a growing amount of research looking at problems with EF and working memory (Sansavini et al., 2011).
- Working memory deficits are one of the most robust findings.
  - Possibly related to slower processing speed impacting working memory (Mulder et al., 2010; Rose et al., 2011).
- Findings are more consistent across studies than in other domains of neuropsychological function.

Preterm Birth: Executive Function & Working Memory

- Children and adolescents born preterm tend to perform worse than term controls on measures of EF (Allin et al., 2008; Anderson & Doyle, 2004; Bayless & Stevenson, 2007; Bohm et al., 2004; Marlow et al., 2007; Taylor et al., 2006):
  - Inhibition
  - Shifting
  - Planning
- Parent ratings on the BRIEF generally highlight problems in (Luu et al., 2011):
  - Global Executive Function
  - Metacognition
  - Initiate
  - Working Memory

Preterm Birth: Working Memory

- Highly correlated with (Lowe et al., 2013):
  - General Cognitive Ability
  - Language
- Deficits in spatial working memory at preschool (Baron et al., 2009; Vicari et al., 2004).
- Visual working memory may be more affected than other domains of neuropsychological function (Nosarti & Froudist-Walsh, 2016).
- Problems with verbal working memory (Aaronoudse-Moens et al., 2009; Clark & Woodward, 2010):
  - Not observed until school-age
  - More evident under high-level demands
Preterm Birth: Working Memory & Plasticity

• Hippocampal volume at term age equivalent is associated with working memory performance in children born extremely preterm by age 2 years (Beauchamp et al., 2008).

• Neonatal injury to the thalamus and striatum that is visible on imaging is predictive of working memory performance by age 7 years (Omizzolo et al., 2014).

• Damage to the thalmo-cortical and cortico-striatal networks results in preservation of major network connections at the expense of smaller network connections (Karolis et al., 2016).

Preterm Birth: Working Memory & Plasticity

• Menegaux et al. (2017) studied working memory in adults who had structural brain injury diagnosed in the neonatal period on imaging:
  – Greater integrity of the splenium of the corpus callosum results in better WM performance in adults born preterm.
  – Adults born preterm with volumetric reductions of the cingulum bundle, demonstrated:
    • Reduced activation of the frontoparietal network during working memory tasks (i.e., 3-back).
    • Increased activation of the insula and surrounding perisylvian regions on harder tasks.
    – This correlated with greater injury to the cingulum and better performance on WM tasks.

Visual Perception
Preterm Birth: Visual Perceptual Skills

• Visual impairment secondary to retinal injury and cortical injury is common (Holmstrom & Larson, 2013).

• Performance of adolescents born very preterm on the Test of Visual Perceptual Skills, 3rd edition was significantly worse than term controls across all subtests (Molloy et al., 2013).
  – These findings remained after excluding adolescents born preterm with visual acuity impairments and IQ < 70.

| Subtest                  | n (V/L) | Mean Difference 0-25 | Mean Difference 26-49 | Mean Difference 50+
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual discrimination</td>
<td>7-18</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
<tr>
<td>Spatial relation</td>
<td>8-12</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
<tr>
<td>Figure sample</td>
<td>8-12</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
<tr>
<td>Visual closure</td>
<td>8-12</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
<tr>
<td>Visual closure</td>
<td>8-12</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
<tr>
<td>Total score</td>
<td>8-12</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
<td>-3.4 (0.45)</td>
</tr>
</tbody>
</table>

Perinatal Brain Injury

Learning & Memory

Preterm Birth: Visual Memory

• Recognition memory for faces and geometric patterns in preterm vs. full-term infants at 5, 7, and 12 months (Rose et al., 2001):
  – Preterm infants had marginally lower novelty scores for faces at 5 and 7 months.
  – Preterm infants had marginally lower novelty scores for patterns at 5 and 7 months.
  – At 12 months, preterm infants demonstrate significantly lower novelty scores for patterns, but marginally better novelty scores for faces.
Preterm Birth: Visual Memory

- Worse performance in adolescents born preterm (Molloy et al. 2014).
  - These differences persist after controlling for FSIQ < 70; neurosensory disabilities; impairments in visual acuity, visuoperception, and visual motor integration.

Table 19. Visual learning and Memory Outcome Controlled Between PVL/GE and Control Group - Continuous Raw Scores

<table>
<thead>
<tr>
<th>Test variable</th>
<th>Mean (SD)</th>
<th>Control</th>
<th>Mean difference (CNS)</th>
<th>F HSQ</th>
<th>Adjusted mean (CNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Learning</td>
<td>27.77 (15.77)</td>
<td>49.54 (24.45)</td>
<td>( -17.8 ) (12.84)</td>
<td>0.05</td>
<td>41.76 (15.65)</td>
</tr>
<tr>
<td>Visual Memory recognition</td>
<td>30.33 (15.72)</td>
<td>52.29 (24.43)</td>
<td>( -21.96 ) (12.84)</td>
<td>0.00</td>
<td>44.25 (15.65)</td>
</tr>
<tr>
<td>Visual Memory recall</td>
<td>30.33 (15.72)</td>
<td>52.29 (24.43)</td>
<td>( -21.96 ) (12.84)</td>
<td>0.00</td>
<td>44.25 (15.65)</td>
</tr>
<tr>
<td>Visual memory total score</td>
<td>68.83 (15.72)</td>
<td>126.26 (24.43)</td>
<td>( -80.43 ) (12.84)</td>
<td>0.00</td>
<td>81.71 (15.65)</td>
</tr>
</tbody>
</table>

Preterm Birth: Verbal Memory

- Preterm adolescents perform worse on measures of (Taylor et al., 2004a):
  - Verbal Learning*
  - Verbal Recognition *
  
  *Effect size is small
  *Most of the difference appears to be driven by the <750 g group.

- No significant differences in delayed verbal recall are observed among preterm adolescents (Taylor et al., 2004a).
Preterm Birth: Foundational Language

• During the first 12 months of life, preterm infants demonstrate (Bozzette et al., 2007; Salerni et al., 2007):
  – Less vocalizations
  – Less synchronization between vocalizations and motor movements
  – More maternal initiatives

• Between 12 and 18 months of life, preterm infants demonstrate (D’Odorico et al., 2011; Van Noort-van der Spek et al., 2010):
  – Less babbling complexity
  – Less phonological complexity of early verbal productions

Preterm Birth: Language

• Many research studies have demonstrated “catch-up” in expressive and receptive lexicons adolescence among those born preterm (Luu et al., 2011; Myers et al., 2010).

• Confrontation naming in adolescence is commensurate with term born controls (Taylor et al., 2004b).

• Worse performance in adolescents on measures of (Taylor et al., 2004a, 2004b):
  – Word Fluency*
  – Synonym production*
  – Pragmatic Language*

*Effect sizes are small.
*Performance decreases with birth weight.

Preterm Birth: Language

• Shorter Mean Length Utterance (MLU) has been observed in children born very preterm and is highly correlated with (Sansavini et al., 2006, 2010):
  – Sex (males < females)
  – Lower maternal level of education

• Predictors of language impairment in later childhood and adolescents (Briscoe et al., 1998; Woodward et al., 2009):
  – Shorter MLU at age 36 months
  – Small expressive lexicon at 36 months
  – Small receptive lexicon at 36 months

• Persistent problems with semantic knowledge and syntax (Van Noort-van der Spek et al., 2012).
Neurosciences Intensive Care Nursery (NICN)
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Co-Directors: Frances Northington, Thierry Huisman, Carl Stafstrom

Study on Perinatal Recovery and OUTcome (SPROUT)
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Liz Cristofalo    Mary Leppert         Ananya Sarkar
Jessica Otto      Natasha Ludwig       Tyneira Terry
Becky Dorner      Frances Northington  
Paul Fine          Sarah Perl
Krysten Garcia    Katie Raja