IMPACT OF PRETERM BIRTH ON THE INFANT BRAIN

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STATEMENT OF INTERESTS

Suzann Campbell is a co-developer of the Test of Infant Motor Performance (TIMP) and Managing Partner of Infant Motor Performance Scales, LLC, the publisher of the TIMP.

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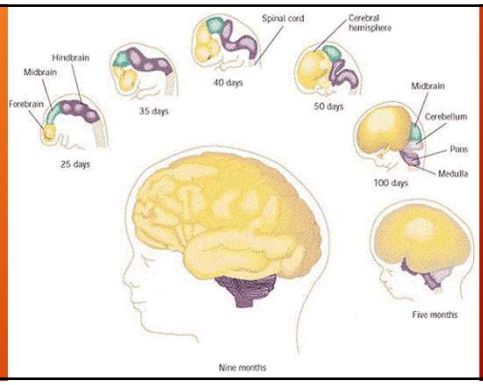
OBJECTIVES: Learner will be able to---

1. Discuss the impact of preterm birth on the infant brain.
2. Describe the positive and potentially negative effects of brain plasticity as a basis for early intervention in the young infant.



BRAIN DEVELOPMENT

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- Brain development begins with a complex process of
  - Neural cell generation
  - Differentiation, and
  - Migration
- Followed by neuronal axonal growth,
- Synaptic formation, myelinization of axons, and
- Experience-driven pruning of synapses and axons to sculpt neuronal circuits.
  - Mottahedin et al Frontiers Cell Neurosci 2017, Hadders-Algra Dev Med Child Neurol 2018

EFFECTS OF NEUROINFLAMMATION

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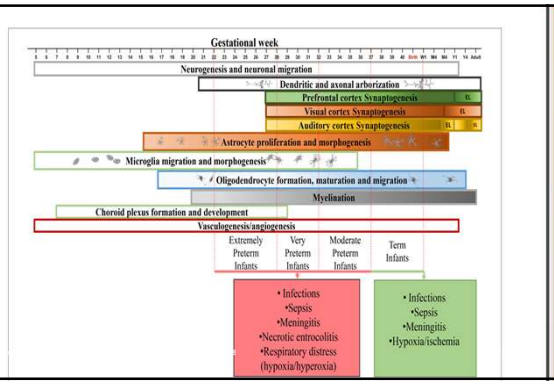
- In the presence of preterm birth, neuroinflammation disrupts the normal process and can lead to over- or under-pruning and circuit disruption
  - Mottahedin et al Frontiers Cell Neurosci 2017, Matas Psychopath 2016



MORTALITY AND MORBIDITY FOLLOWING PRETERM BIRTH

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- Although survival rates around the world vary with resources, mortality in this group in the U.S. is now only about 10%. Nevertheless surviving infants have high rates of disability, around 40%, which have not decreased significantly.
- Although the overwhelming emphasis on early identification of disability is on cerebral palsy (CP), it is less prevalent than other disabling conditions in the most at-risk group of infants born extremely preterm, i.e., at less than 28 weeks gestational age (GA).
  - Rogers & Hintz Sem Perinatol 2016

ASSOCIATIONS WITH NEURODEVELOPMENTAL OUTCOMES

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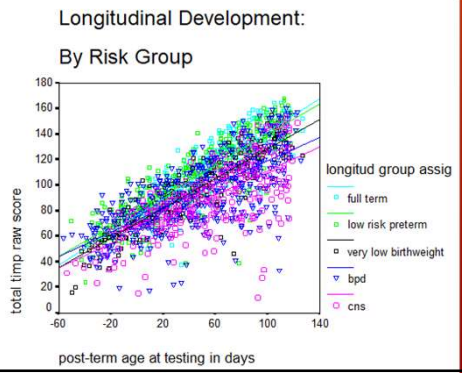
- Neurodevelopmental outcomes are associated with
  - Perinatal variables such as GA at birth, clinical stability, medical comorbidities, and acquired brain injury
  - Postnatal complications such as prolonged need for tube feeding or oxygen as well as genetics, family SES, and access to developmentally supportive therapeutic interventions
    - Rogers & Hintz Sem Perinatol 2016

TEST OF INFANT MOTOR PERFORMANCE SCORES BY RISK GROUP AND AGE



WHICH ARE THE HIGHEST INCIDENCE DISABILITIES FOLLOWING EXTREMELY PRETERM BIRTH?

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- Cognitive and behavioral disability
  - Developmental quotients average 5-17 points below peers; more than half have diagnosed moderate to severe disability
  - Autism spectrum disorder in 25%
  - 4 times the risk of attention deficit/hyperactivity disorder
  - Emotional disorders in 9%
- Note that many of these conditions are not identifiable in early infancy.
  - Rogers & Hintz Sem Perinatol 2016

WHICH ARE THE HIGHEST INCIDENCE DISABILITIES FOLLOWING EXTREMELY PRETERM BIRTH?

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- Sensorimotor disability
  - Cerebral palsy in 15%
  - Developmental coordination disorder rate much higher than the 5-6% incidence in the general population
  - Hearing impaired in 4%
  - Visual impairment in 2%
  - Sensory processing dysfunction in 40%
- Note that most of these conditions can be identified in early infancy.
  - Rogers & Hintz Perinatol 2016, Hadders-Algra Dev Med Child Neurol 2018

TAKE-HOME POINT: ASSESSMENT STRATEGIES MUST BE TARGETED

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- Infants born preterm are at risk for a variety of motor, cognitive, and behavioral disabilities.
- Assessment strategies should be tailored to the types of outcomes expected and the timeline within which each can be identified.
- Follow-up with age corrected for prematurity for prolonged periods of time is necessary.
- More emphasis should be placed on defining and measuring functional abilities of significance to families rather than reporting only dichotomous outcomes like impaired/not impaired.

FRONTIERS IN MEDICAL MANAGEMENT

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- Evidence from research has resulted in advances in management of pulmonary and visual impairment and in reduction of mortality in especially vulnerable populations
- Current emphasis is on neuroprotection and preventing the secondary damage caused by inflammatory responses of the immune system to brain injury.

FRONTIERS IN MEDICAL MANAGEMENT

- For example, one of the outstanding successes of contemporary neonatology is head cooling for reducing disability caused by hypoxic-ischemic encephalopathy (HIE) in term infants.
  - Johnston, Fatemi, Wilson, Northington Lancet Neuro 2011; Pillers J Perinatol 2017
- Success resulted in attempts to apply to infants born preterm but less successful
  - Herrera & Bidegain Earl Hum Dev 2018
- Most successful prenatal medical intervention is fetal brain protection by magnesium sulfate
  - Chollat et al Front Neurol 2018, Shepherd et al Cochrane Rev 2017

FRONTIERS IN MEDICAL MANAGEMENT

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- The frontier in animal studies and early clinical trials is in attempts to identify additional means for positively influencing neural plasticity.
  - Kaur et al J Neuropathol Exp Neurol 2017, Perlman Clin Ther 2006, Shiow et al Glia 2017

TAKE-HOME POINT: FRONTIERS IN PHYSICAL THERAPY RESEARCH

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- We must be prepared to participate in evaluating the effects of these new neuroprotective medical therapies on impairment, functional activity, and participation,
- AND evaluate the ability of our therapeutic intervention to contribute to improved outcomes when used in conjunction with these pioneering medical neuroprotective strategies.

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NEUROPLASTICITY DEFINED

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- Neuroplasticity is the dynamic biological capacity of the CNS to undergo
  - Maturation
  - Change structurally and functionally in response to experience, and to
  - Adapt to injury
- Achieved by modulating subsets of genetic, molecular and cellular mechanisms that influence the dynamics of synaptic connections and neural circuitry formation culminating in gain OR loss of function.
  - Ismail et al Eur J Paediatr Neurol 2017

PATTERNS OF NEUROPLASTICITY

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- Developmental plasticity
- Adaptive (experience-dependent) plasticity, for example, following intense motor skill training
- Reactive plasticity to pre- and postnatal CNS injury
- Excessive plasticity as in overuse injury
- Plasticity inducing brain vulnerability (HIE)

PATTERNS OF NEUROPLASTICITY 1

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- Developmental plasticity, typical
  - Neurogenesis, synaptogenesis and synaptic pruning are the building blocks of normal neuroplasticity.
  - Genetically programmed with critical or sensitive periods during which the brain is most amenable to change.

PATTERNS OF NEUROPLASTICITY 2

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- Adaptive (experience-dependent) plasticity
  - Re-organization that promotes or improves adaptive function in response to intervention, such as intensive motor skill training
  - Subserved by integrated mechanisms involving axonal and dendritic spine growth and bouton formation, dendrite sprouting, and synapse formation and elimination.
  - Changes in receptors are associated with memory formation which is enhanced in the immature brain.
  - New learning is stored in synaptic networks that are dynamic over time.

EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO NEUROPROTECTION

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- NIDCAP for—
- Infants born preterm between 28 and 33 weeks, no known developmental risk factors
  - Better development of frontal and occipital brain regions
  - Better Bayley II performance
    - Als et al Pediatr 2004

EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO NEUROPROTECTION

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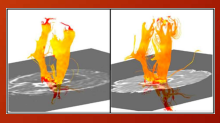
- NIDCAP for—
- INTRAUTERINE GROWTH RETARDATION
  - Better development of bi-hemispheric connections and occipital regions involved in visual processing
  - Better pull-to-sit and attention performance
    - Als et al J Perinatol 2012



EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO NEUROPROTECTION

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- PARENT SENSITIVITY TRAINING
  - Mother-infant Transaction Program to reduce stress
    - Improved white matter microstructure
    - No effect on total brain volume
    - No effect on medical outcomes
    - Milgrom et al Pediatr Res 2010
  - Family Nurture Intervention to calm
    - Increased EEG power
    - Welch et al Acta Paediatr 2017

PATTERNS OF NEUROPLASTICITY 3

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- Reactive plasticity following deprivation or CNS injury
  - Development of "work around" inter- and intra-cortical connections in response to injury, albeit with impaired structure and function.
  - Recovery differs by brain region: fine motor control and speech are less amenable to reactive plasticity.
  - Recovery from perinatal brain insult differs depending on
    - Timing of insult relative to PMA: corticospinal tract particularly susceptible in third trimester
    - Stage of neurodevelopment in which insult occurs: periventricular area in infant born before 34 weeks GA, basal ganglia and cortical infarct more common in mature infant
    - Integrity of plasticity mechanisms

EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO PRETERM BIRTH

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- In 47 infants born before 33 weeks of gestation but without brain injury, more extreme prematurity was associated with increased functional connectivity between the thalamus and the lateral primary sensory cortex and reduced connectivity between the thalamus and cortex in prefrontal, insular and anterior cingulate regions.
- What does this mean?
  - Toulmin et al PNAS 2015

EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO PRETERM BIRTH

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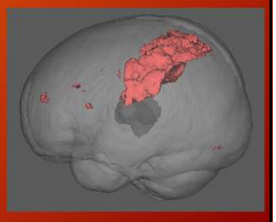
- The lateral parietal cortical network is involved in processing sensory signals from face, lips, jaw, tongue and throat, engendering the hypothesis that early exposure to oral feeding may serve to increase functional connectivity to these regions of cerebral cortex



EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO PRETERM BIRTH

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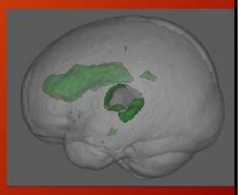
- The networks with reduced connectivity are those supporting executive, integrative and cognitive functions (including attachment behaviors) which may be related to the various cognitive and behavioral impairments common in infants born preterm.
- Lesions in afferent projections may correlate better with motor dysfunction than damage to corticospinal tract.
  - Toulmin et al PNAS 2015, Ismail et al Eur J Paediatr Neurol 2017, Matas et al Psychopathol 2016, Madhavan et al J Mag Reson Imaging 2014



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EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO BRAIN INSULT

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- A second example is development of the corticospinal tract (CST) in infants who have hemiplegia as a result of a neonatal stroke.
- Under normal circumstances, descending CST fibers on the ipsilateral side regress and become non-functional.
  - Staudt J Anat 2010, Madhavan et al J Mag Reson Imaging 2014

EXAMPLE OF NEUROPLASTICITY IN RESPONSE TO BRAIN INSULT

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- In the presence of neonatal stroke, ipsilateral fiber tracts are sustained and functional, but contribute to poor use of paretic hand and cause mirror movements on the less involved side in children with hemiplegia.
- If insult occurs after competitive loss of ipsilateral tracts, useful hand function is unlikely to be spared.
  - Staudt J Anat 2010, Madhavan et al J Mag Reson Imaging 2014

PATTERNS OF NEUROPLASTICITY 4

- Excessive/destabilizing
  - Overuse syndromes such as focal task-specific dystonia in musicians or writers
- Virtually never seen in children

PATTERNS OF NEUROPLASTICITY 5

- Excitotoxicity following HIE
  - Brain energy crisis with age-dependent vulnerability of excitatory glutamate neurotransmitters is a mechanistic pathway for extending neural damage alongside ischemia-induced inflammation, mitochondrial damage and oxidative stress
- Associated with seizures

TAKE-HOME POINT: NEUROPLASTICITY MECHANISMS AND OUTCOMES VARY

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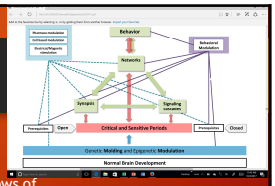
- It is important to remember that plasticity responses are not always beneficial.
- Interventions adopt multiple strategies for success
  - Neuroprotective strategies aim to prevent maladaptive responses to injury.
  - Interventions to promote development aim to improve functional performance through promoting experience-dependent neuro- AND musculoskeletal plasticity.

TIME-SENSITIVE HEIGHTENED PLASTICITY RESPONSES



- Sensitive periods of brain development create "windows of opportunity" for neuromodulatory interventions that augment plasticity responses and potentially improve clinical outcomes.
- Examples of behavioral neuromodulation interventions include
  - Physical therapy and occupational therapy programs
  - CIMT for hemiplegia; combined with transcranial stimulation
  - Cognitive and behavioral interventions, including parent education

TIME-SENSITIVE HEIGHTENED PLASTICITY RESPONSES

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- Sensitive periods of development have been identified for interventions for visual and hearing impairments, but we as movement specialists should be responsible for identifying these periods with motor developmental significance.
- We are only beginning to define which early motor interventions are effective, but continued research is needed to identify when, and at what dosages, these can be most effective.

TIME-SENSITIVE HEIGHTENED PLASTICITY RESPONSES

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- Furthermore, research is needed to improve the ability of families to commit to the requirements of challenging exercise programs in order to increase compliance for greatest effectiveness.
  - Medine-Mirapeix et al Eur J Phys Rehabil Med 2017
- Families should be involved in research to assist in identifying the information and functional outcomes of most importance to them.
  - Rogers & Hintz Sem Perinatol 2016

CONSIDERATIONS WHEN CONTEMPLATING ASSESSMENT AND INTERVENTION IN THE NICU

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- Protection of the fragile infant
- Sensitive periods for enhancing neuroplasticity
- Family empowerment
- Evidence from well-designed and executed controlled clinical trials
- Identification of the individual Infant's skills and challenges
  - GA at birth; current CA
  - Co-morbidities
  - MRI results, chronic lung disease
  - Functional activity performance