Long-term outcomes of traumatic brain injury in infancy and early childhood

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Objectives for presentation

• To summarize research concerning long-term outcomes of TBI in infancy and early childhood.
• To describe recent non-human animal and human research regarding the outcomes of early TBI
• To discuss practical implications of research on early TBI for clinical neuropsychologists
Why study pediatric TBI?

- #1 cause of pediatric death and disability in U.S.
- Annual incidence: 200-300 head injuries/100,000 children
- Annual economic cost of pediatric TBI in the U.S. = $7.5 to $10 Billion
Why be concerned about early TBI?

Figure 2. Average Annual Traumatic Brain Injury-Related Rates for Emergency Department Visits, Hospitalizations, and Deaths, by Age Group, United States, 1995–2001

Children, older adolescents, and adults ages 75 years and older are more likely than others to sustain a TBI.
“Accidents” do happen!

But can we explain outcomes?
Is a younger brain a better brain?

Effects of age-at-injury on recovery and outcome
Case example: 3 year old, penetrating TBI

Acute

10 yrs post
Progressive cognitive decline relative to age

- Chronological Age
- Mental Age (WPPSI-R/WISC-III)
- Receptive Language (PPVT-R)
- Visuo-Motor Integration (VMI)
- Memory (Sentences/DS)

Mental Age (years) vs. Time since insult (yrs)
Progressive developmental gap

Time post injury

<table>
<thead>
<tr>
<th>M.A.C.A (months)</th>
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<tbody>
<tr>
<td>Late HI</td>
</tr>
<tr>
<td>Early HI</td>
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</tbody>
</table>

-4 mths 24 mths
Differences in recovery

Longitudinal Composite IQ Scores by Age and Severity of Brain Injury

Ewing-Cobbs, Barnes, & Fletcher, Developmental Neuropsychology, 2003
No long-term improvement in IQ

Anderson et al., *Brain*, 2004
Progressive lag in academic achievement

Ewing-Cobbs et al., Developmental Neuropsychology, 2004
What about long-term outcomes?

- Few studies lasting into adulthood
- Research challenges
  - Retrospective designs
  - Measurement of severity
  - Selective attrition
  - Non-standardized outcome measures
- Nonetheless, bulk of evidence shows poor outcomes for young children with severe TBI
Asikainen et al., *Brain Injury*, 1996

- 496 S with TBI, followed for at least 5 years, admitted to rehabilitation program
- Age at injury correlated with outcome
  - S aged 7 yrs or less at time of injury suffered severe disability as measured by Glasgow Outcome Scale more often than older age groups
  - Less capable of independent employment than children injured at 8-16 years of age
Cattelani et al., *Brain Injury*, 1998

- 20 adults (ages 18-29) initially referred for TBI between 8 and 14 years of age
- IQ scores in low-average to average range
- On GOS
  - 20% severe disability
  - 25% moderate disability
- Social maladjustment prominent
Klonoff et al., *J Neurol Neurosurg Psychiatry*, 1993

- 23-year follow-up of 159 adults with mean age at injury of 8 years
  - Injuries relatively mild
- Composite measure of neurological status best predictor of outcome
  - Post-acute IQ also was reliable predictor
- Unemployment rate low (4%)
- 30% report leisure restricted
Jonsson et al., *Brain Injury*, 2004

- 8 patients with severe TBI, mean age of injury at 14 years, assessed at 1, 7, and 14 years post injury
- Verbal IQ declines over time
- Poor attention and working memory
- Verbal learning most impaired
Koshkiniemi et al.,
Arch Pediatr Adolesc Med, 1995

• 39 children with severe brain injury at less than 7 years of age, evaluated in adulthood (> 21 years of age)
• Only 59% able to attend typical school
• IQ low-average to average in 70% (mean 85)
• IQ and injury severity predict outcomes
• Only 23% able to work full-time
  - 0% if injured < 4 years of age
Nybo et al.,
*J Inter Neuropsych Soc.,* 2004

- 27 children with severe TBI < 7 years of age, evaluated in later adulthood (mean 40 years), from Koshkiniemi et al.
- 89% independent in ADLs
- 33% working full-time
  - 74% unchanged in vocational status
- Cognitive flexibility (CANTAB Intradimensional/Extradimensional Shift Test) predicted full-time employment
Prospective study of birth cohort

Examined effect of mild head injury < age 10
  - Divided according to outpatient/inpatient treatment
  - Compared to non-injured cohort

Inpatients show increased inattention and conduct disorder at ages 10 to 13
  - Most often apparent in those injured before age 5

No clear effects for cognitive/academic measures
Anderson, Newitt, & Brown (unpublished)

- Long-term functional outcome in adults following childhood TBI
  - Retrospective study of adults with a history of mild/moderate and severe TBI in childhood
  - Issues investigated: education, employment, relationships and social skills, leisure, mental health
Sample inclusion criteria

• 2-16 years at time of injury
  - Diagnosis of traumatic brain injury, including period of altered consciousness

• Currently 18-30 years of age
Sample recruitment

- 251 individuals contacted
- 99 participants and parents completed study
  - Mild/moderate TBI, N = 70
  - Severe TBI, n = 30
Measures

• Demographic questionnaire
  - SES, medical and developmental history, education/employment, interventions, family/social history
  - Parent report
• NEO Personality Inventory-Revised
  - Self report
• WAIS-III
Measures

- Modified Sydney Psychosocial Reintegration Scale
  - Parent/self report
  - Domains
    - Work and leisure
    - Relationships
    - Living skills
NEO Personality Inventory - Revised

- Mean T scores for all domains in average range
- No relationships found with gender, injury severity, disability, or age at injury
Intellectual function

Mean IQ scores for Mild, Moderate, and Severe injury severity.

- VIQ
- PIQ
- FSIQ

Injury severity categories:
- Mild
- Moderate
- Severe

Mean IQ scores range from 80 to 130.
Initial conclusion

- Few deficits on standardised psychological measures (NEO, WAIS-III)
- Measures may not capture functional impairments (education, employment, psychosocial) identified in adults following childhood TBI
Educational help required post-TBI

<table>
<thead>
<tr>
<th>Injury severity</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Mild/moderate</td>
<td>0%</td>
</tr>
<tr>
<td>Severe</td>
<td>100%</td>
</tr>
</tbody>
</table>

- No help
- Tutoring
- Integration
- Special school
Educational levels post-TBI

<table>
<thead>
<tr>
<th>Injury severity</th>
<th>&lt; 12 yrs</th>
<th>12 yrs</th>
<th>Technical college</th>
<th>University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
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</tbody>
</table>
Employment status post-TBI

- **Injury severity**
  - Mild/Moderate
  - Severe

- **Percentage**
  - Unemployed
  - Unskilled
  - Skilled
  - Professional

Graph showing the percentage of employment status post-TBI for individuals with mild/moderate and severe injury severity.
Psychological problems post-TBI

![Bar chart showing the percentage of psychological problems after TBI by injury severity (Mild/Moderate and Severe). The chart indicates that the percentage of people with no psychological problems is highest in Mild/Moderate injuries, while the percentage with a psych diagnosis is highest in Severe injuries.]
Quality of life post-TBI

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean Score</th>
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<tbody>
<tr>
<td>Work/Leisure</td>
<td>Mild TBI</td>
</tr>
<tr>
<td></td>
<td>Moderate TBI</td>
</tr>
<tr>
<td></td>
<td>Severe TBI</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

- Mild TBI: Red line
- Moderate TBI: Yellow line
- Severe TBI: Green line
Final conclusion

- More severe TBI in childhood is associated with:
  - Need for more educational support
  - Poor educational achievement
  - Low employment status
  - Poor psychological function
  - Poor quality of life
  - High frequency of social isolation
Are we asking the wrong question?

- Not whether TBI matters, but for whom
- Group differences are less interesting than individual differences
  - Who has poor outcomes (and why)?
- Search for mediators and moderators of outcomes
  - Injury-related factors
  - Non-injury-related factors
Age-related differences in causes of TBI

Figure 4. Average Annual Traumatic Brain Injury-Related Rates for Emergency Department Visits, Hospitalizations, and Deaths, by Age Group and External Cause, United States, 1995–2001

Falls are the leading cause of TBI; rates are highest among those ages 0 to 4 and those age 75 and older.
Age differences in incidence & etiology

Pediatric TBI: Etiology by Age

Incidence (cases/100,000/yr)

Age group

<1 year 1-4 5-12 13-16

Other Accidental
Other Undetermined
Non-Gun Assault
Gun Assault
Transport
Fall

Durkin MS, et. al. 1998
Physiological distinctions in childhood TBI

**Biomechanics**
- Thinner skull
- Greater proportional cranial mass

**Energy metabolism**
- Increased cerebral glucose metabolism

**Vascular reactivity and autoregulation**
- Greater brain water content
- Increased susceptibility to cerebral edema

**Neurotransmission**
- Increased excitatory amino acid receptors
Changes in brain metabolism with age

**RODENT**

- Enzymatic Machinery For Glycolysis & Glucose Oxidation is Mature
- Ketone Metabolism - Nehlig 1992
- Glucose Metabolism - Nehlig 1988

**HUMAN**

- Glucose Metabolism - Chugani et al., 1987

**Birth**

- Pre-Suckling period

**Age**

- Human: Birth, .5yr, 1yr, 2yr, 3yr, 4yr, 5yr, 10yr, 15yr, 20yr, 25yr, 30yr, 35yr, 40yr, 45yr, 50yr, 55yr, 60yr
Changes in cerebral blood flow with age

Cerebral Blood Flow-Nehlig et al., 1989
Cerebral Blood Flow-Chiron et al., 1992
Fluid percussion injury model
Morris Water Maze

M.L. Prins, UCLA Division of Neurosurgery
MWM acquisition in normal development

Rates of Learning

P17: -2.7s/block
P28: -4.2s/block
Adult: -6.4s/block
Developmental plasticity & enriched environments

Enriched environment effects

- Increased cortical thickness
- Increased neuronal size
- Greater dendritic arborization
- Increased glia and capillaries
- More synapses
- Improved neurocognitive performance
- More robust effects in young animals
Concussion in developing animals: Morphology and behavior

Rat pups show no significant morphological changes or behavioral differences after experimental brain concussion.
Occipital cortical thickness increases after housing in an enriched environment, but FAILS to do so after a moderate concussive injury.

Morris water maze performance improves after enrichment, but does not do so after developmental concussion.

Fineman, Giza, et.al., J Neurotrauma, 2000
Early TBI and altered dendritic arborization

EE increases cortical dendritic branching, and developmental concussion impairs the normal dendritic response to rearing in EE.

Ip, Giza, et al., J Neurotrauma, 2002
What about humans?

• Role of family and parenting in development
  - In school-age children with TBI, family environment moderates behavioral outcomes following severe TBI
  - In preschool children, parenting is a powerful influence on social development and psychosocial adjustment

• Might the family environment, and particularly parenting, influence recovery from TBI occurring during infancy and early childhood?
Ohio preschool TBI project

- Multi-site study in 3 to 6 year old children
- Prospective recruitment of children with moderate to severe TBI and comparison group of children with orthopedic injuries.
- Longitudinal follow-up of children and families at baseline, 6 months, 12 months, and 18 months post-injury
Ohio preschool TBI project

- Study began in fall 2002
- Multiple sites
  - Children’s Hospital, Cincinnati, OH
  - Rainbow Babies and Children’s Hospital, Cleveland, OH
  - Children’s Hospital, Columbus, OH
- Investigators
  - S. Wade (PI), H. G. Taylor (Cleveland PI), K. O. Yeates (Columbus PI)
Study hypotheses

- Moderate to severe TBI adversely affects families more than OI (i.e., traumatic injuries not involving the brain)
- Pre- and post-injury parent and family characteristics predict children’s outcomes after TBI
  - Even after controlling for children’s pre-injury status and injury severity
Causal model

Mediating processes

Family burden and distress, parent-child relationships, parent coping, interventions

Predictors

Nature and severity of TBI

Pre-injury child and family status

Outcomes

Family response to injury event and its consequences

Effects of injury on child

Predictors

Nature and severity of TBI

Pre-injury child and family status

Outcomes

Family response to injury event and its consequences

Effects of injury on child
Study groups and selection criteria

- **All children**
  - Hospitalized for trauma
  - 3-6 years age at injury
  - No history of abuse or prior neurological disorder
  - English-speaking household

- **Severe TBI**
  - Blunt trauma, GCS < 9

- **Moderate TBI**
  - Blunt trauma, GCS 9-12, or GCS >12 with persistent LOC or neuroimaging abnormality

- **Orthopedic injury (OI)**
  - Fracture without evidence of CNS insult
Child measures

- Cognitive and neuropsychological skills
  - Social information processing
- Academic achievement
- Early school performance
- Social competence
- Adaptive behavior
- Behavioral adjustment
Family and parent measures

- Parent psychological distress
- Perceived family burden
- Other stressors and resources
- Parent-child interactions
  - Warmth and mutuality
- General family functioning
Future research needs

• Prospective, longitudinal designs
• Efforts to avoid selective attrition
• Neuroimaging to assess severity
• Better outcome measures
  - Social cognition
  - Emotional regulation
• Environmental moderators
  - Parenting and parent-child interactions
So what?

I was wondered were my brain was.
Implications for evaluation

• Neurobehavioral functioning after early TBI is multi-determined
  - Conventional measures of injury severity do not tell the whole story
    • Advances in neuroimaging will help
  - Evaluating expected status is difficult
    • Multiple methods and measures
  - Evaluating environmental context is important
    • Standard measures are available
Implications for evaluation

• Neurological and ecological validity of neuropsychological testing is constrained by focus on cognition
  - Poorest outcomes are psychosocial in nature
• Neuropsychological testing does not tap important aspects of functioning
  - Mental state understanding (“theory of mind”)
  - Emotion regulation
  - Emotive communication
Implications for management

- Multi-factorial model implies need for multiple levels of intervention
  - Pharmacotherapy
  - Cognitive rehabilitation
  - Educational intervention
  - Behavioral health services
  - Family support
Implications for management

• Future prospects?
  - Genetic therapy
  - Metabolic therapy
  - Peer relationships intervention
  - On-line family intervention
An ounce of prevention....