

Longitudinal Research on Two Common Brain-Related Conditions in Children: Findings and Implications



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No Conflicts to Report

Objectives

- Provide overview of reasons for research on children with brain-related conditions
- Illustrate this area of research by summarizing research on traumatic brain injury and preterm: consequences, predictors, longitudinal change
- Consider implications for clinical practice

Types of Brain Disorders

- Developmental/genetic: learning disabilities, attention deficit hyperactivity disorder (ADHD), autism, Down syndrome and other genetic disorders
- Perinatal brain insult: preterm birth, hypoxic ischemic encephalopathy, stroke, fetal alcohol syndrome
- Post-natal brain insult: traumatic brain injury, childhood-onset stroke, epilepsy, meningitis, lead exposure, brain tumors, cranial radiation for cancer

Reasons for Research

- What problems do children with brain disorders have at different ages in cognition, learning, and behavior and how do these problems evolve with age?
- Do assessments of cognitive skills help predict problems in learning, behavior, and daily functioning?
- Are some measures more sensitive to the effects of the disorder than others and thus more useful in determining subtle consequences?

- What factors should be considered in predicting outcomes? Are certain types of complications or brain injuries associated with worse outcomes, and what role do environmental factors play?
- Can treatments be developed to promote better outcomes?
- What can studies of these children tell us about brain-behavior relationships and about normal development?

Advantages of Life Course Perspective

- Focuses on evolving identities with new experiences, roles, and challenges
- Encourages study of precursors/predictors of childhood learning and behavior problems and provision of anticipatory guidance
- Provides insight into nature and origins of later-emerging problems

Principles of Research on Brain Disorders in Children

- Consistent with “life-span” approach, different outcomes and needs at different points along the way
- Developmental status is dynamic -- may be malleable but problems often persist

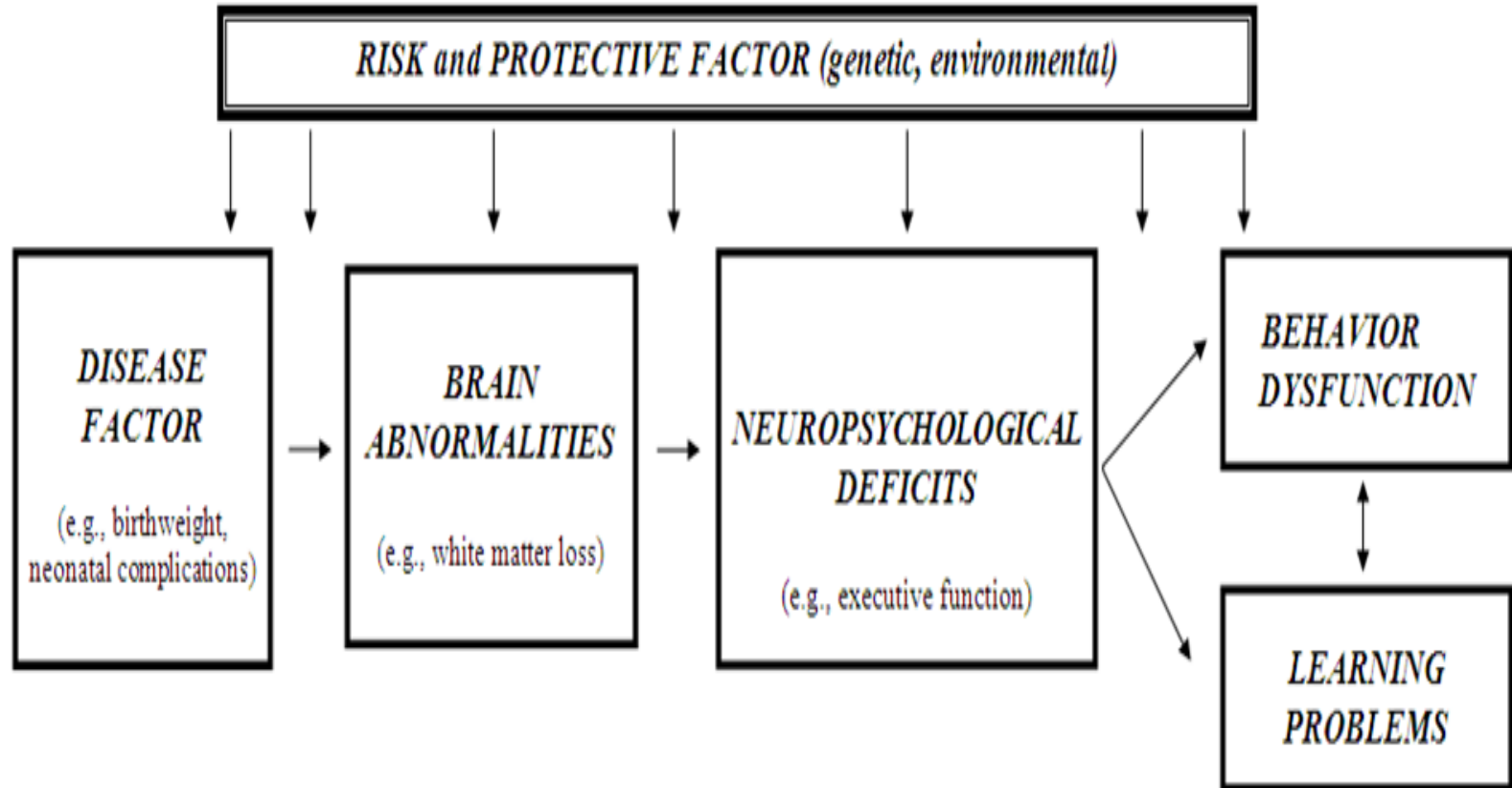


"This is the path to adulthood. You're here."

Other Principles

- Outcomes related to multiple factors: brain integrity, child traits, family and school environments
- Cognition can not be reduced to a single measure like IQ but includes multiple distinct skills
- Goals:
 - Advance understanding of the causal antecedents of problems in learning and behavior
 - Optimize outcomes

Framework for Examining Outcomes of Brain Disorders



Research Illustrations: Effects of Traumatic Brain Injury (TBI) and Preterm Birth

- Background on these conditions
- Case examples
- Findings from multiple longitudinal studies
- Clinical implications

The Need for Pediatric TBI Research

- One of the most common causes of death and long-term disability; 1.8 million in US sustain a TBI in childhood (Zaloshnja et al., *J Head Trauma Rehab* 2008;23(6), 394-400)
- Most with mild TBI but nearly 150,000 living with significant social, behavior, physical, or cognitive problems; \$60 billion in medical costs
- However, prior to 1990 there were few prior studies of long-term effects, role of the family in the child's recovery, or treatments to improve outcome

Need for Research Also Motivated by Clinical Assessments of Pediatric TBI: A Case Example

- Girl hit by car on bicycle at age 7; in coma with multiple injuries, hospitalized and in rehabilitation center for several months
- Home tutoring, then back to school for part-time for rest of grade 2, then repeated with reduced day but didn't fit in
- Continued this way through grade 3, with speech therapy and remedial help, then Developmental Handicapped program from grades 3-12

Assessment Findings

- *Parent and teacher reports:* incomplete work, short attention span, poor short-term memory and difficulty with abstract concepts, silliness, limited social interactions, exaggerated emotions, dependency, poor sense of time
- *Test results:* borderline to low average IQ, deficits in attention, motor coordination, speed of processing, executive functioning, and memory

- *Family issues:* focus on child to exclusion of others, difficulties getting others to understand child's limitations, management of child, effects on siblings, difficulties maintaining personal and family goals

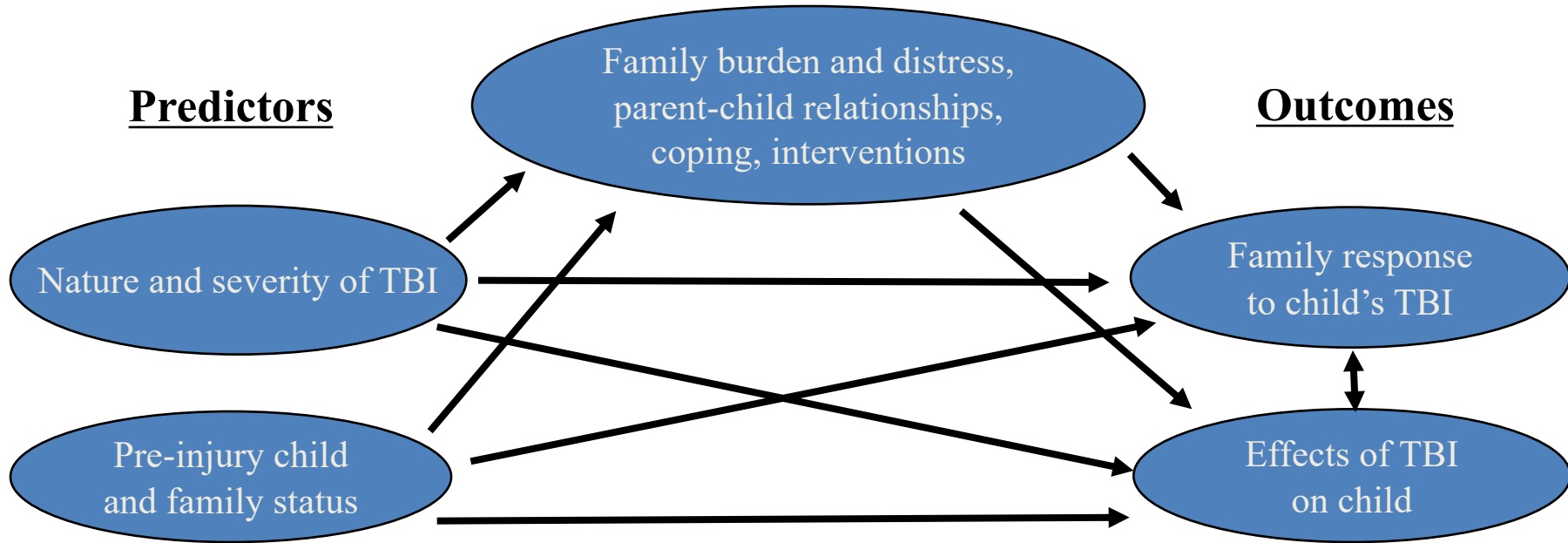


Framework for Conceptualizing Research

Mediating Processes

Predictors

Outcomes



Overview of Presentation

- Describe a long-term Ohio-based research collaboration on pediatric TBI
- List research aims of our studies and summarize major findings
- Consider clinical implications, future directions, and what our experience suggests about the research process

Credit Due to My Collaborators (partial list)

- Ohio
 - Terry Stancin (MetroHealth Medical Center, Cleveland)
 - Keith Yeates (NCH, now Alberta Children's, Calgary)
 - Shari Wade (Cincinnati Children's)
- Outside Ohio
 - Michael Kirkwood (Colorado Children's, Denver)
 - Maureen Dennis (Hospital for Sick Children, Toronto)
 - Erin Bigler (Brigham Young University, Provo, Utah)
 - Kenneth Rubin (University of Maryland)
 - Tanya Brown (Mayo Clinic, Rochester, Minnesota)

The “Ohio” Studies

1. Original follow-up of school-age children with moderate-severe TBI compared to children with orthopedic injuries (OI) from shortly after injury to 6 years post-injury
2. Second follow-up of younger (3- to 7-year-old) children with moderate-severe TBI compared to children with OI from shortly after injury to 7 years post-injury
3. Third, cross-sectional study of social outcomes in school-age children with moderate-severe TBI compared to children with OI 1-5 years post-injury

Aims of Studies of Mod-Sev TBI

- Determine effects of pediatric TBI on the family
- Examine association of measures of the family environment on the child (including family burden and stress related to the child's injury)
- Evaluate changes in the child and family over time post-injury and the factors associated with these longitudinal changes

The “Ohio” Studies -- Continued

4. Two follow-up studies of children with mild TBI/concussion compared to OI from shortly after injury to 1 year post injury (first study on course and correlates) or to 6 months post-injury (second study on early predictors)*
5. Series of multiple RCTs to determine efficacy of online family problem solving therapy (plus access to internet resources) compared with internet resources only for improving child behavioral and family outcomes

Aims of Studies of Mild TBI Concussion

- Describe the natural history of PCS following mild TBI using multi-method, multi-informant measurement
- Examine injury characteristics and non-injury child and family factors associated with PCS
- Explore consequences and early predictors of persistent PCS

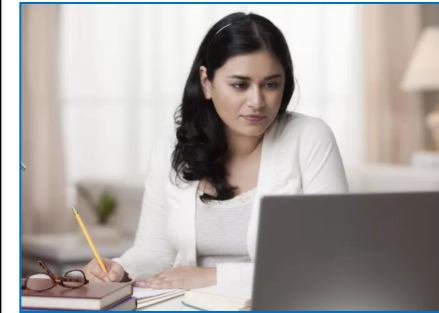
Aims of Online Therapy Studies

- Help children and families cope with adverse effects of moderate-severe TBI using online therapy
- Determine if the online therapy is more effective than providing families with access to online resources only
- Examine both immediate effects of therapy and maintenance over time after completion of therapy
- Identify factors associated with positive response to therapy

Two Conditions Compared in Online Family Problem Solving Therapy RTCs



Online Family Problem Solving Therapy



Internet Resources Only

Online Family Problem Solving

- 7-10 core sessions and 4 supplemental sessions
- Initial face to face meeting with therapist
- Subsequent meetings via videoconferencing
- Each session has 2 components:
 - A self-guided web module
 - A synchronous session with the therapist

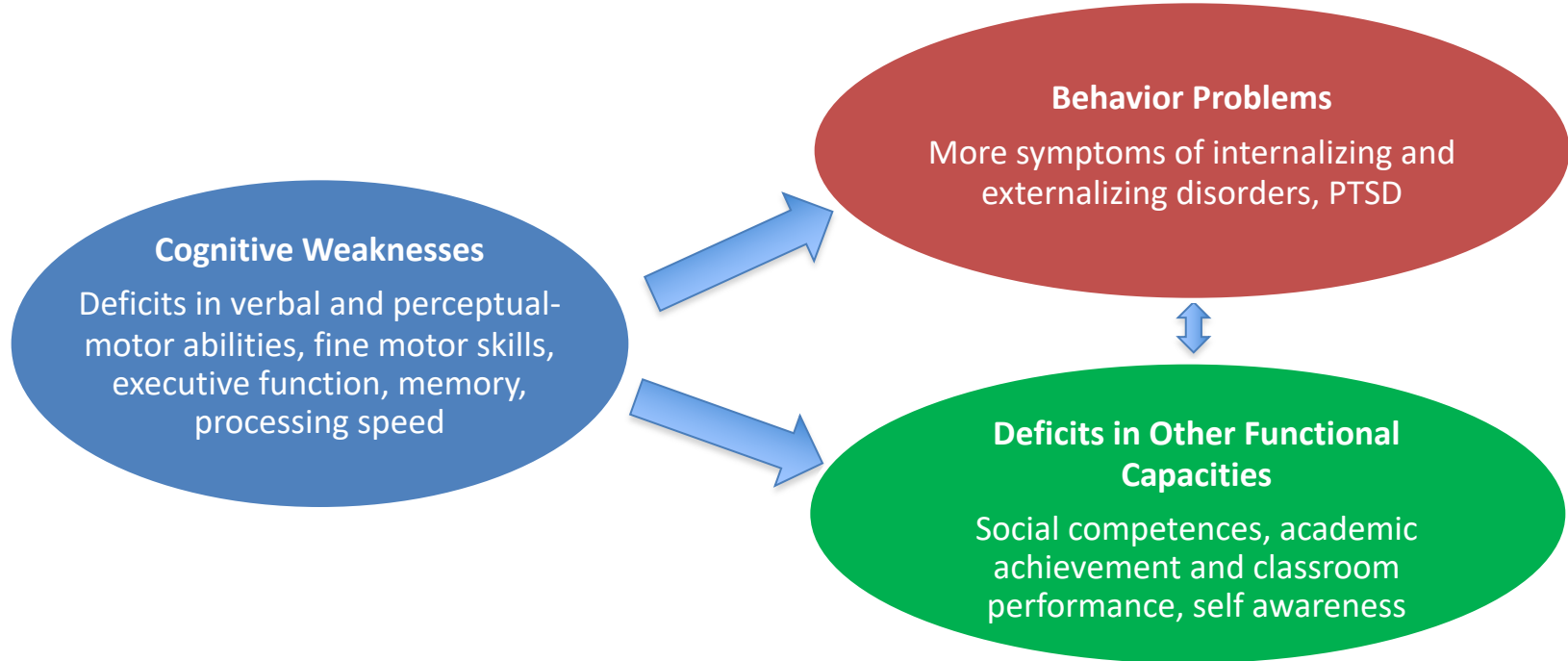
Core Intervention Modules

- Setting Goals
- Staying Positive and Handling Stress
- Solving Problems and Getting Organized
- Staying in Control (Self-Regulation) and Controlling Anger
- Verbal and Nonverbal Communication
- Social Behavior and Problem Solving
- Taking Care of You

What We Learned About Mod-Sev TBI:

1) Children are adversely affected in multiple ways

(Treble-Barna et al., *J Neurotrauma*, 2017)



Adverse Effects on the Child

Cognitive weaknesses



Poor school performance



Social isolation

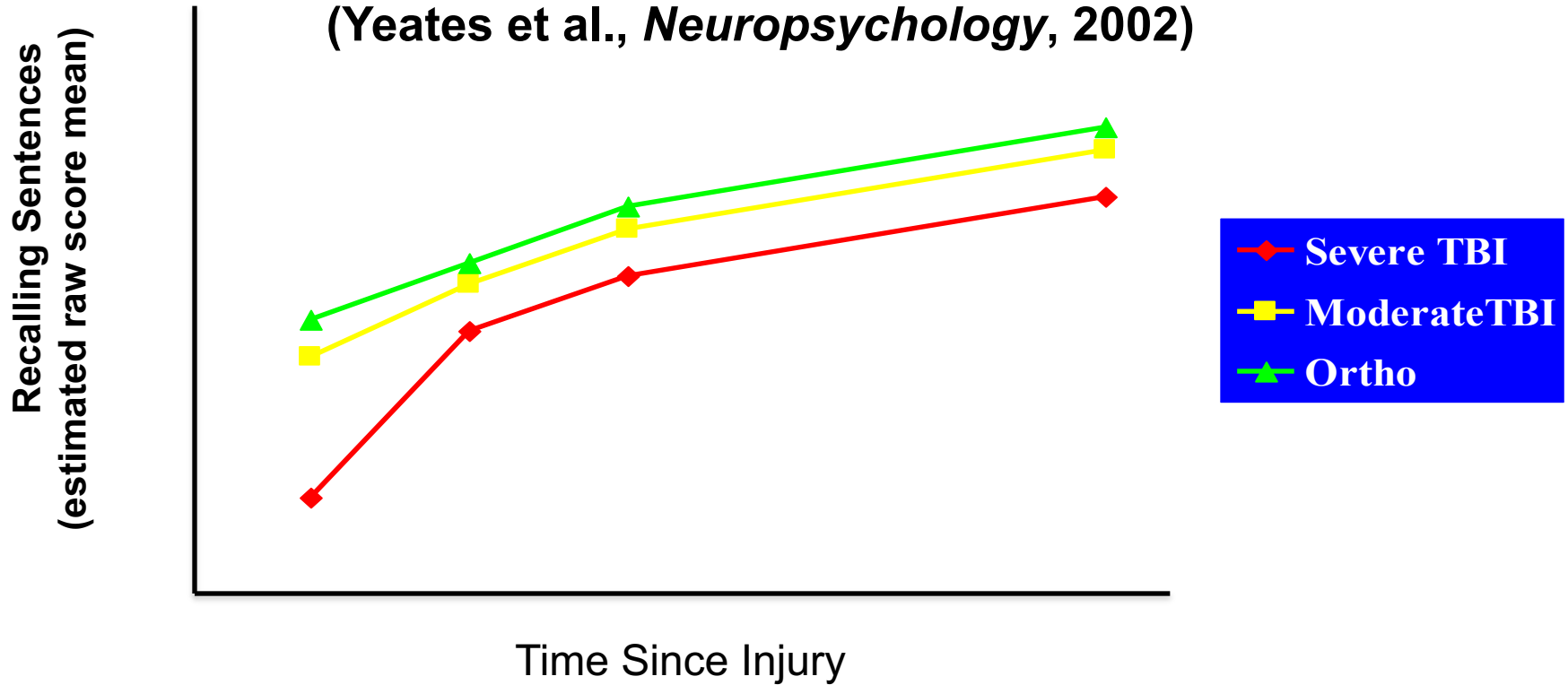


Behavior problems



2) Effects persist – “recovery” of immediate memory

(Yeates et al., *Neuropsychology*, 2002)



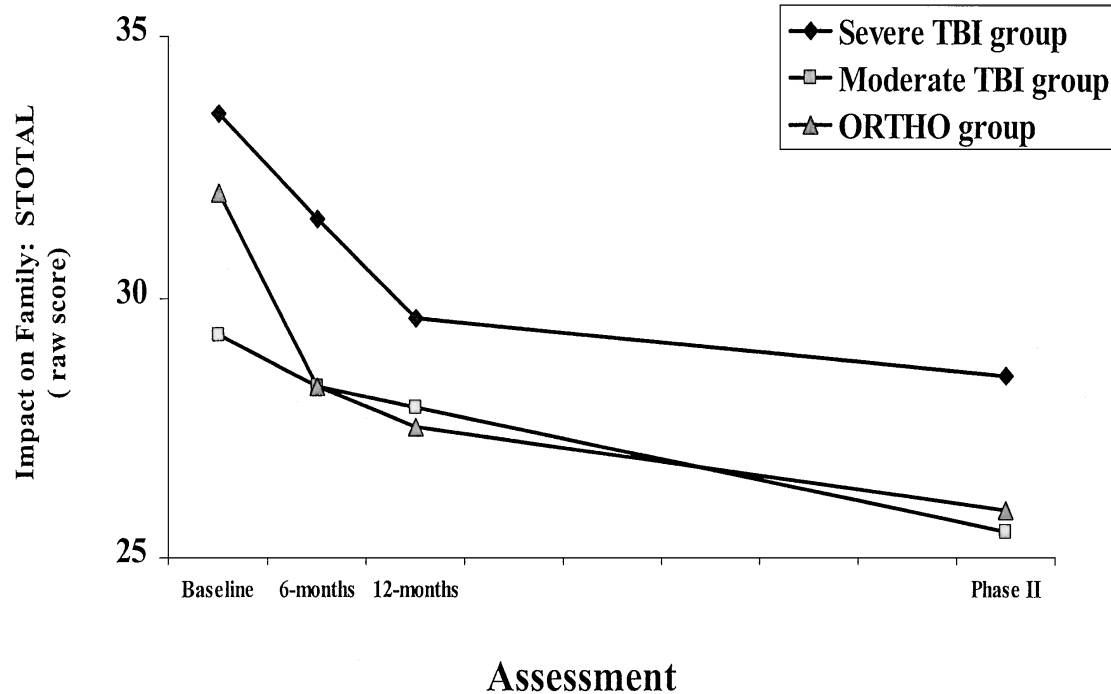
3) Adverse effects on child are associated with multiple factors

- Worse outcomes for children with pre-injury behavior problems, severe TBI, sleep problems, other injuries
- Better outcomes with increasing time post injury (recovery) and for children with higher pre-injury IQ (cognitive reserve)
- Some consequences differ for boys and girls
- Evidence for moderating effects of genetic factors (with focus on dopamine-related and inflammatory genes)

4) Families are adversely affected

- More family burden – caregiver stress related to factors such as concerns regarding child's behavior problems and future, reactions of others to injury, sibling adjustment
- More self-reported caregiver psychological distress
- More family dysfunction -- conflict, communication problems, lack of support
- These adverse effects persist in many families

Group Differences in Negative Family Impact Across Follow-up (Wade et al., *J Head Trauma Rehabil*, 2002)



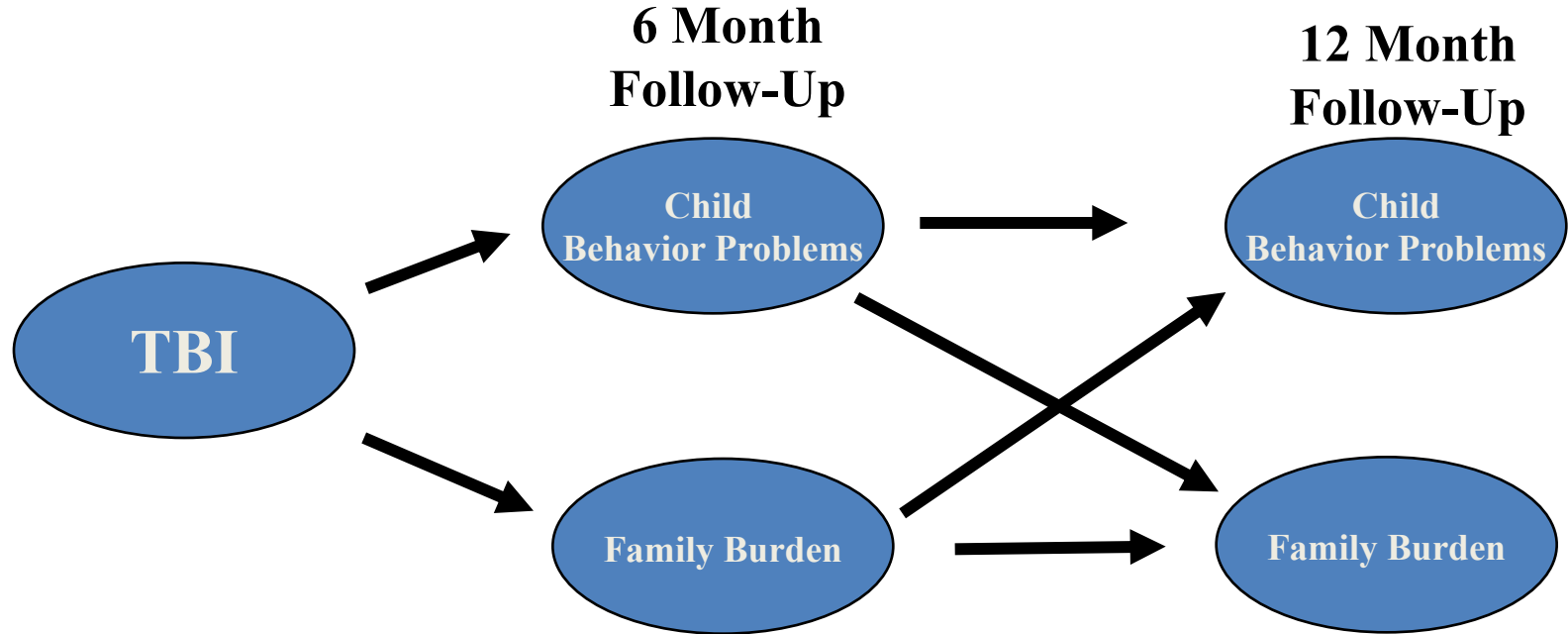
5) Adverse effects on family are related to family characteristics

- Coping style: better with acceptance; worse with denial and active coping
- Lower SES
- Fewer interpersonal resources
- More interpersonal stressors

6) Family factors are related to poorer child outcomes

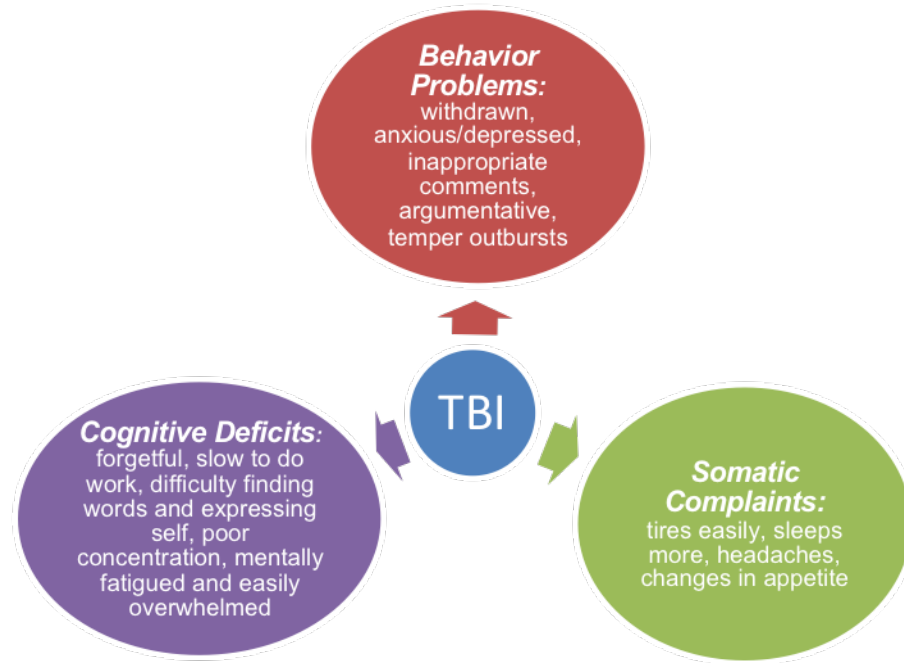
- Lower family SES
- Lower caregiver interpersonal resources and more interpersonal stressors
- Less “sensitive” parenting (warm responsiveness)
- Permissive or authoritarian parenting style
- Injury-related family burden

7) Associations of Child and Family Outcomes are Bidirectional (Taylor et al., *J Int Neuropsychol Soc*, 2001)



What We Learned About Mild TBI:

1) Mild TBI is associated with different types of PCS (Ayr et al., *J Int Neuropsychol Soc*, 2009)



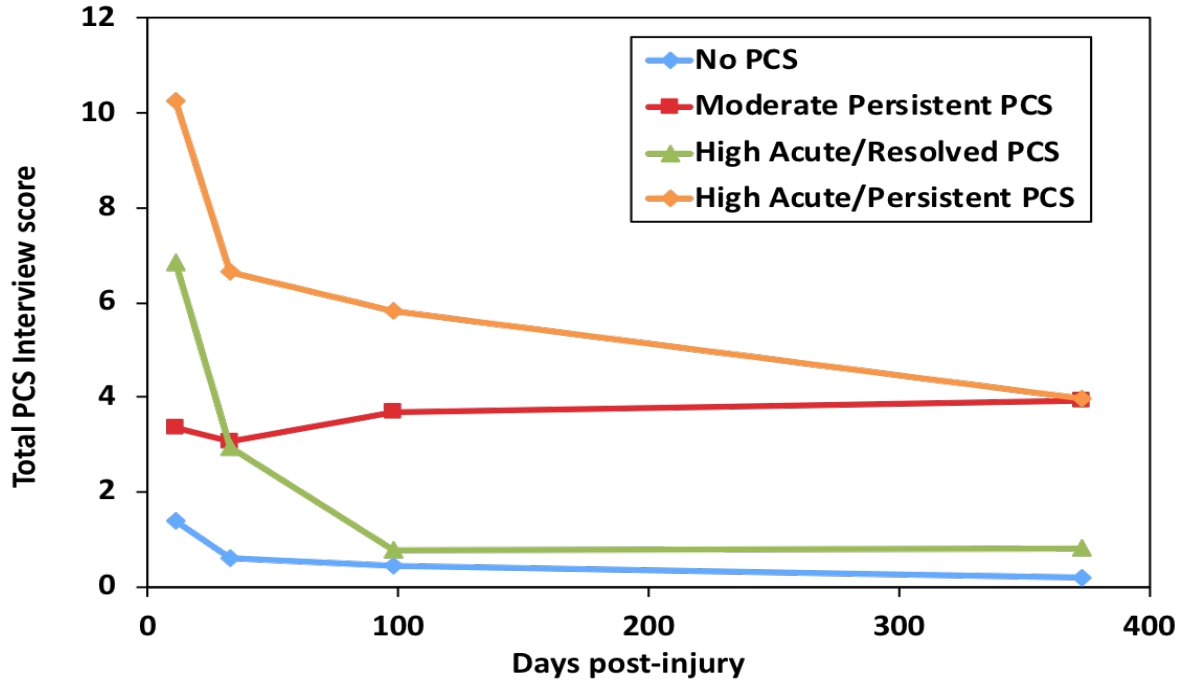
2) Effects persist to 1 year post-injury in some children

(Moran et al., *J Pediatr Psychol*, 2012; Taylor et al., *J Head Trauma Rehabil*, 2015; Yeates et al., *Arch Pediatr Adolesc Med*, 2012)

- Cognitive PCS
- Behavior problems
- Poorer quality of life

3) Patterns of recovery vary

(Yeates et al., , Pediatrics, 2009)



4) Factors associated with persistent post-concussion behavior problems include:

(Taylor et al., *Neuropsychol*, 2010)

- Younger age
- Indications of more severe injury:
 - Hospitalization
 - loss of consciousness,
 - neuroimaging abnormality
 - vehicular accidents
 - Other (non-head) injury

What We Learned About Online Family Problem Solving Therapy for Mod-Sev TBI

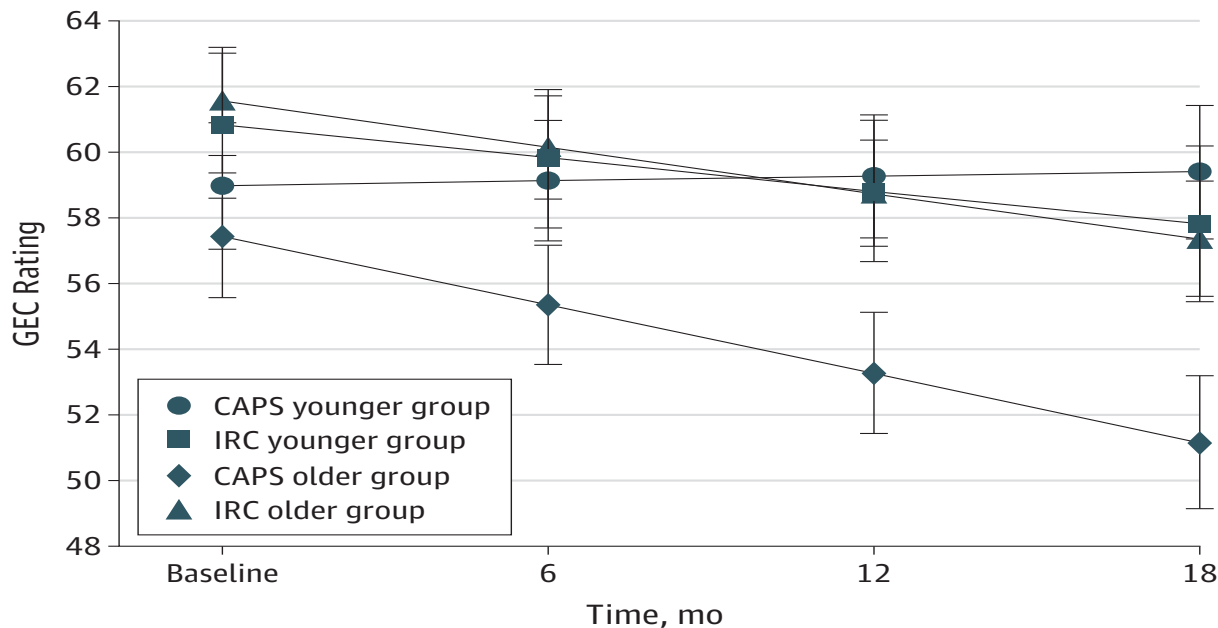
- 1) **Online therapy has more positive effects on family and child outcomes than internet resources**
 - Greater reductions in caregiver distress
 - More positive behavior changes in child (reduced symptoms of internalizing problems and executive dysfunction, higher quality of life, and teen-reported family conflict)

2) These effects are not universal but vary by:

- TBI-related factors: TBI severity, time since injury
- Participant characteristics: sex, SES, behavior problems prior to injury, age at time of intervention, computer usage
- Caregiver depression

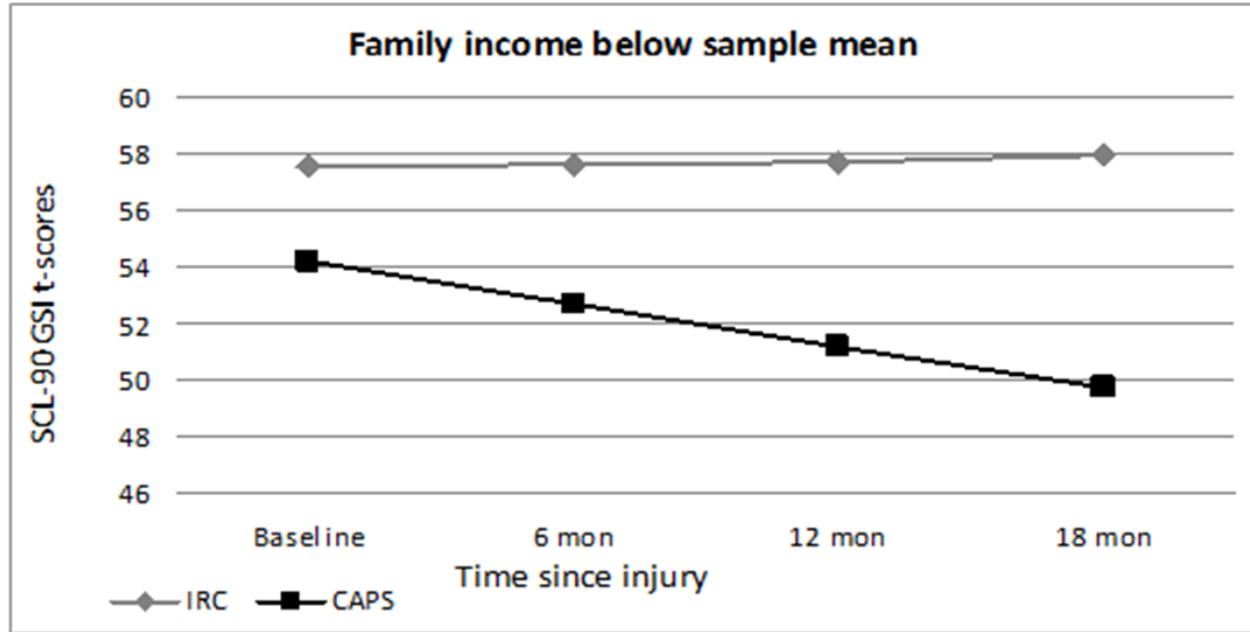
Positive effects of online therapy (CAPS) compared to online resources (IRC) on BRIEF in older youth

(Kurowski et al., *JAMA Pediatr*, 2014)



Positive effects of Online Therapy (CAPS) compared to internet resources (IRC) on parent distress in lower income families

(Petranovich et al., *J Pediatr Psychol*, 2015)



Clinical Implications

- Although children show varying degrees of recovery, this is a complex process, involving interaction of injury and pre-injury children characteristics, family and genetic factors
- Families are affected in multiple ways (burden, distress, goals, parent-child interactions)
- Some families are more affected than others, depending on family characteristics (interpersonal resources and stressors, coping)

Clinical Implications--Continued

- Consider family problems as potentially contributing to child's difficulties or obstructing progress, and increasing family resources as way to facilitate child's progress
- Response to family therapy is variable; related to multiple injury and non-injury factors
- Children with TBI and their families have unmet needs for educational and psychosocial services

Future Research Directions

- Better understand treatment and experiential factors related to recovery from severe TBI – the first year post-injury may be especially critical
- Examine biomarkers of injury severity and further explore the role of genetic factors
- Further understanding of neural basis of family influences on the child and of variations in recovery

Applications and Implications for Your Research and Clinical Practice

Preterm Birth

- 10% of live births preterm (PT, GA<37 weeks), 1-2% extremely preterm (EP, GA<28 weeks)
- Decreasing mortality in recent decades with continuing neurodevelopmental disability, including health problems, weaknesses in cognitive and academic skills, and behavioral and social problems
- Continuum of effects through more common moderate and late PT births (GA 32-33 and 34-36 weeks, respectively)

Neurodevelopmental Outcomes of Preterm Birth

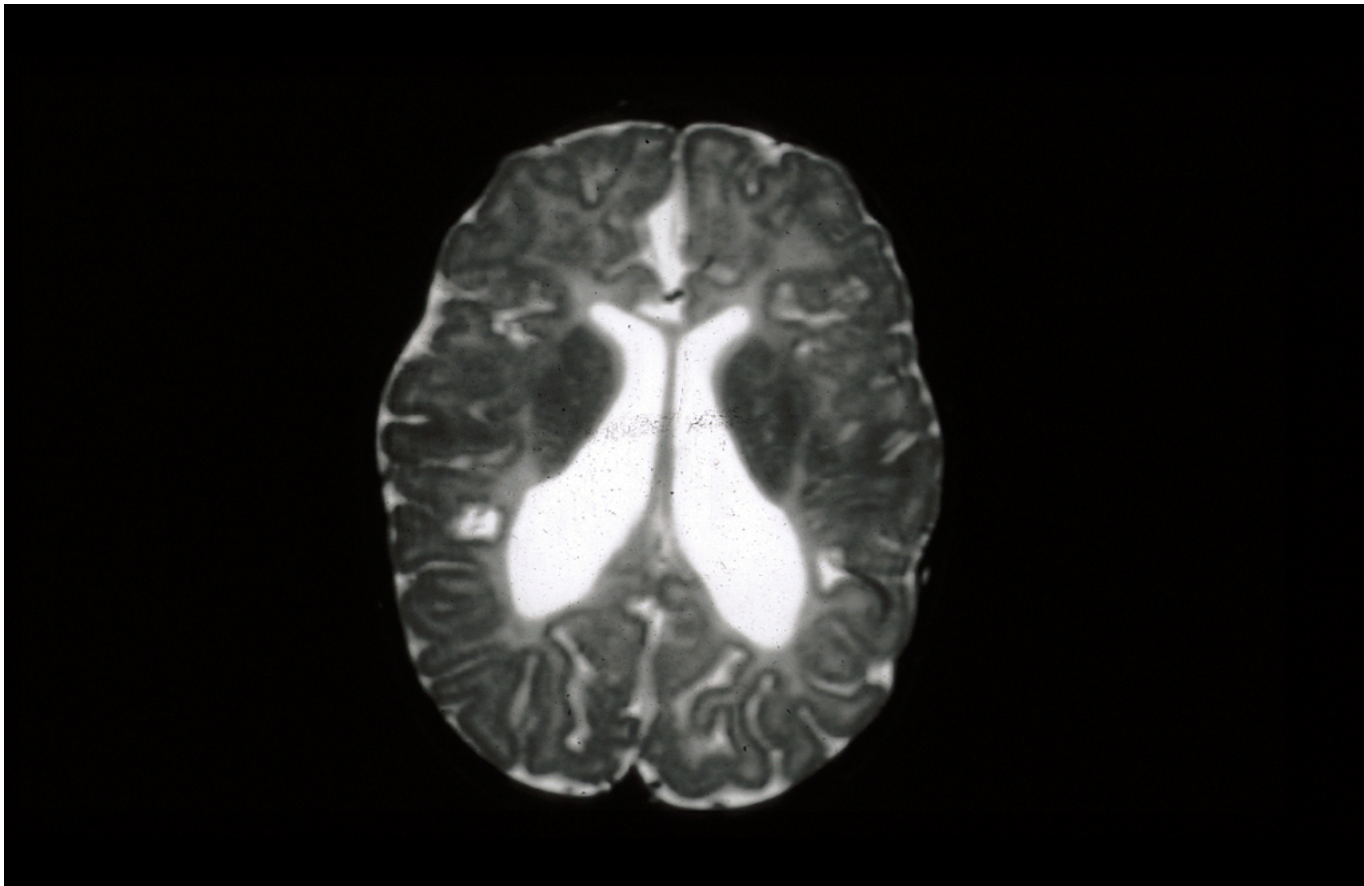
- Age dependent with variable and uneven impairments, frequently involving multiple areas of health and development
- Multiple contributing factors: degree and type of perinatal brain insult, physical health problems, genetic and environmental factors
- Outcome tell us how and why children are affected to better inform efforts to optimize outcomes



GA 23 weeks, 550 g

Birth Complications Related to Poorer Developmental Outcomes

- Germinal matrix hemorrhage & IVH
- White matter abnormalities
- Reduction in brain volumes, especially in subcortical and periventricular gray matter and in the cerebellum, and in connectivity
- Bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, patent ductus arteriosus, postnatal steroids



Axial image of 6-month-old showing enlarged, ventricles, cystic PVL, and thinning of white matter

Review of Outcomes Across Key Developmental Periods



Infant-Toddler
Period:
Birth-2 years

Early
Childhood:
3-5 years

Middle
Childhood:
6-10 years

Adolescence:
11-17 years

Emerging
Adulthood:
18-25 years

Case Study of “Mary”

- **Research participant:** First met as participant in study of children with <750 g birth at age 7 years and followed multiple times (ages 11, 12, 13, 14 and 16)
- **Birth History:** 439 g birth weight, GA 27 weeks, BPD; 5½ month NICU stay
- **Continued follow-up:** clinical assessments in 20’s and updated interview at age 32 years

- **Infant-toddler period:** home on oxygen; re-hospitalizations for RSV, hearing loss, vision problems; 2-year Bayley: 64 PDI, 81 MDI



Research Findings: Infancy & Toddlerhood

- Cardiovascular, respiratory, and eating and sleeping problems, poor growth
- Low Bayley scores or neurosensory impairments in about half of those with more extreme prematurity
- Weaknesses in vocabulary and word use, task persistence and self-regulation, making transitions, lower social competence and engagement, symptoms of ASD

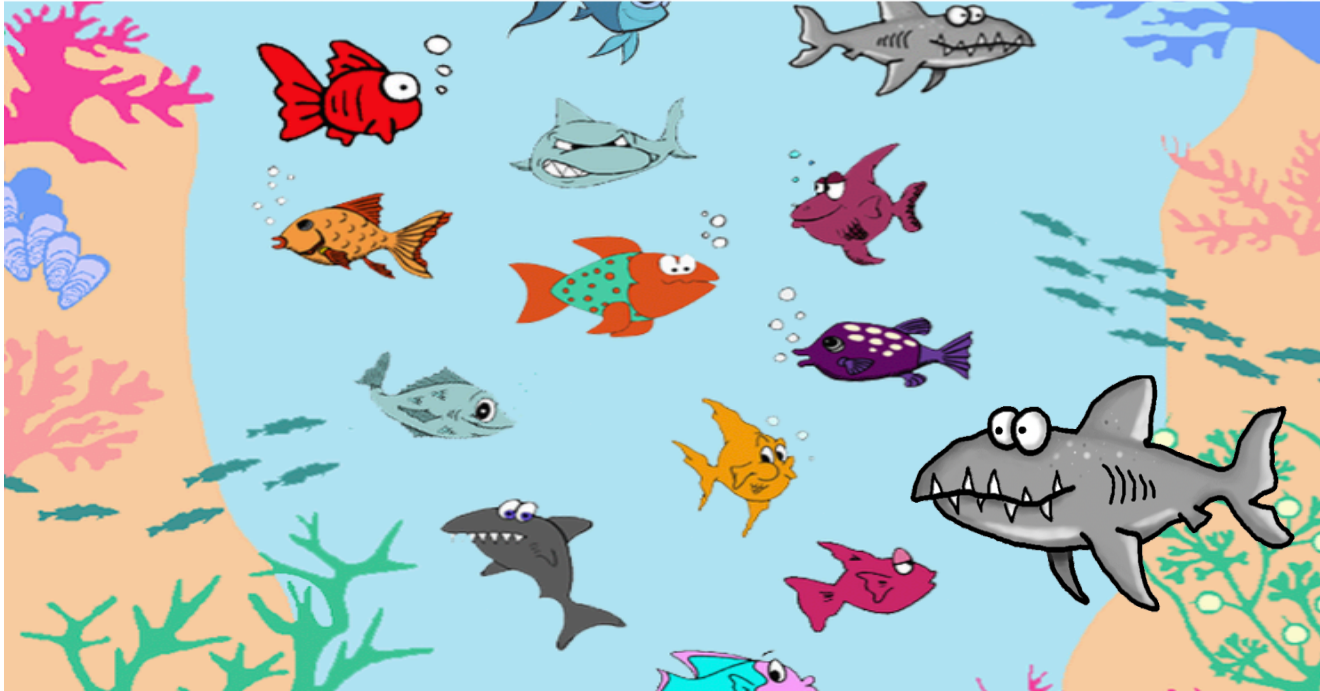
- **Early childhood:** respiratory illnesses; early intervention program then preschool with extra year in pre-kindergarten; lack of social interaction at school and was anxious, fearful, easily startled; fine and gross motor problems



Research Findings: Early Childhood

- Weaknesses in IQ, executive function, verb production and social use of language, motor coordinator
- Poor school readiness, including deficits in self-regulation and social-emotional functioning

Go No-Go Attention Task



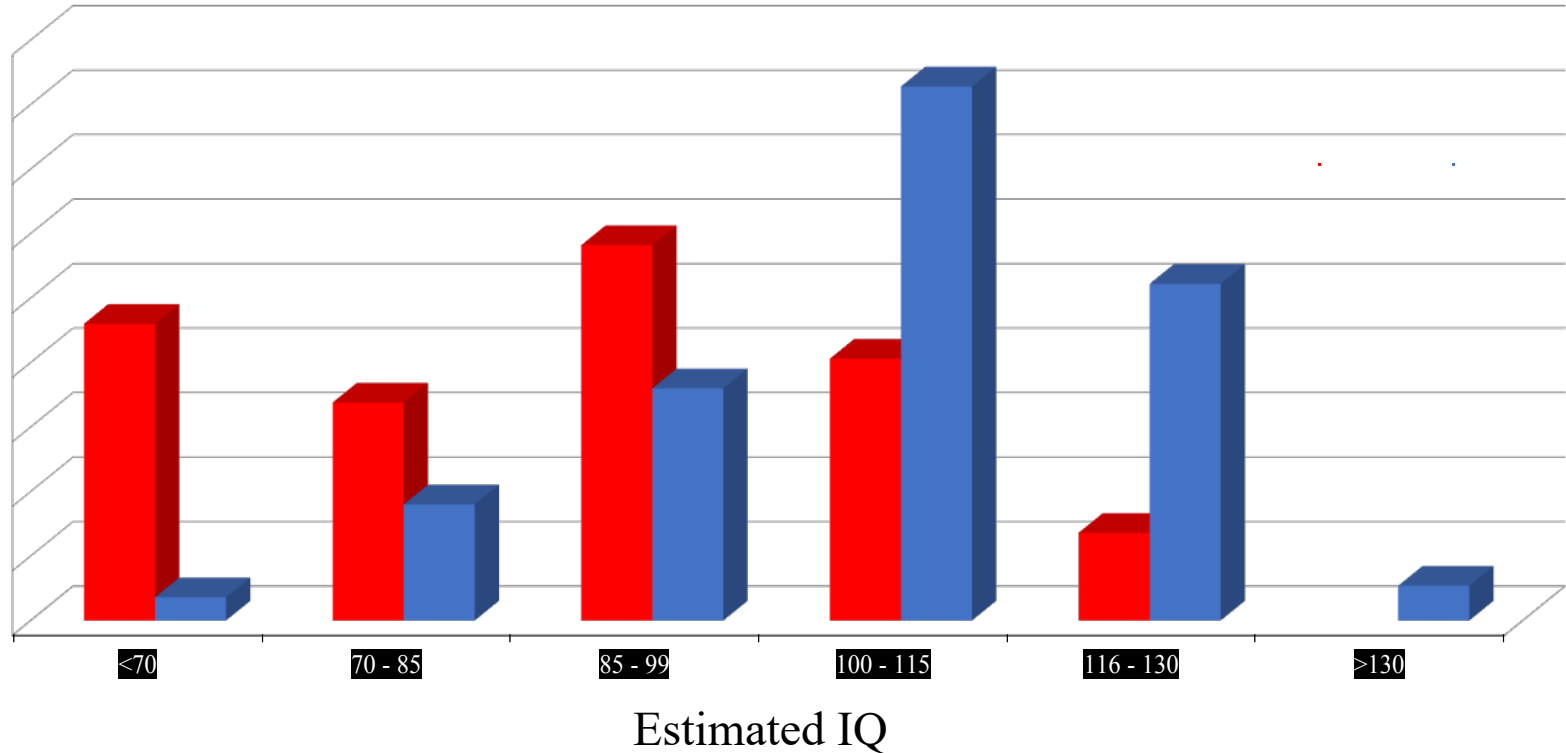
- **Middle Childhood:** poor growth and continued respiratory problems; verbally proficient but rambled with difficulties with summarizing information, math story problems, and science; private tutoring with small group help and speech therapy at school; a few friends but continued social reticence and counseling for anxiety



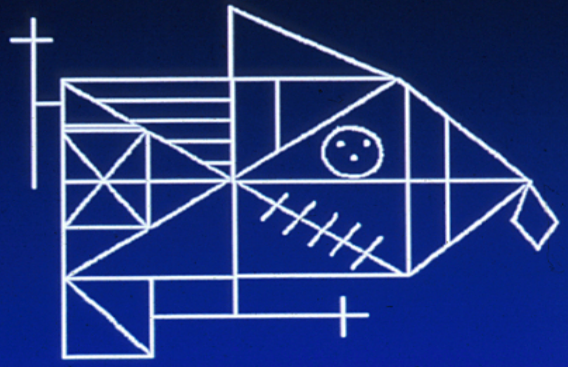
Research Findings: Middle Childhood (Early School Age)

- Weaknesses in IQ, but especially in spatial and working memory, motor and perceptual motor skills, executive function, memory, and math
- Preterm behavioral phenotype: ADHD (primarily inattentive), internalizing symptoms, social problems (symptoms of ADHD)

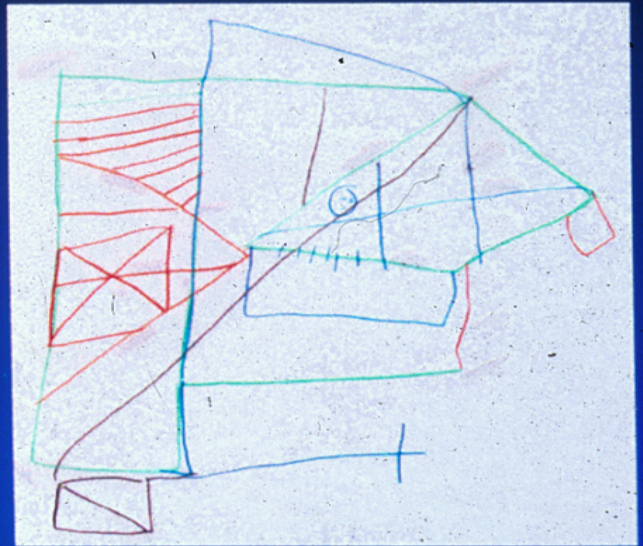
Distribution of IQ Estimates in EP and NBW Groups at Age 6 Years (Orchinik et al., JINS, 2011)



REY OSTERRIETH COMPLEX FIGURE



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- **Adolescence:** Catholic high school with small group resource help; difficulties in math and science; received class notes from regular classes; socially awkward and self-conscious but not withdrawn; graduated on time with B average; small brain volumes on research MRI



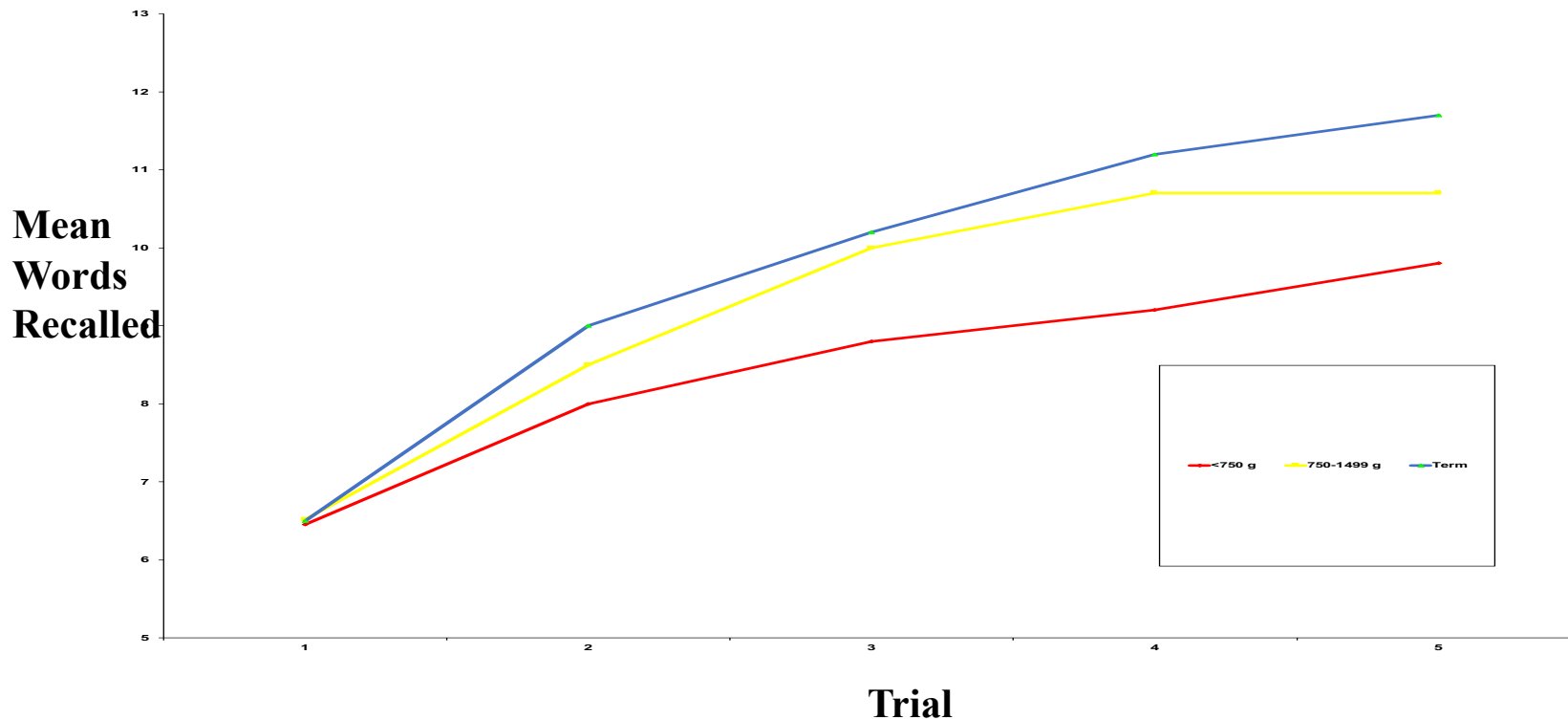
Mary's Test Findings and Interventions

- IQ scores in 70s in middle school and 83 in high school but average reading decoding and math computation scores throughout schooling
- Strengths in verbal and rule-based learning (word reading, spelling, math facts) but deficits in reading comprehension, math problem solving, processing speed, perceptual-motor skills, executive function
- Interventions: new learning difficult and easily overwhelmed so important to break down assignments, use explicit teaching of concepts, practice to mastery, engage in learning

Research Findings: Later School Age and Adolescence

- Asthma, vision problems (visual acuity, stereopsis, convergence)
- Weaknesses in IQ, most notably language processing, executive function, and visuo-constructive skills – less in vocabulary, object recognition, sustained attention
- Persistence of preterm behavioral phenotype, including symptoms of ASD
- Learning disabilities

Memory Problems in Preterm Children at 11 Years (Taylor et al., *Child Neuropsychology*, 2000, Vol 6)



- **Emerging Adulthood:** Completed 4-year college with good grades but with extensive help in academic support center; lived in dorm and then shared nearby apartment; passed teaching exams with accommodations including extra time.



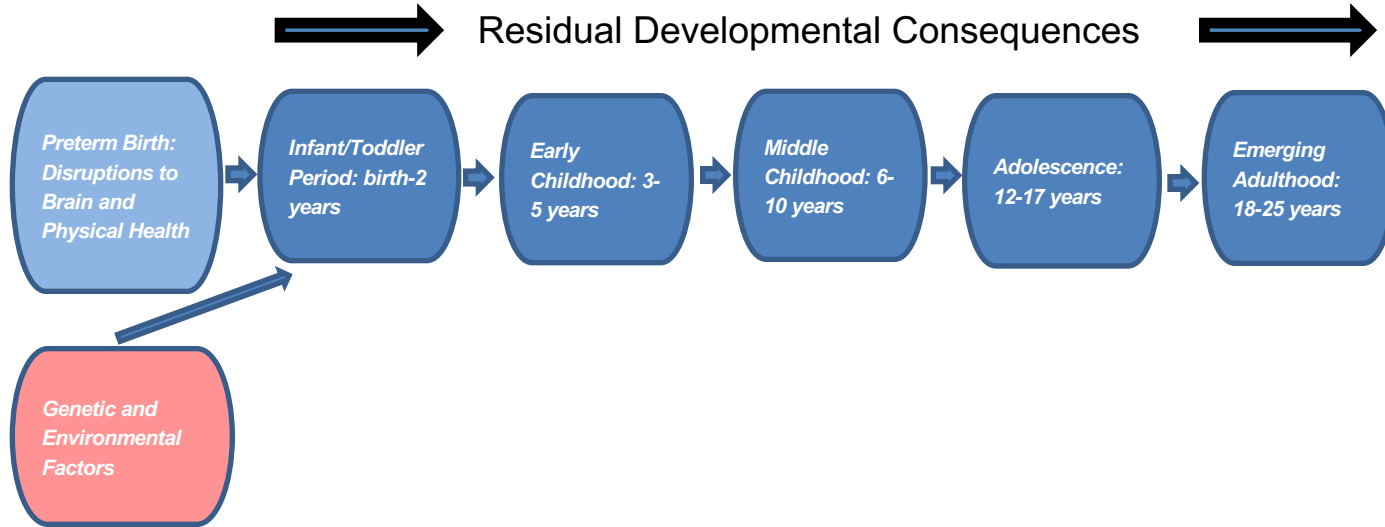
- **Update at age 32 years:** difficulties managing a classroom so worked as reading tutor; tutoring program defunded and now in post-graduate medical assistant program; sociable, happy, and active (runs student exchange program, enjoys theatre) but can be socially immature and has difficulties developing close friendships



Research Findings: Adulthood

- Asthma, elevated blood pressure
- Weaknesses in IQ, executive function, memory and learning, processing speed
- Behavior problems similar to those in adolescence, with less risk taking and social engagement
- Lower educational attainment, independence, lower levels of employment and income, though majority do well

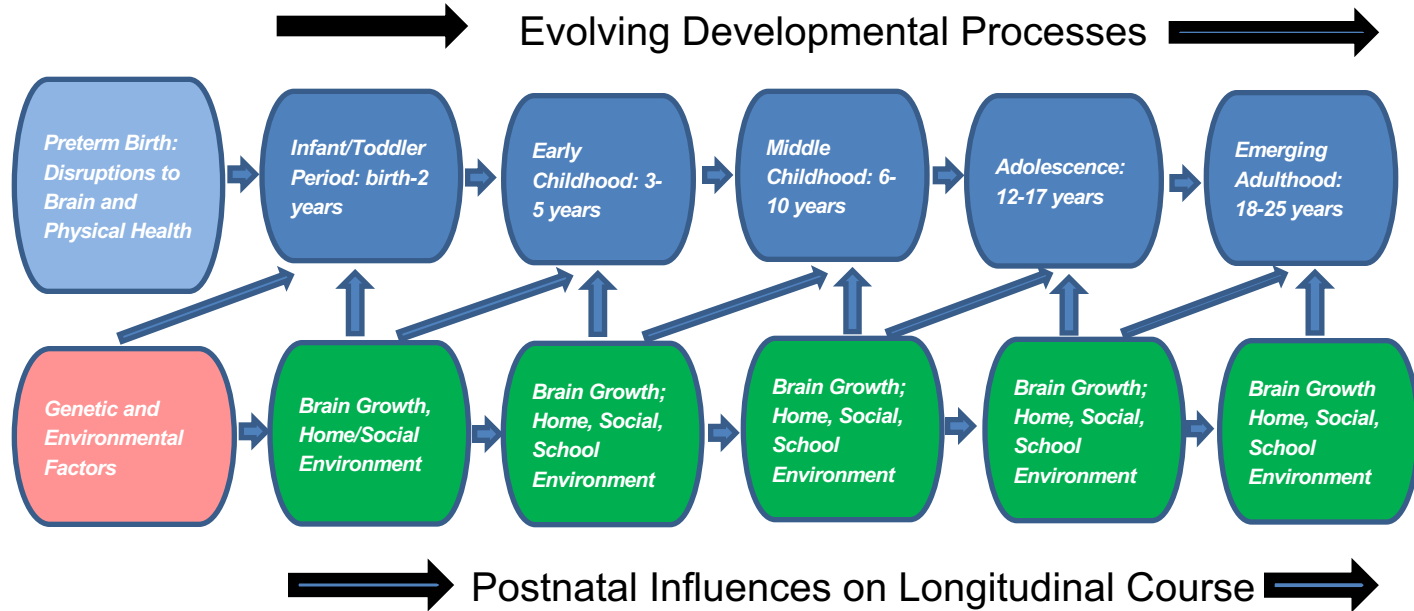
Outcomes as Manifestations of “Developmental Origins of Health and Disease”



Support for Later Outcomes as Effects of Early Abnormalities

- Associations of neonatal brain abnormalities with later cognitive and academic skills
- Correlations of cognitive and motor skills in infancy and early childhood with outcomes in later childhood, adolescence, and young adulthood

Outcomes as Manifestations of an “Unfolding Developmental Process”



From Seed to Flower: Illustration of “Unfolding Developmental Process”



Evidence for Viewing Outcomes as “Unfolding Process”

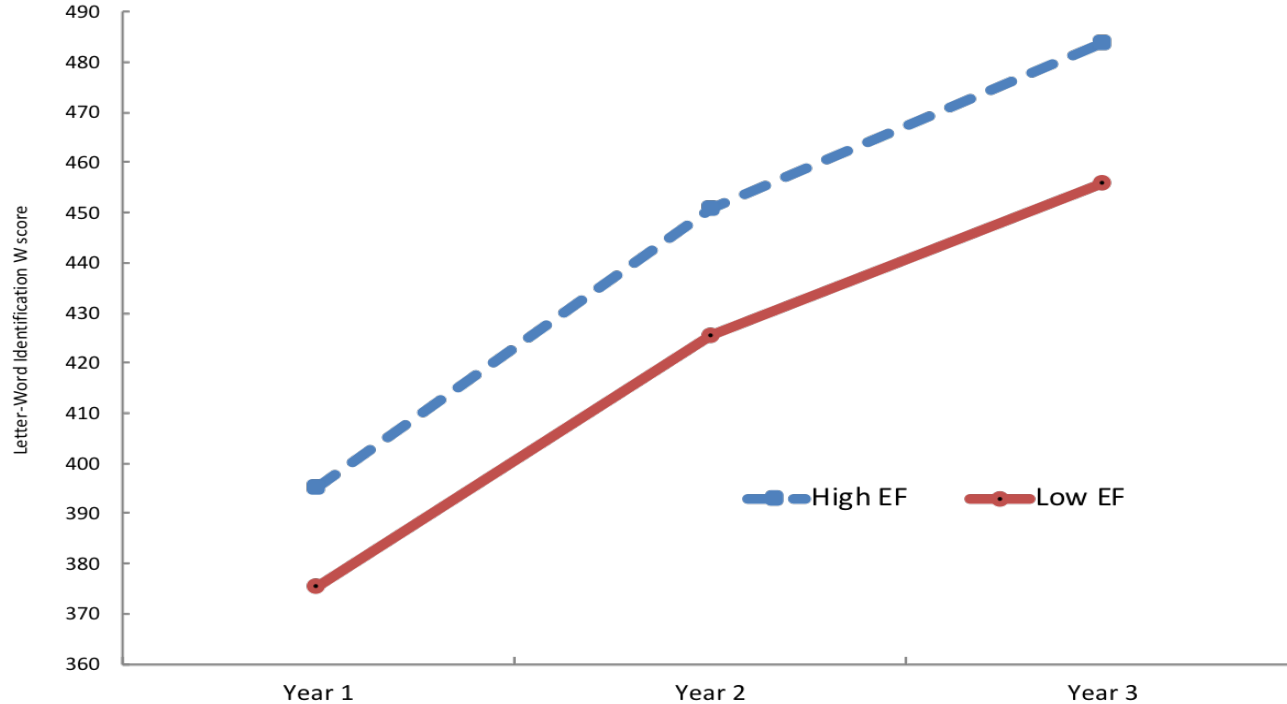
- Our studies and others showing positive effects of more advantaged family environments (as reflected in higher SES, more positive parents, lower parent distress) on outcomes of preterm birth
- Findings from our Early Learning Progress Study of children with extreme prematurity demonstrating that:
 - Tests of executive function and parent report of ADHD predict subsequent academic achievement
 - Some preterm children are resilient

Early Learning Progress Study (Taylor, Hack and colleagues)

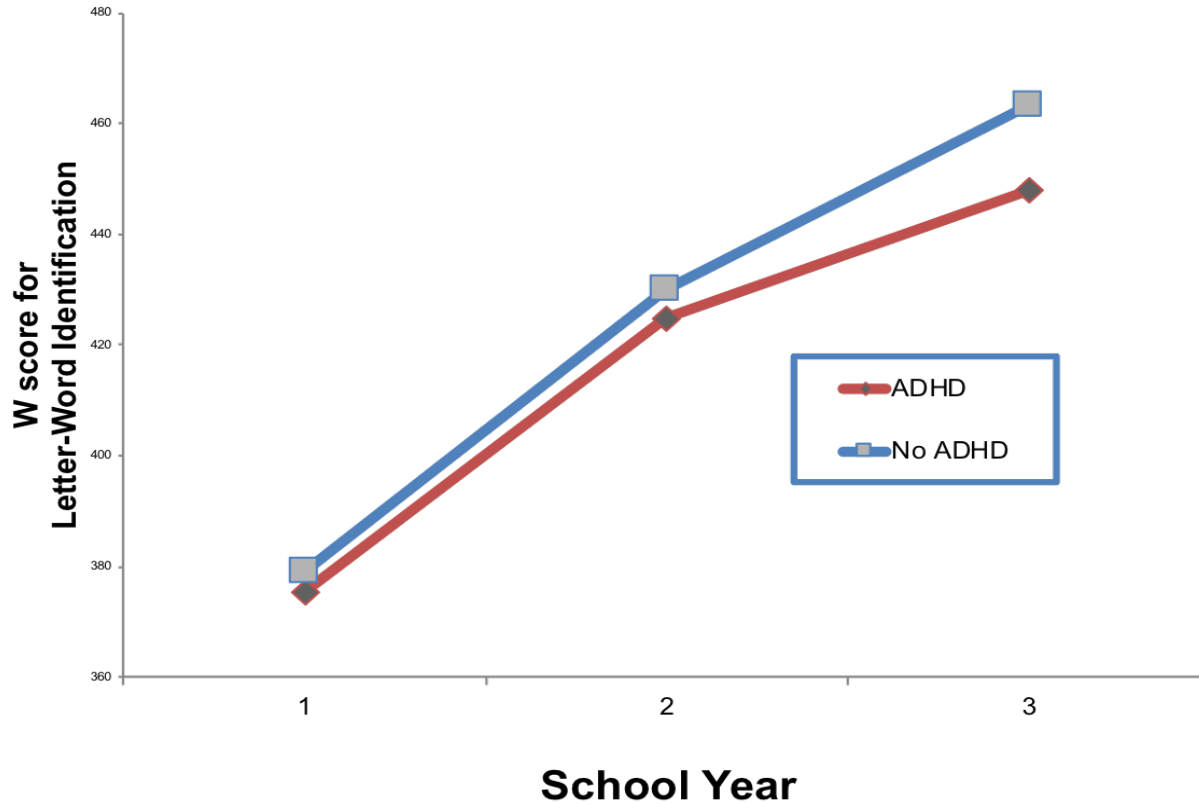
- Recruited extremely preterm (EPT) children (GA <28 weeks or <1000 g birth weight) and normal birth weight (NBW) classmates during first year in kindergarten (2001-2003 birth cohort)
- Assessed children annually on comprehensive battery of neuropsychological tests and parent ratings each year for first 3 school years

Lower Score of Tests of Executive Function in Kindergarten Predicts Slower Growth in Reading

(Taylor et al., *Neuropsychology*, 2018)



ADHD in Kindergarten Predicts Slower Growth in Reading (Taylor et al., *Learning and Individual Differences*, 2018)

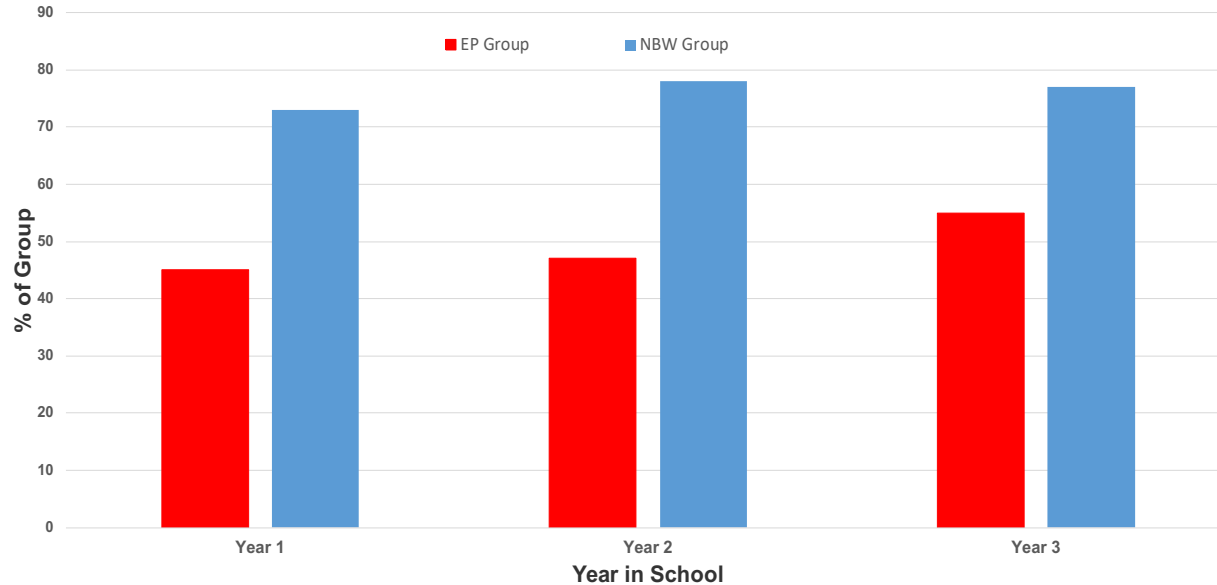


Are Some Children Resilient, and if so Why?

(Taylor et al., *JINS*, 2018)

- Defined "resilience" as adaptive competence:
 - Scores in broad average range on achievement tests
 - Absence of parent ratings of child behavior problems
- Compared EP and NBW groups on rates of adaptive competence across first 3 school years
- Explored differences between adaptive (resilient) and maladaptive EP children

ELP Study: Rates of Adaptive Competence in EP and NBW Groups Across First 3 School Years



Factors Related to Resilience in Children with Extreme Prematurity

- Less parent burden and distress; absence of neurodevelopmental impairment age 2 years corrected
- Higher cognitive skills, SES, home stimulation for learning, quality of parent-child relationship

Relevance of Viewing Child as on a Developmental Pathway

- Different and evolving pathways: early effects may largely resolve in some but persist or even worsen in others
- Multiple influences: neonatal status, brain abnormalities, early developmental and cognitive functioning, behavior (ADHD), home environment
- Unmet developmental needs: may exacerbate deficits in some children

Clinical Implications

- Neuropsychologists: Awareness of profiles of deficits, age-related changes, life-span perspective, advocate for approaches to intervention targeted to individual needs
- Other health care professionals: promote awareness of potential long-term effects, need to identify early if possible and provide anticipatory guidance
- Parents and teachers: seek evaluations and age-appropriate interventions, build for the future
- Policy Makers: better system for identifying special needs, accessing appropriate interventions, and improving continuity of care

Future Research Directions

- Mechanisms underlying risk and resilience
- Interventions focusing on:
 - Families in the NICU and post-discharge
 - Educational methods targeted to children's specific needs, including ways to enhance school readiness skills
 - Promotion of compensatory strategies, coping, and socialization
- Implications for functioning and health in adulthood

**Your Experiences and Challenges in
Working with Children Born Preterm
and Their Families, or with Other
Brain-Related Conditions**