

Mental Health and Brain Abnormalities in Children with PAE and Co-Occurring Risks

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Disclosure of Conflict of Interest

- CL's spouse is an employee of General Electric Healthcare
- The speakers declare no other affiliations (financial or otherwise) with pharmaceutical, medical device or communications organizations
- None of the speakers will make therapeutic recommendations for medications that have not received regulatory approval.

Objectives

1. Identify underlying neurological correlates of mental health in children and youth with prenatal alcohol exposure (PAE).
2. Identify how neuropsychological processes of children and youth with PAE are associated with mental health issues.
3. Describe how mental health issues in FASD impacts diagnosis and service delivery.
4. Explore how co-occurring exposures interact with PAE.

Child Development Centre



Development of a Cumulative Risk Diagnostic Clinic (CRDC)

- A Collaboration between Health and Children's Services
 - Literature Review and Expert Consultation
 - Two-year pilot with Paediatrics for Kids in Care (P-KIC) (2011-2013)
- CRDC Established (2015-Present)

CRDC Background: Individuals Have Other Adverse Exposures

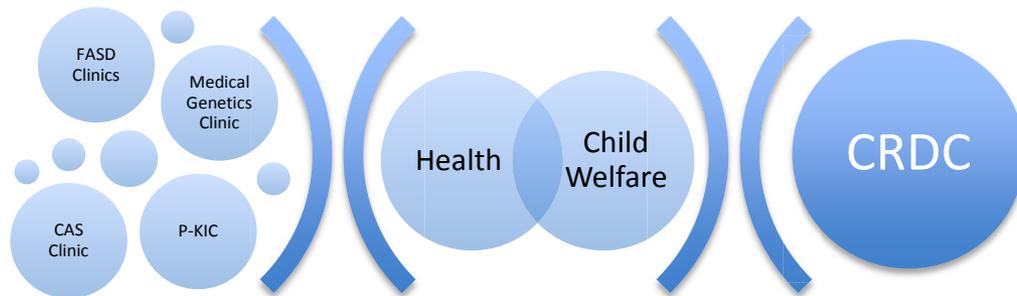
- Community pediatricians' feedback that PAE is **not the only important exposure**.
- Child Welfare feedback that the comprehensive journey of a child and understanding the resulting **functional needs** is a priority.
- Literature regarding the importance of postnatal exposures on child outcomes.
- Our local clinical and research collaboration with Developmental Psychiatry, the Child Abuse Service, and Medical Genetics.

Cumulative Risk in FASD Populations

Exposure	ACH Data (N=52) (2010)	Washington/DPN (N=1,400) Astley, 2010	CRDC Pilot (2011-2013)
Tobacco	89%	62.4%	44%
Marijuana	50%	36.5%	19%
Any Street Drugs	27%	No Data	50%
Any Maltreatment	67%	No Data	100%
Neglect	56%	64.4%	94%
Physical Abuse	37%	34.3%	50%
Sexual Abuse	33%	23.5%	25%
Witness to IPDV	33%	No Data	100%
Multiple Caregiver Change	69%	Yes	100%

CRDC: Goals

- Articulate developmental/functional deficits and mental health profiles.
- Articulate cumulative risk/exposure (causative factors) and subsequent diagnostic profiles when applicable (including FASD).
- Collaborate in cross-sectional service planning and case management.



Two Children's Stories

- **Cindy, Age 6**

- Referred for an FASD Assessment
- Maternal Prenatal Stress
- Pre-natal Substance Use
- Multiple Moves
- Rage, inconsolable, disrupted sleep and developmental delays
- Generational story – mom has FASD

- **Dustin, age 15**

- Prenatal exposure – alcohol and drugs
- Little to no pre-natal care
- Family history of serious mental illness
- Multiple losses
- Significant neglect 0-3
- Multiple caregivers/placements
- FSIQ – 77, limited functional skills for adulthood

- Is FASD (any single category) the Only Lens for Understanding Outcome?



What if....

- We only looked at the prenatal alcohol exposure....
- We ranked the pre-natal exposure as the most important (or only) exposure....
- The interventions were guided only by the FASD story....

Background:

PAE is an Important Exposure

- Individuals with FASD have:
 - Multiple Deficits
 - Cross Many Different Cognitive Domains
 - Include Significant Mental Health Symptoms

Background: Attribution in FASD

- Features of FASD are complex and multifaceted
 - originating with organic brain damage caused by alcohol
 - but interacting with genetic and **other influences**
- Over the lifespan features may be exacerbated or mitigated by **experience**

Background: Heterogeneity of Outcome

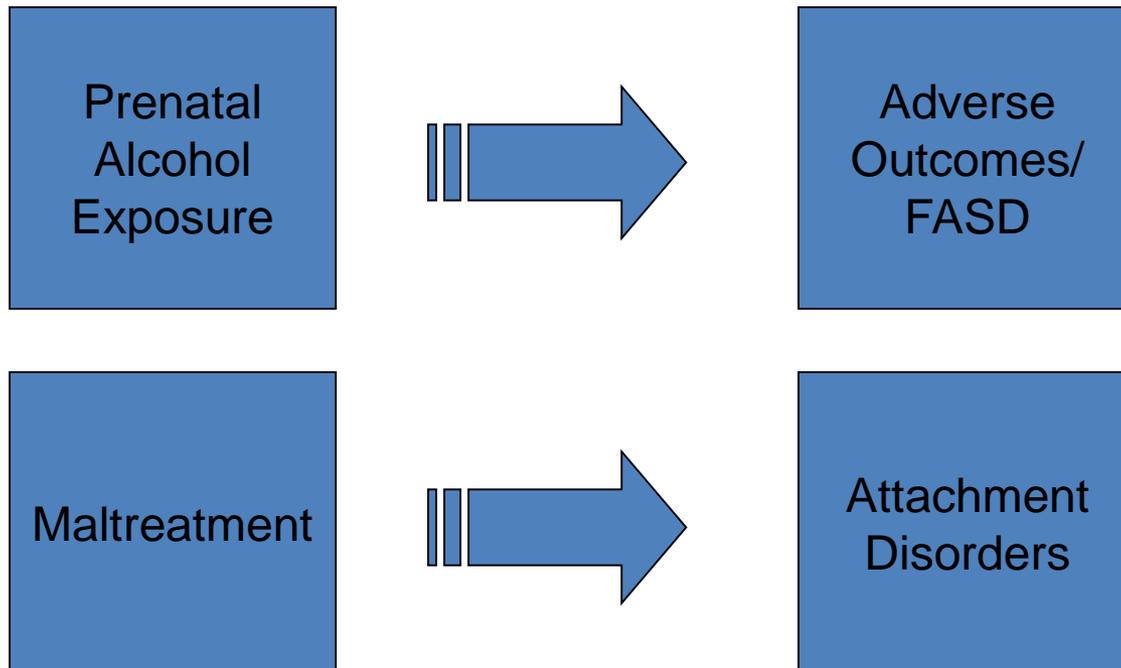
- A universal finding in groups of children exposed to multiple adverse experiences or risk factors (Rutter, 2007).
- Not all children exposed to risk have adverse outcomes
 - A proportion of children show resilience?

Background: Psychiatric Disorders in FASD

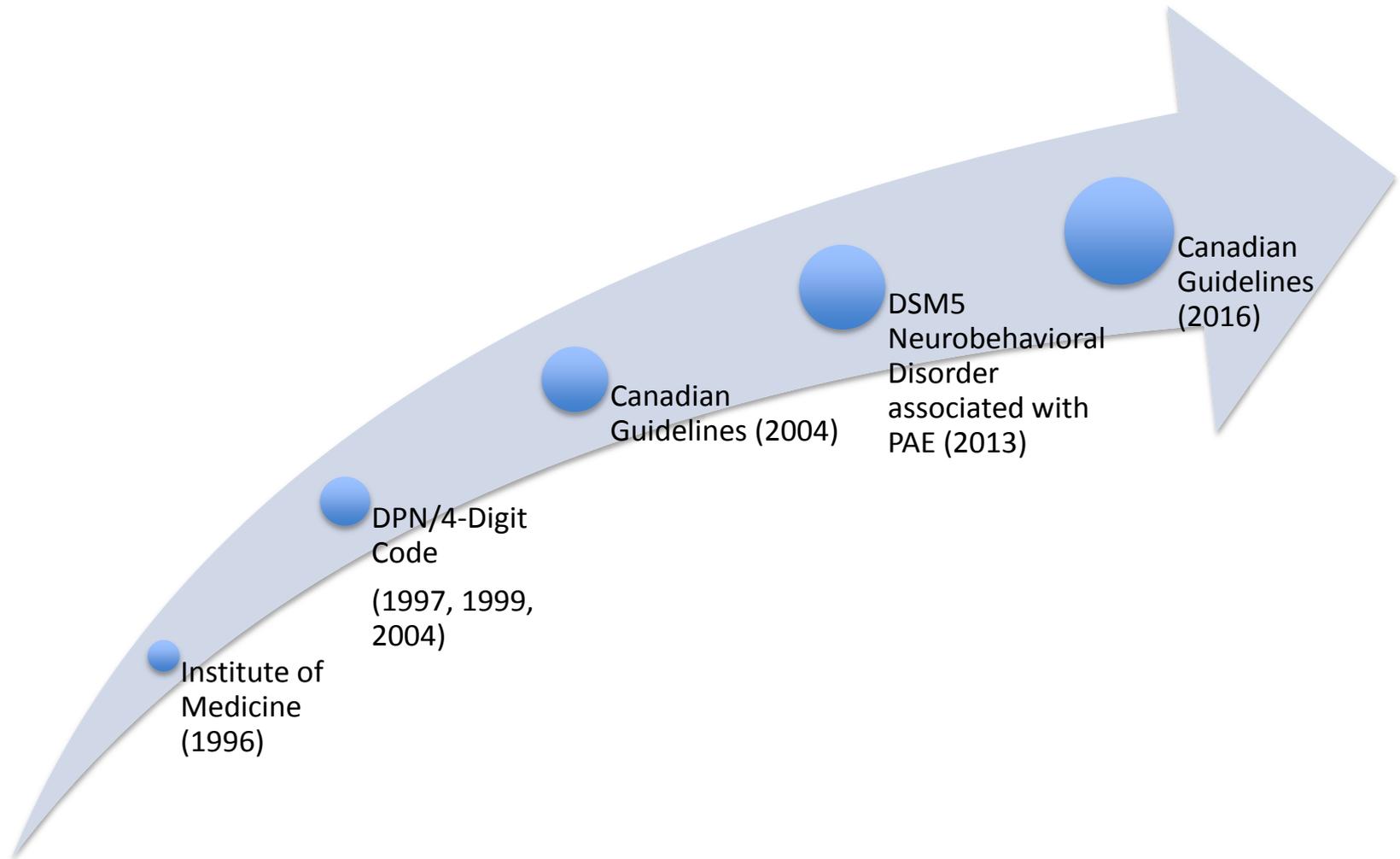
- No unique psychiatric disorders in children with FASD
 - Rates of any psychiatric disorder increased over baseline population rates
- Primary disability related to prenatal alcohol exposure versus related to other cumulative risk factors?
- Psychiatric morbidity often major contributor to functional impairment

Models of Risk, Resilience and Outcome

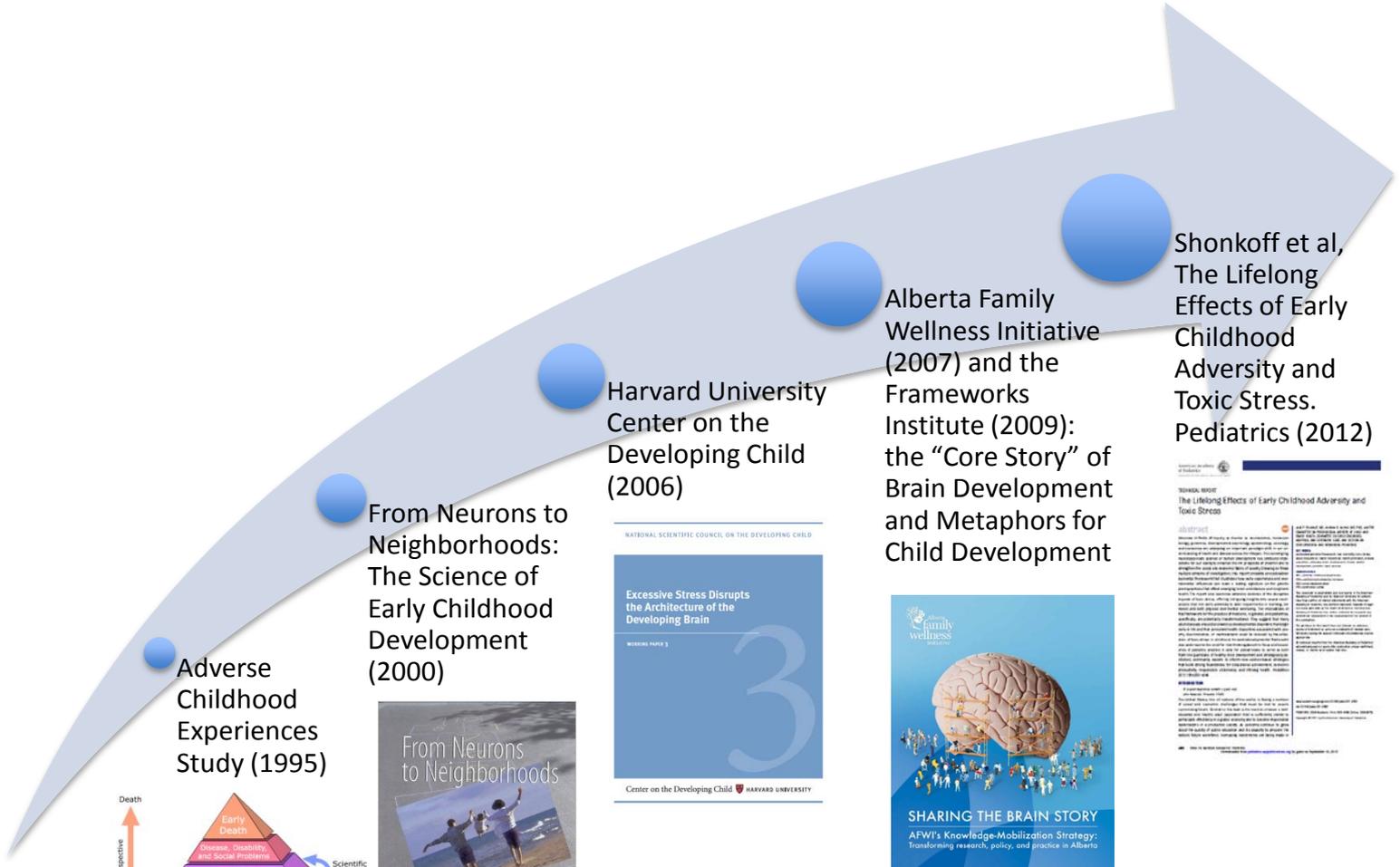
- Frame attribution, trajectories and prognosis
- Guide prevention and intervention
- **Linear Causality Models:**



Integrating Evidence: Prenatal Alcohol Effects on Child Outcomes



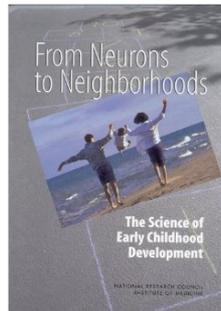
Integrating Evidence: Postnatal Effects on Child Outcomes



Adverse Childhood Experiences Study (1995)

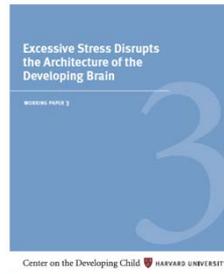


From Neurons to Neighborhoods: The Science of Early Childhood Development (2000)

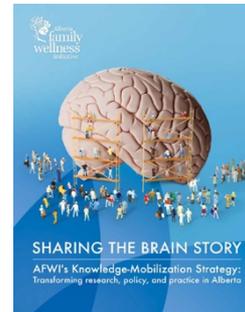


Harvard University Center on the Developing Child (2006)

NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD



Alberta Family Wellness Initiative (2007) and the Frameworks Institute (2009): the "Core Story" of Brain Development and Metaphors for Child Development



Shonkoff et al, The Lifelong Effects of Early Childhood Adversity and Toxic Stress. Pediatrics (2012)



Integrating Evidence: Prenatal AND Postnatal Effects on Child Outcomes

Single Risk

Multiple Risk Models (1979)

- Rutter
- Sameroff
- Greenspan



Source: Bronfenbrenner (1976)

Bronfenbrenner's Ecological Model (1979)

Allostatic Load Models (1998)

Developmental Psychopathology

- Cicchetti (1989)
- Sroufe and Colleagues (2005)

THE DEVELOPMENT OF THE PERSON



THE MINNESOTA STUDY OF RISK AND ADAPTATION FROM BIRTH TO ADULTHOOD

L. Alan Sroufe,
Byron Egeland, Elizabeth A. Carlson,
and W. Andrew Collins

- Are there ways to understand complex stories in the lives of individuals with multiple-risks?
- Moving forward with research related to multiple risks . . .



Risk Models

- Cumulative Risk:
 - Total number of risk exposures predicts maladaptation, regardless of the specific risks
 - Linear and threshold models
 - The number of factors carries more importance than the experience of any one exposure
 - e.g. Adverse Childhood Experiences (ACE) Research
- Dimensional Risk: e.g. threat versus harm
- Timing of Risk: early versus late
- **Case definition for exposures or combinations of exposures has been a challenge.*

Received: 4 September 2018 | Revised: 24 December 2018 | Accepted: 8 January 2019

DOI: 10.1002/bdr2.1464

WILEY **Birth Defects
Research** 

ORIGINAL RESEARCH ARTICLE

Characterizing adverse prenatal and postnatal experiences in children

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Quinn Andre^{2,3} | Christina Tortorelli⁵ | W. Ben Gibbard^{2,6}

Research Exposure Reporting and Ranking Framework

- Integrates **cumulative risk** and **dimensional risk** models
- **Dimensional** risks categorized into:
 - Prenatal alcohol
 - Prenatal other substance exposure
 - Prenatal toxic stress
 - Threat: harm or threat of harm
 - Deprivation: failure to meet basic needs
- **Timing of Risk:** early (before 2-years) versus late
- **Cumulative model:** a 4-digit ranking system similar to that used for diagnosing FASD (Astley, 2004)

Research Exposure Reporting and Ranking Framework

- Seven exposure variables overall:
- **Adverse Prenatal Exposures:**
 - PAE
 - Other Prenatal Substance Exposure
 - Other Prenatal/Maternal Toxic Stress
- **Adverse Postnatal Exposures:**
 - Early Postnatal Threat
 - Early Postnatal Deprivation
 - Late Postnatal Threat
 - Late Postnatal Deprivation

Exposure Case Definitions and Criteria

TABLE 1 Exposure definitions and criteria for scores. Adverse exposures were assessed on a Likert-type scale from 1 to 4. Specific criteria for Ranks 3 and 4 are shown below for each variable. Criteria for Ranks 1 and 2 are not shown, as they were the same for all variables. Scores of 1 represent a confirmed absence of any exposure, whereas 2 represents unknown exposure (generally due to insufficient information)

Exposure type	Description	Rank 3	Rank 4
Prenatal alcohol exposure	Consumption of any form of alcohol during pregnancy	Exposure to prenatal alcohol not meeting criteria for a score of 4 or confirmed exposure of unknown amount	High exposure of ≥ 7 drinks/week or ≥ 2 binge episodes (≥ 4 drinks on one occasion) at some point in pregnancy
Other prenatal substance exposure	Exposure to harmful substances including marijuana, nicotine, cocaine, methamphetamines, and opioids during pregnancy.	Exposure to nicotine or marijuana of any amount; low frequency use of other substances, or confirmed use of unknown amount	High frequency use (≥ 5 times in pregnancy) of an illicit substance (cocaine, methamphetamines, opioids, etc.)
Other prenatal toxic stress	Harm or threat of harm to the mother and fetus during pregnancy; lack of prenatal care, housing, food, or income to meet needs; maternal mental health problems.	Symptoms of a mental health problem (undiagnosed), lack of prenatal care, housing/food/income insecurity < 3 months, OR a single instance of domestic violence or sex trade work	DSM 5 diagnosis of mental health disorder, domestic violence or sex trade work at least twice during pregnancy, housing/food/income insecurity ≥ 3 months, or multiple exposures
Early postnatal deprivation (<24 months)	The basic needs of the child not being met or a risk of needs not being met, including attachment needs.	One care transition (excluding from hospital), housing/food/income insecurity, or loss of caregiver (e.g., death, incarceration)	Multiple care transitions (≥ 2), neglect, or multiple exposures
Late postnatal deprivation (≥ 24 months)	Same as above	Same as above	Same as above
Early postnatal threat	Harm or threat of harm, including physical, emotional, sexual abuse; or witnessing violence, substance abuse, or criminal activity in the home.	Witnessing substance use or domestic violence, caregiver with mental illness	Abuse of any kind, or multiple exposures
Late postnatal threat (≥ 24 months)	Same as above	Same as above	Same as above

Our Research Study Cohort

- Applied to 77 children:
 - aged 2.8-15.9 years; 43 male/34 female
 - Recruited from: 1) Calgary and Region Child and Family Services; 2) FASD parent support groups; and 3) the Cumulative Risk Diagnostic Clinic (CRDC)

DOCUMENTATION ON RISKS

- Pre- and post-natal risks
- Variety of records: birth, legal, adoption, and child and family services
- Self-report

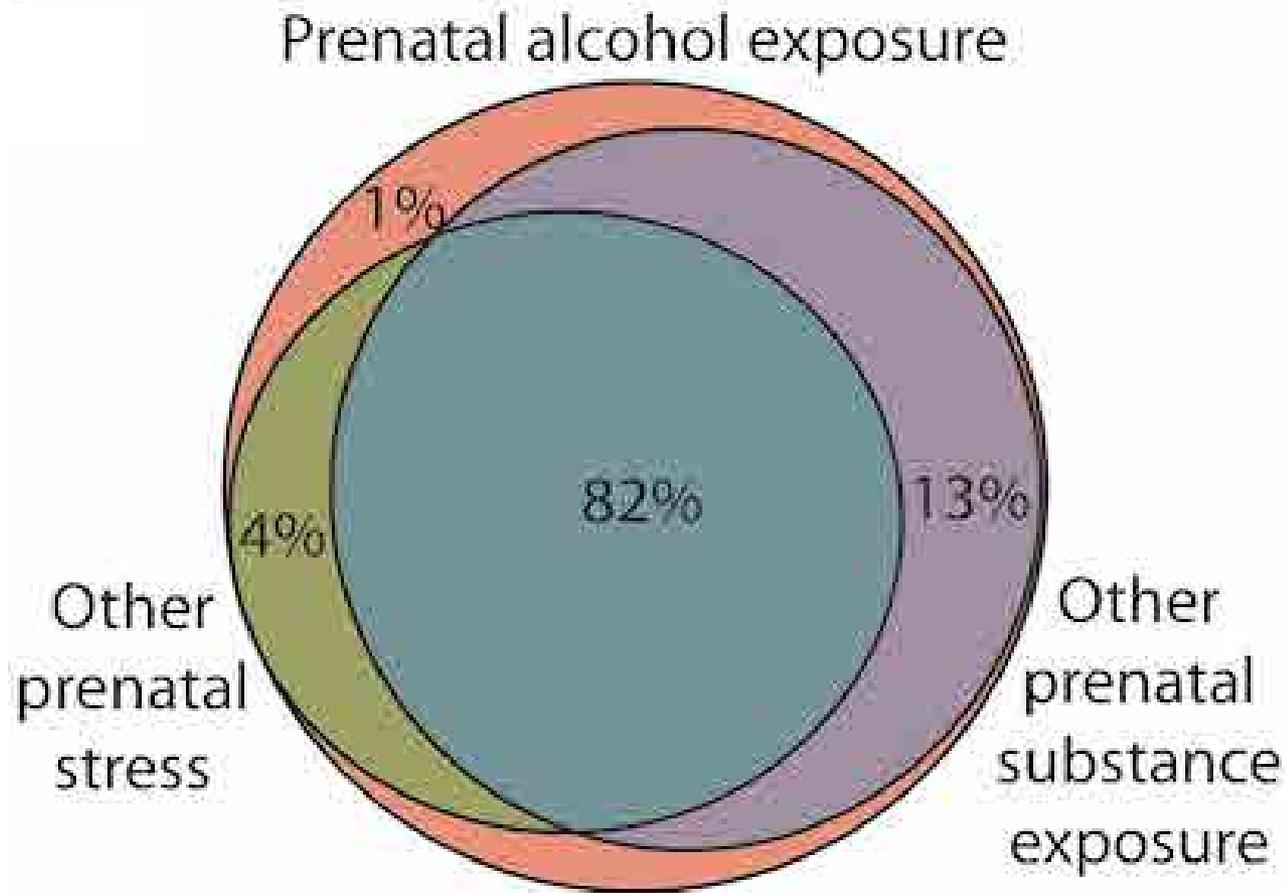
COMPREHENSIVE ASSESSMENTS

- Cognitive functioning/IQ
- Academic ability
- Executive functioning
- Memory
- Mental Health

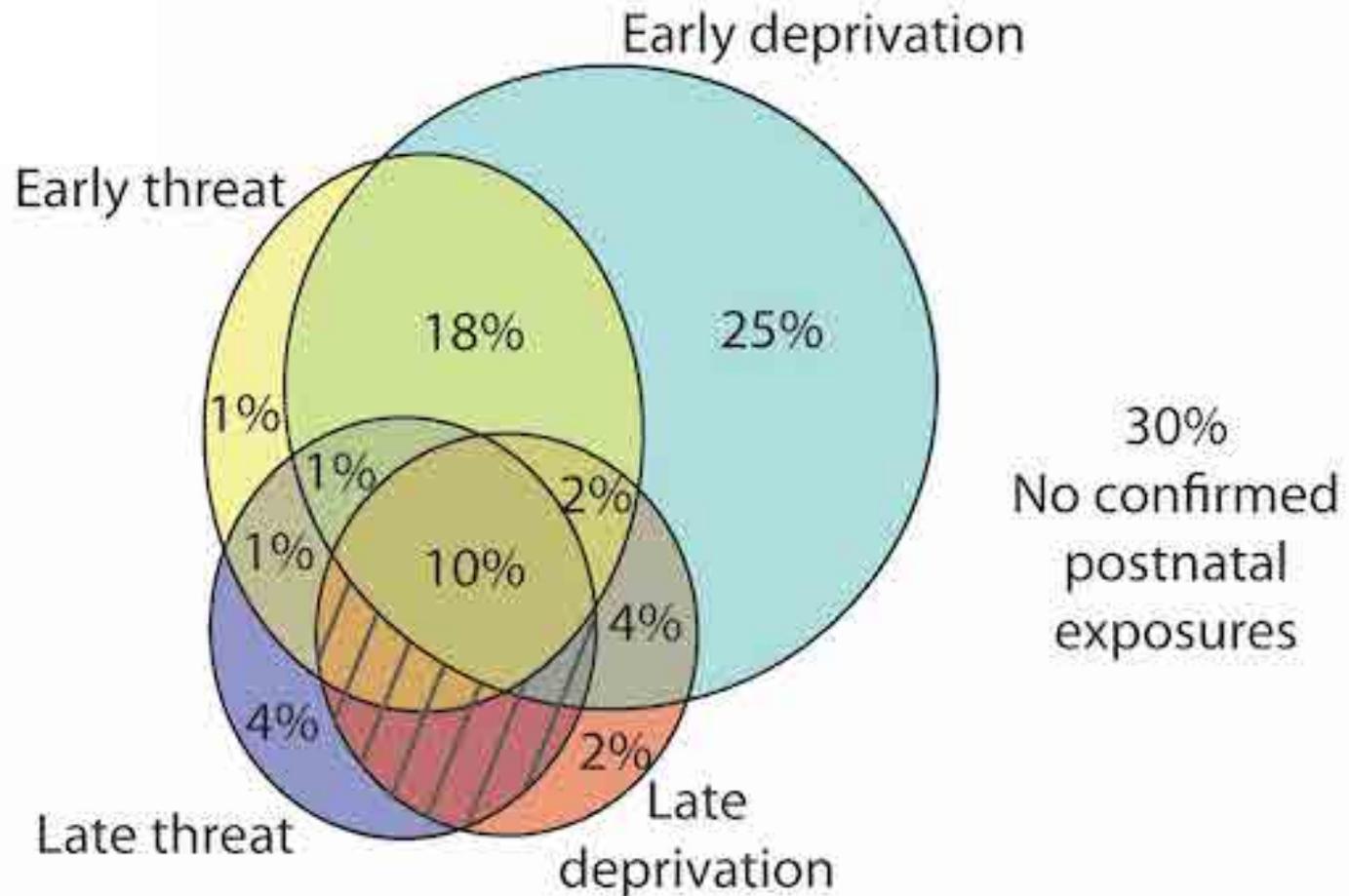
BRAIN IMAGING

- Diffusion MRI (dMRI)
- Resting state fMRI (rs-fMRI)
- Anatomical imaging (T1-weighted)

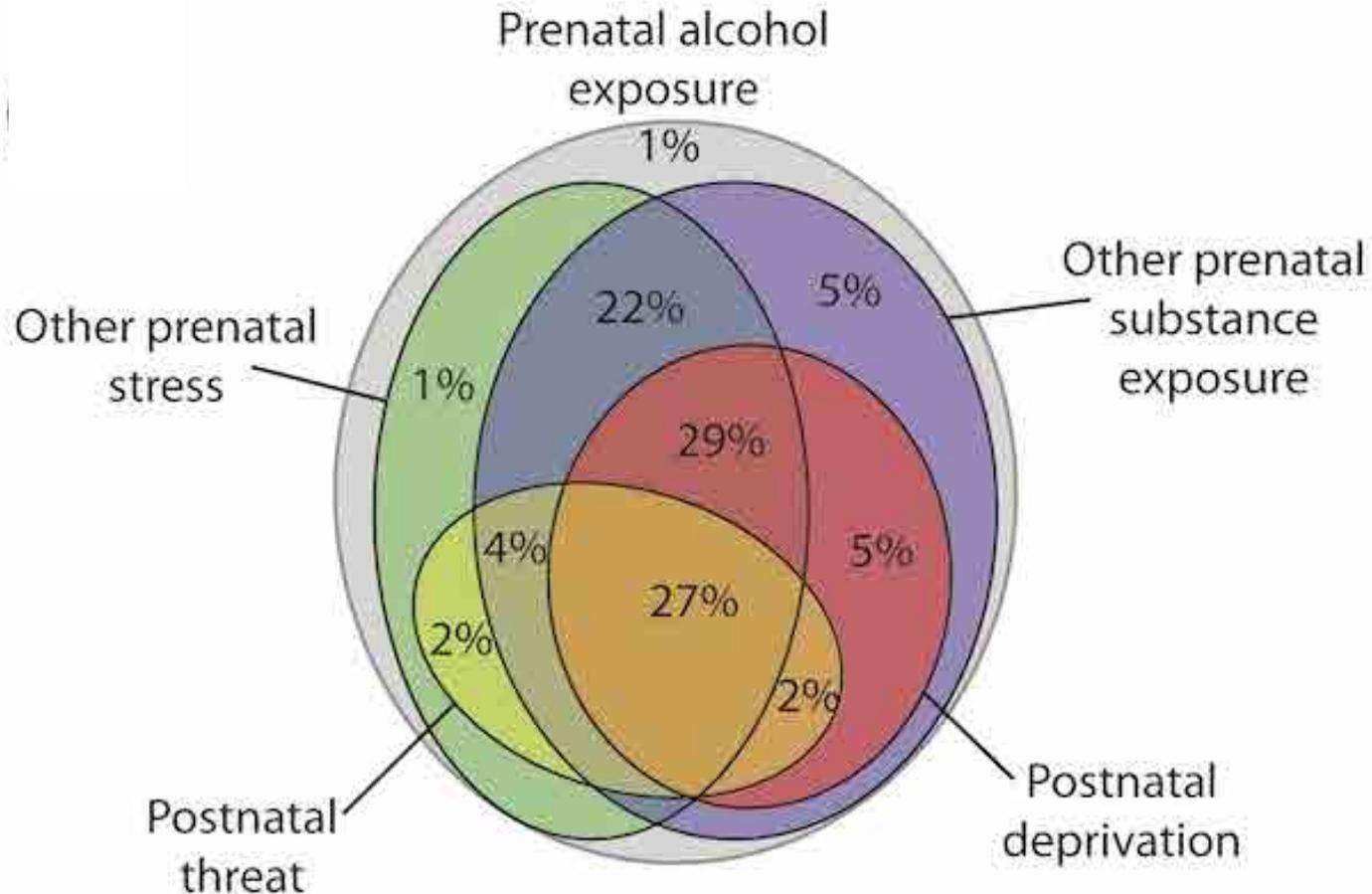
Prenatal Exposures



Postnatal Exposures



Overlapping Exposures



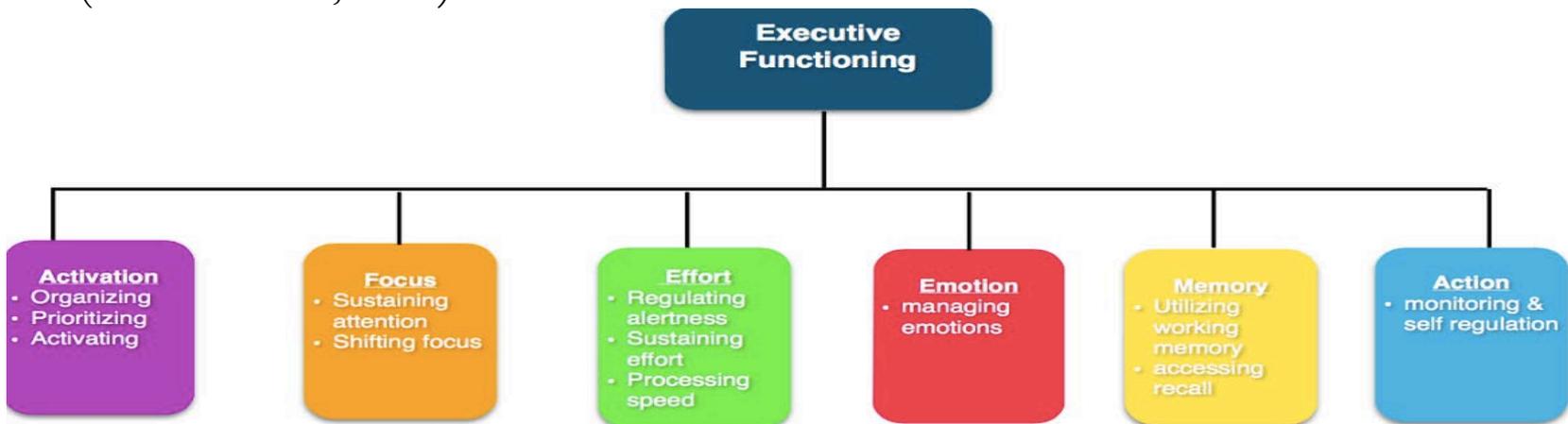
**Mental Health in
Individuals with PAE:
Role of
Neuropsychological
Processes**

Mental Health in Individuals with PAE

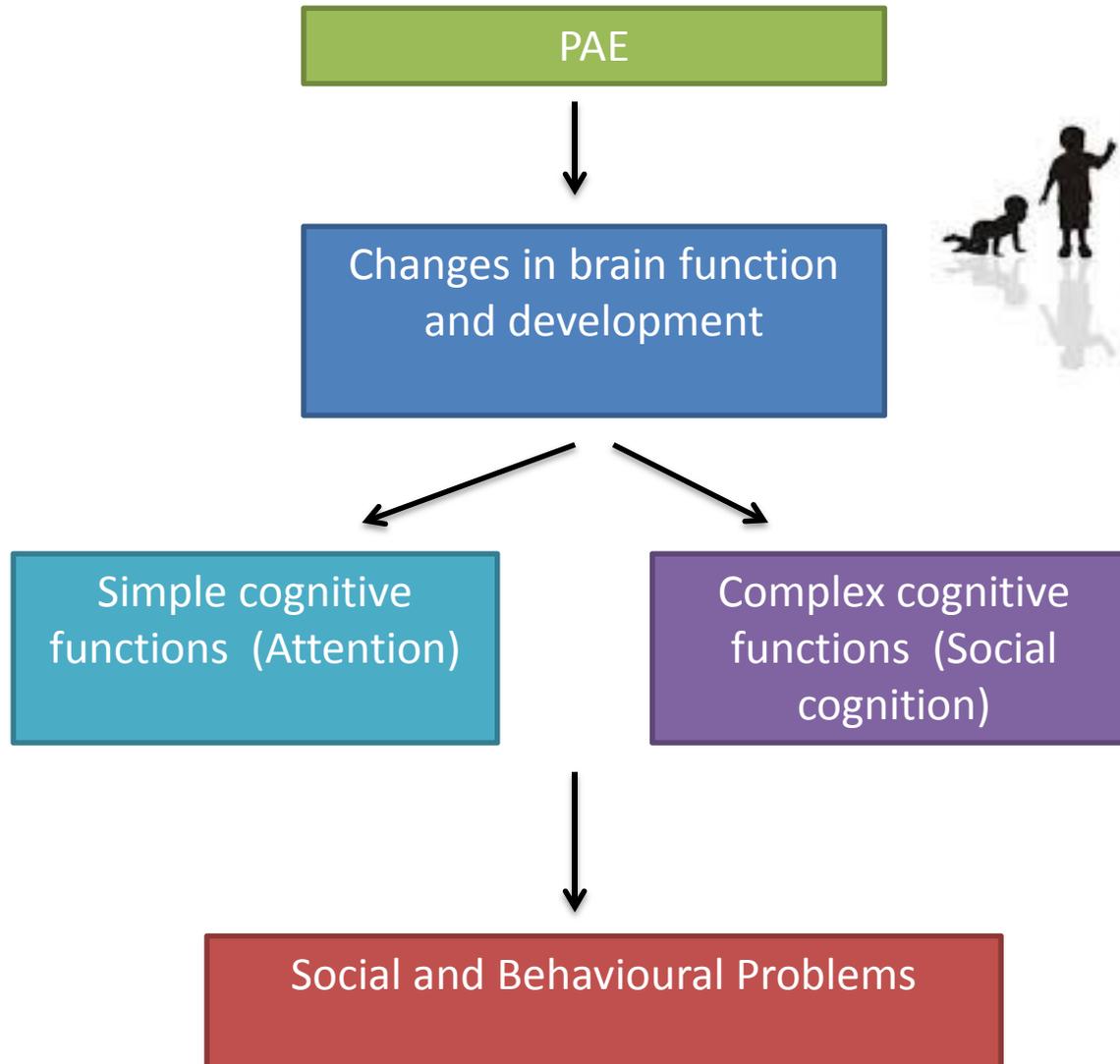
- Over 90% of individuals with FASD have co-occurring mental health issues (Pei et al., 2011)
- Internalizing and externalizing issues
 - Hyperactivity and depression most common
 - At risk for suicide and substance use
- Problems that emerge in childhood don't disappear with age
 - Lay the foundation for the development of later, more severe issues in adulthood

Neurobehavioural Outcomes

- Individuals with FASD often display various, yet heterogeneous, neurobehavioural impairments (Kodituwakku et al., 2009)
- Executive functioning (EF) is an area of significant impairment (Rasmussen et al., 2013)
- Poor performance on tasks involving processing of complex information & integration of information (Mattson et al., 2011)



MH and Neurobehavioural Outcomes



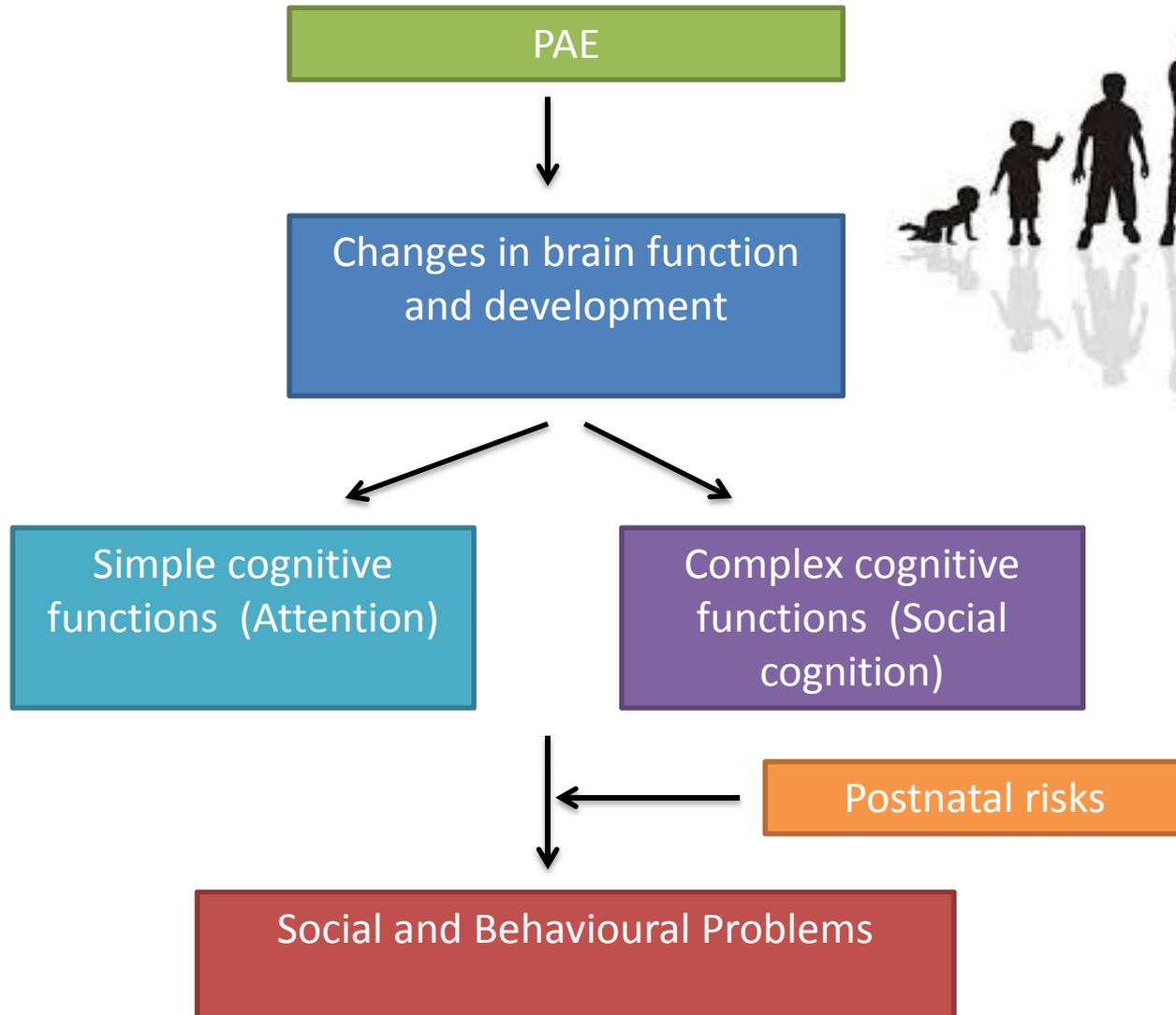
Role of Postnatal Risks

- Difficult to disentangle neurodevelopmental impact of PAE exposure from other postnatal risks
- Few studies have examined the **interaction of both exposures** (Price et al., 2017)
 - Exposure to both PAE and maltreatment is associated with higher risk of neurodevelopmental deficits than either exposure alone
 - Compounding relationship

Objectives

1. Investigate the association between mental health symptoms and neuropsychological processes
1. Determine if and how postnatal risks impact this relationship

MH and Neurobehavioural Outcomes



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DOCUMENTATION OF RISKS

- Pre- and post-natal risks
- Variety of records: birth, legal, adoption, and child and family services
- Self-report (when available)

COMPREHENSIVE ASSESSMENTS

- Cognitive functioning/IQ
- Academic ability
- Executive functioning
- Memory
- Mental Health

BRAIN IMAGING

- Diffusion MRI (dMRI)
- Resting state fMRI (rs-fMRI)
- Anatomical imaging (T1-weighted)

Sample

- **29 youth with documented PAE**
- 7.9yrs – 15.9yrs ($M= 10.4$, $SD= 2.33$)
- 18 males/11 females
- FSIQ 87.07 (59-106; Low average range)
 - Verbal Comprehension 85.90 ($SD=12.68$)
 - Perceptual Reasoning 93.07 ($SD=14.19$)
- 48.3% ($n = 14$) FASD dx
- 62% ($n = 18$) youth experienced postnatal risks



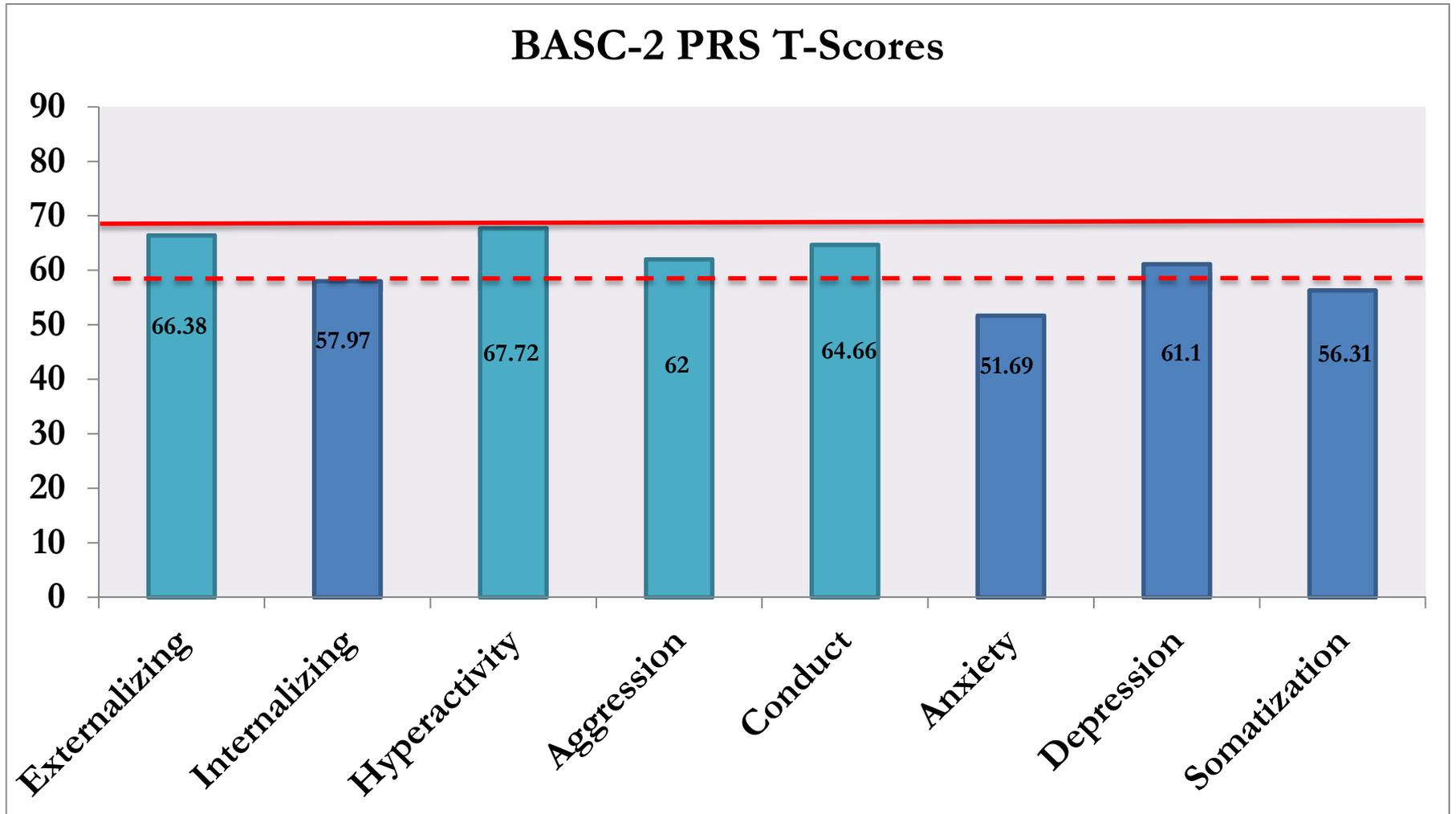
Methods

Visit Type	Assessing	Measure(s)
3 hour Lab visit	IQ	WASI-2
	Academic functioning	WIAT-III (math, reading & spelling)
	Executive functions	NEPSY-II (selected subtests); BRIEF
	Memory	CVLT-C
	Behavioural & Social-Emotional Functioning	BASC-2, CDI-2, MASC-2, DERS (self-report + caregiver)
Phone Interview (Caregiver)	Mental Health	K-SADS-PL
	Pre- and post-natal risks	Risk Assessment

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	Pre- and post-natal risks	Risk Assessment

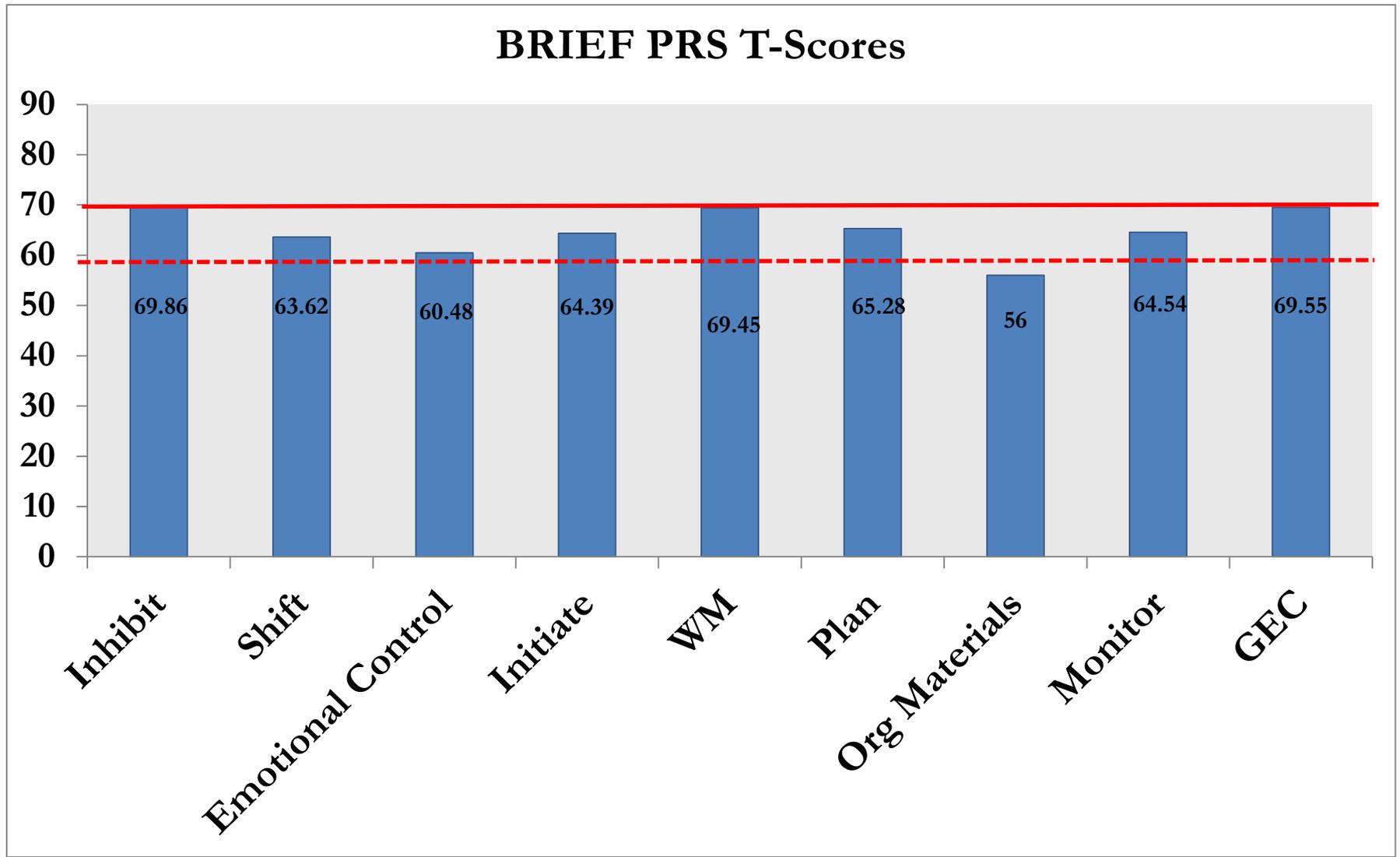
Preliminary Findings: Mental Health Symptoms



Preliminary Findings: Neuropsychological Outcomes

- **Academic Abilities**
 - Average performance on subscales related to reading
 - Below average performance on subscales related to math
- **Executive functioning**
 - NEPSY-II: Average to below average on comprehension of instructions, speeded naming and narrative memory

Preliminary Findings: Neuropsychological Outcomes



Preliminary Findings

- Age, IQ, and academic functioning *not* related to mental health symptoms
- Females ($M = 66.82$) more likely to experience internalizing mental health symptoms than males ($M = 52.56$), $F(1,27) = 5.06$, $p .033$.
- Executive functions (BRIEF PRS) significantly predicted mental health symptoms, all $ps < .05$.
 - Except anxiety

Preliminary Findings

Externalizing Issues

- Inhibiting
- Working memory
- Monitoring
- Planning

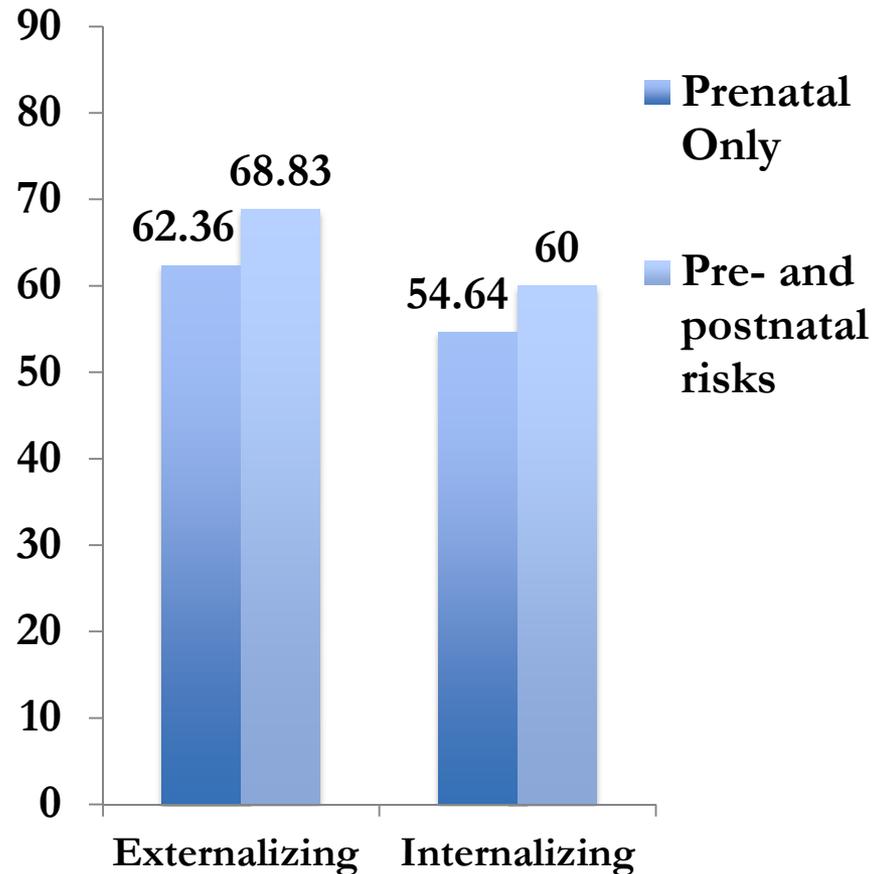
Internalizing Issues

- Emotional control
- Shifting
- Monitoring
- Global executive composite



Preliminary Findings

- Exposure to both pre- and postnatal risks did not predict severity of mental health symptoms, all p s $>$.05.
 - BUT some interesting trends related to MH and neuropsychological outcomes



Conclusions

- Mental health symptoms are **common** in children and youth with PAE
- Deficits in executive functions are associated with mental health symptoms
 - Emotional control and depression
- Youth who have been exposed to pre- and postnatal risks *may* experience **more severe mental health symptoms**
 - **BUT** fewer neuropsychological deficits

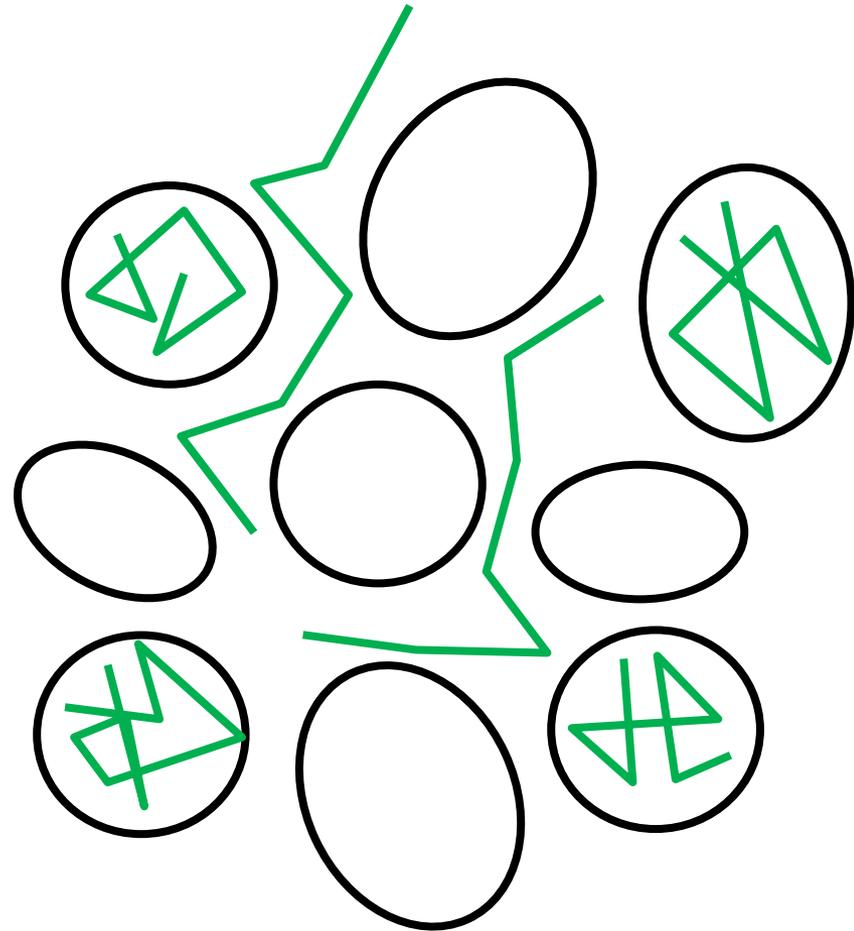
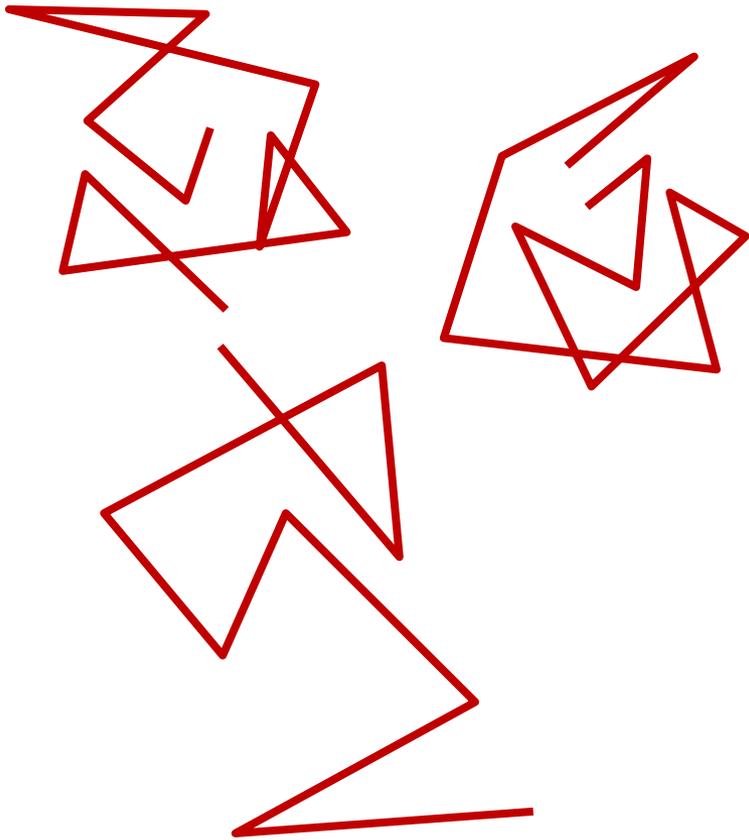
Brain Alterations



MRI

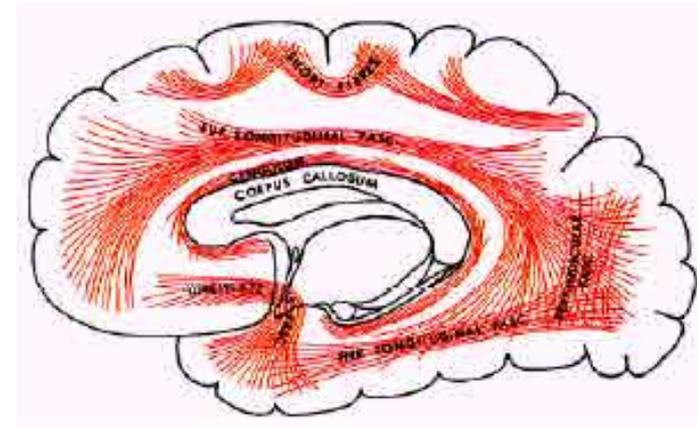
- 3T research-dedicated MRI scanner at ACH
- 77 children 2-16 years
 - 45 young: 2-7 years
 - 32 youth: 7-16 years

Water Diffusion

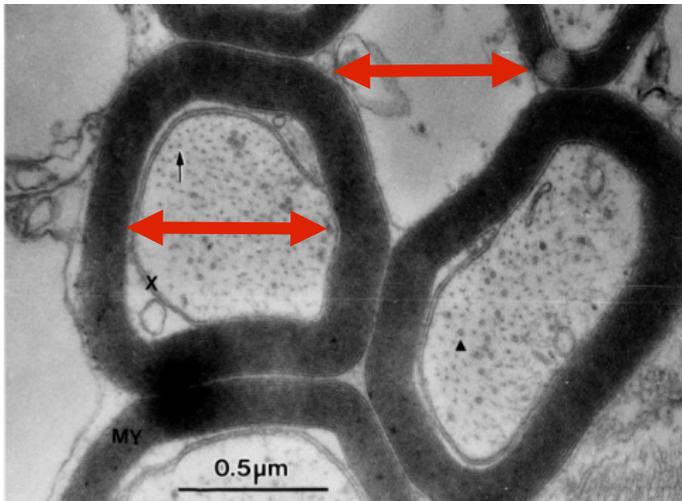


Diffusion in Brain White Matter

- White matter creates barriers to diffusion
 - Water follows path of least resistance

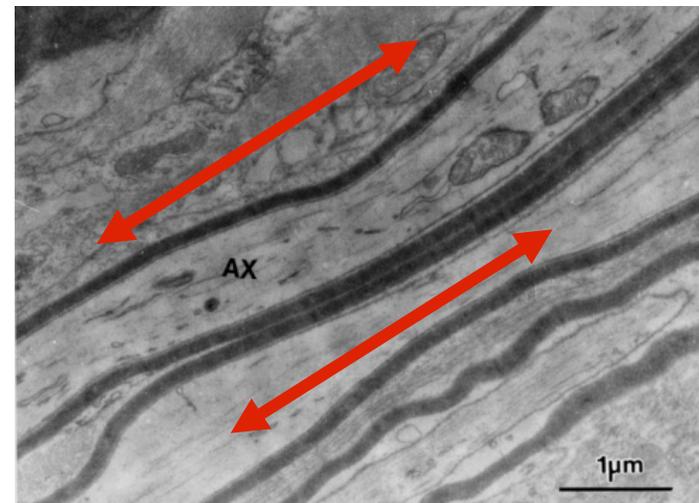


Perpendicular to Tract



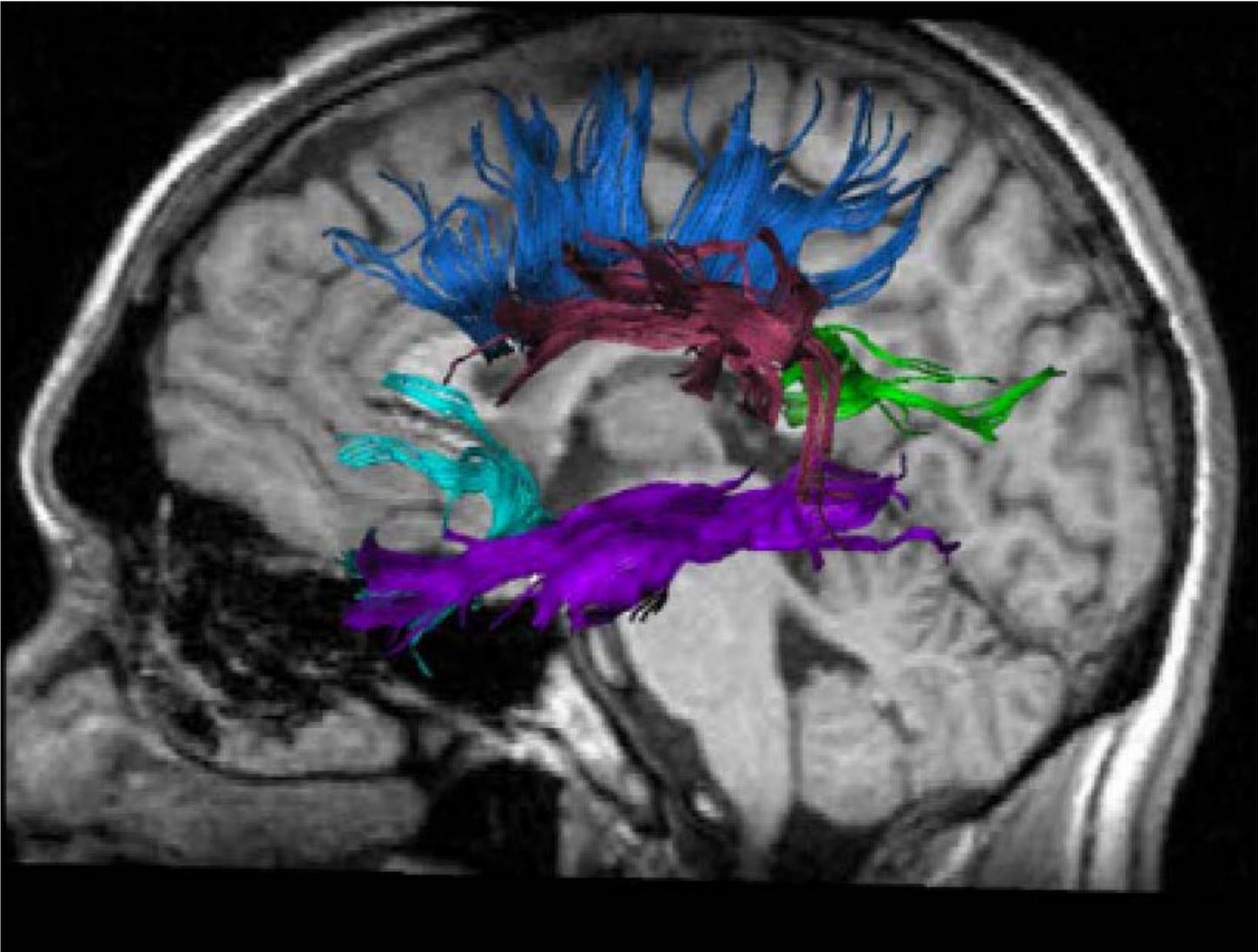
Slower water diffusion

Parallel to Tract



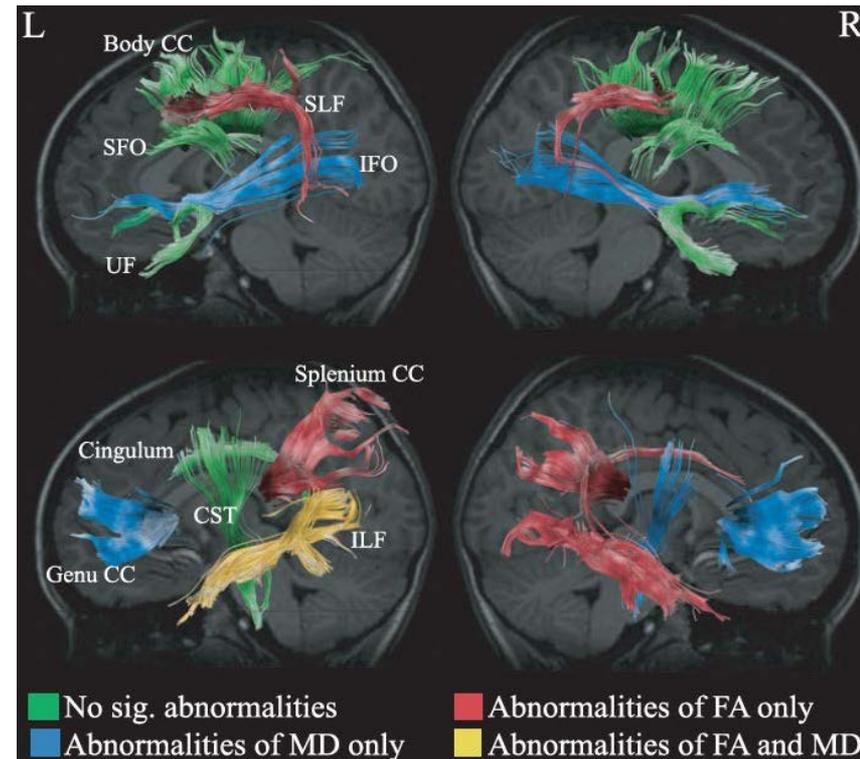
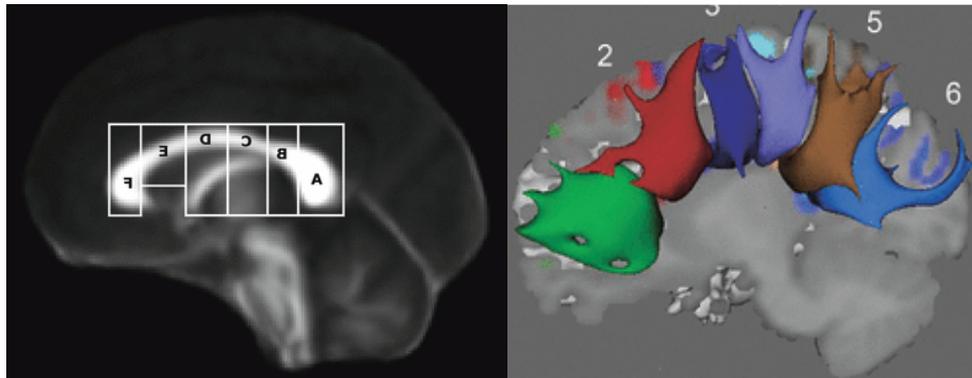
Faster water diffusion

Tractography



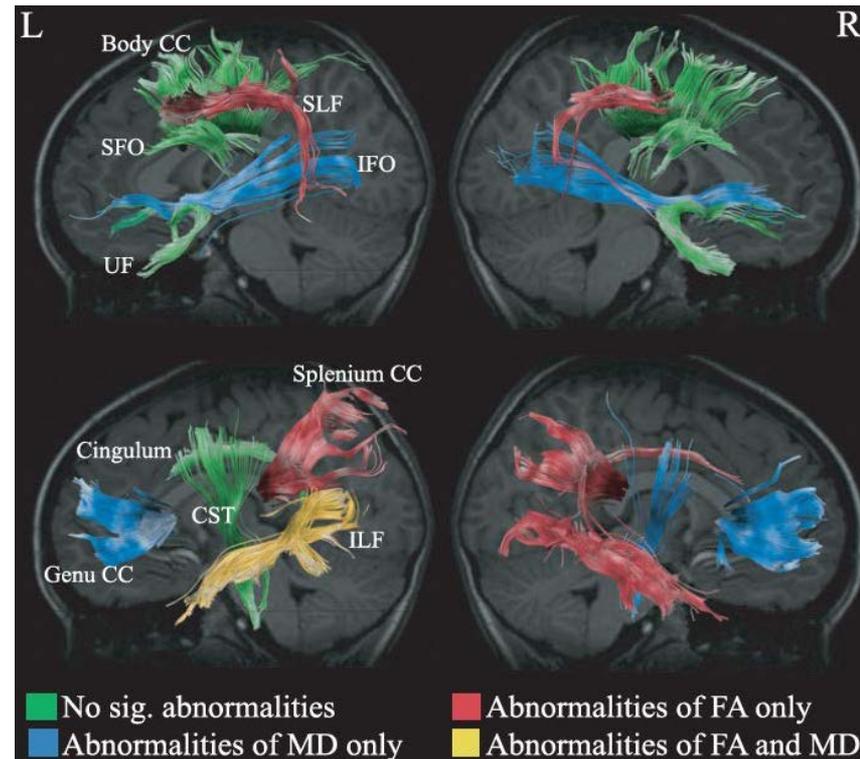
Neuroimaging in FASD

- Altered corpus callosum
- Structural brain abnormalities are widespread
- Include areas known to be implicated in internalizing and externalizing disorders
 - Frontal/temporal regions



Neuroimaging in FASD

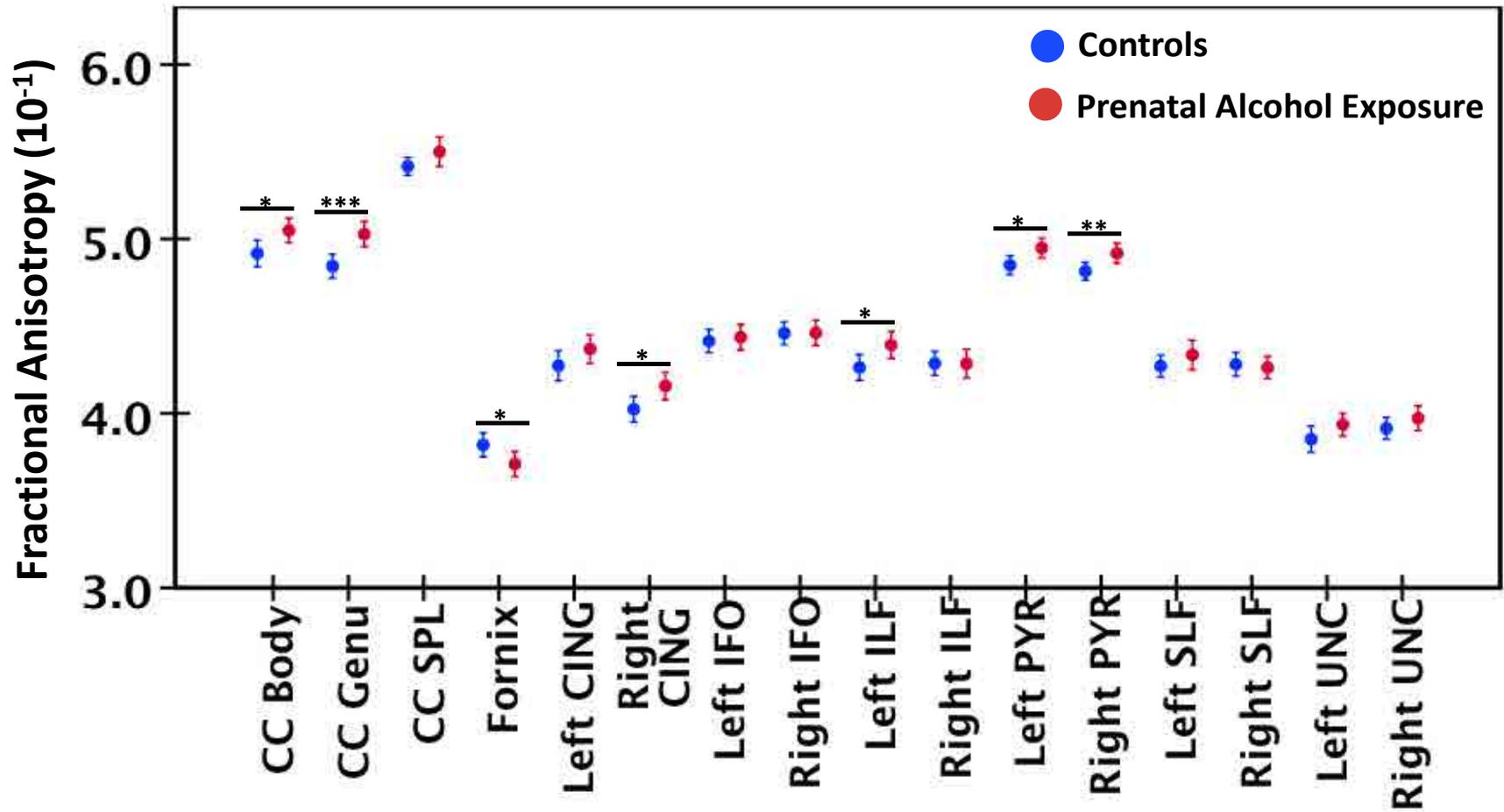
- Altered corpus callosum
- Structural brain abnormalities are widespread
- Include areas known to be implicated in internalizing and externalizing disorders
 - Frontal/temporal regions
- Studies focus on 8 years +
- Do not consider of postnatal exposures



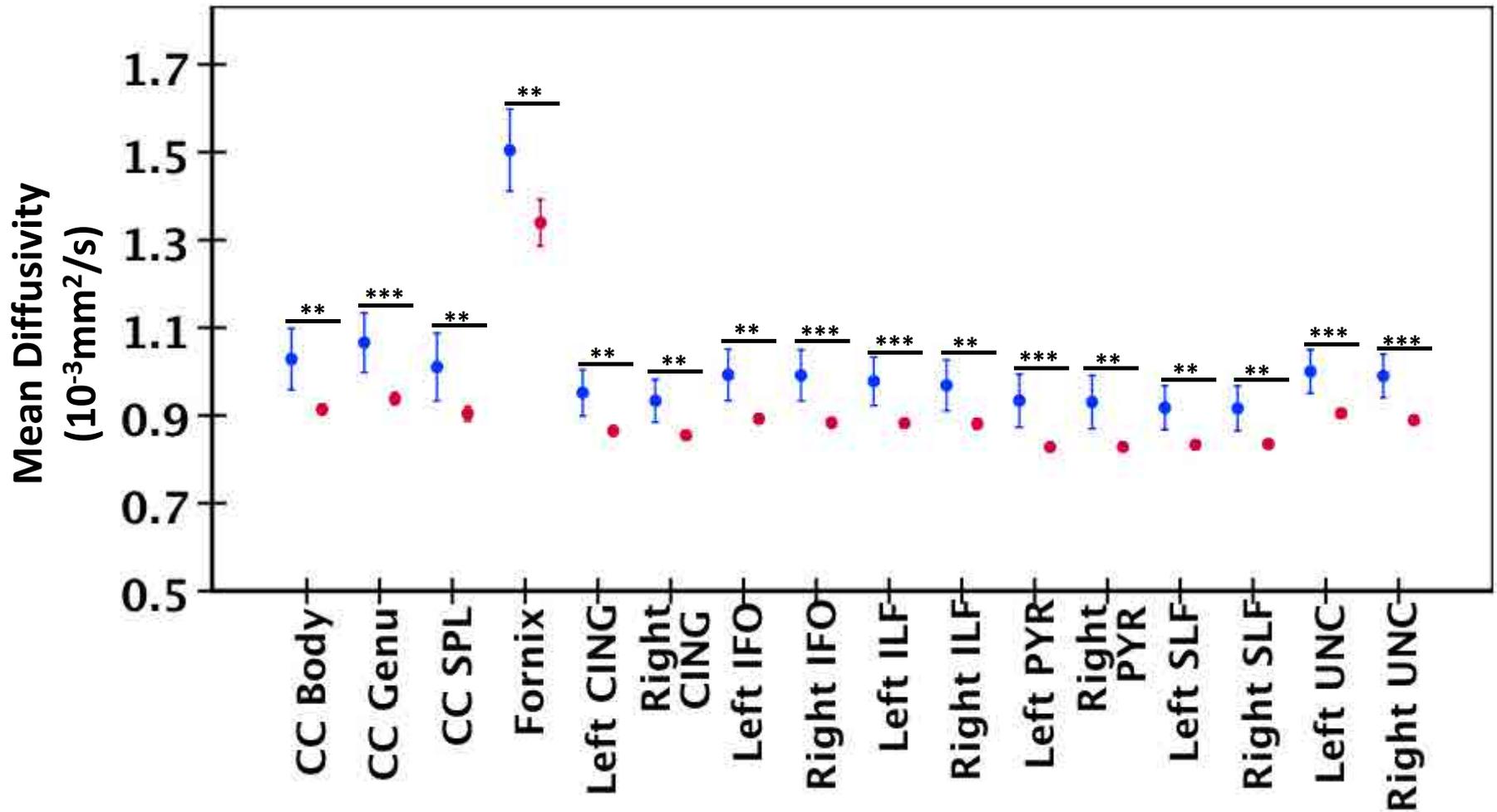
Our Population

- 45 young children with PAE: 2-7 years
 - 80% with postnatal exposures (abuse, neglect, etc.)
 - Matched unexposed controls
- 32 older children/adolescents with PAE: 7-16 years
 - 50% with postnatal exposures
 - Matched unexposed controls
- Diffusion tensor imaging

Young Children with PAE

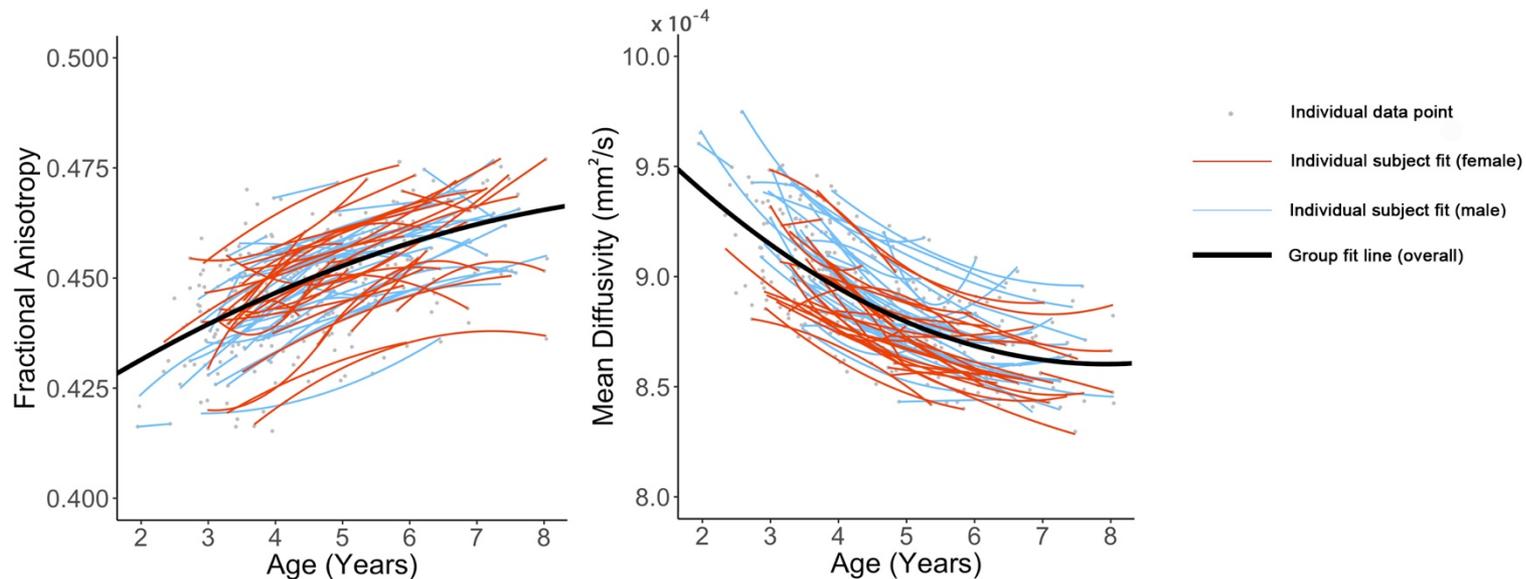


Young Children with PAE



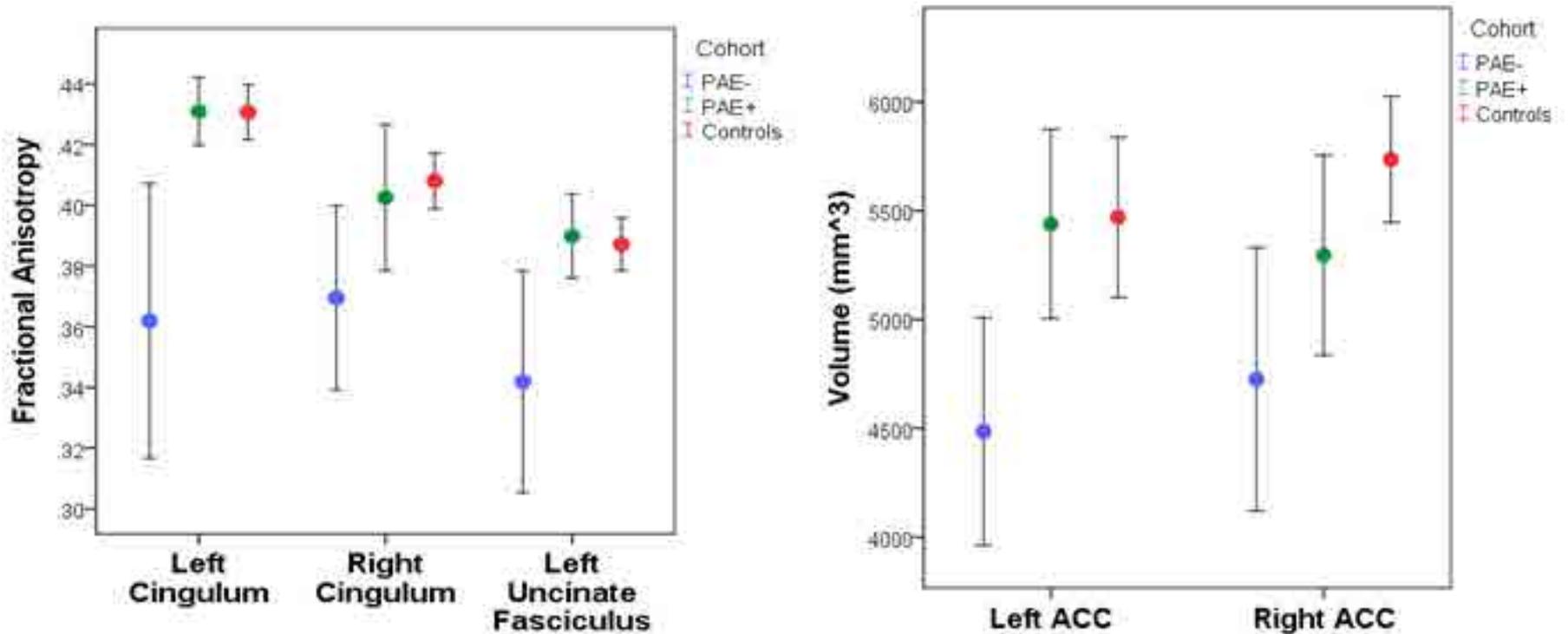
Young Children with PAE

- Higher FA, lower MD
 - More myelin, more densely packed white matter

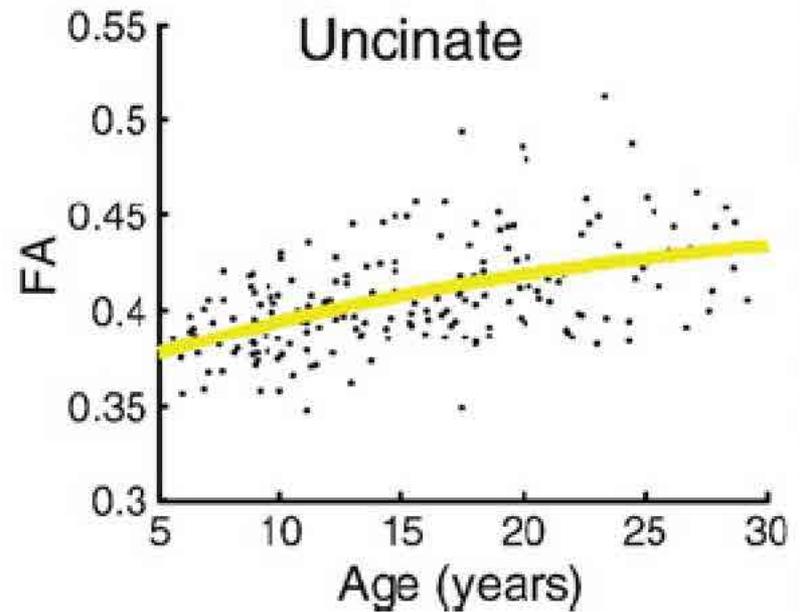
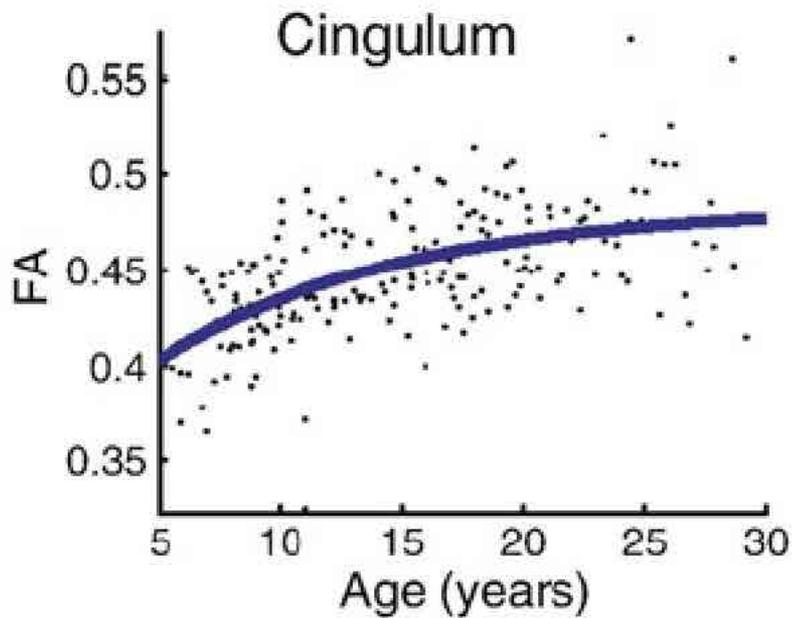


- FA increases, MD decreases with age

Brain Structure in Youth with PAE

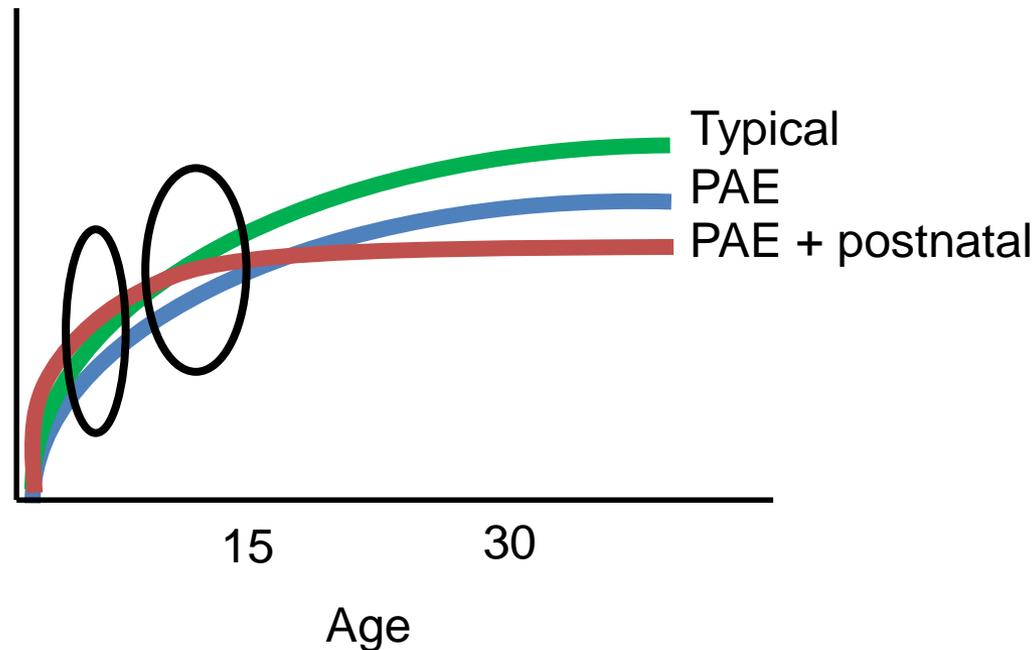


Typical Brain Development

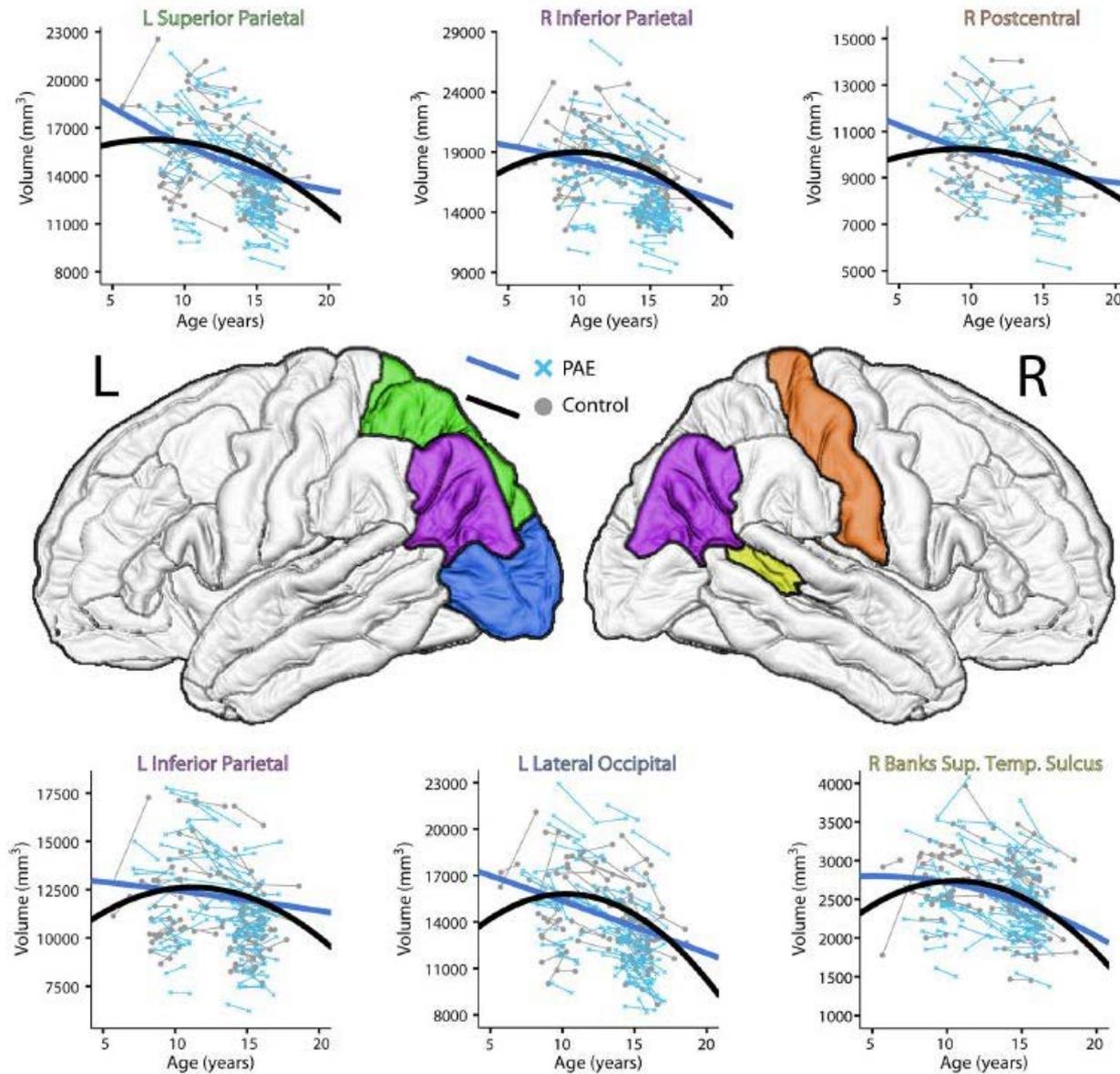


Altered Brain Development

- Trajectories are altered by PAE
- Different profiles at different times

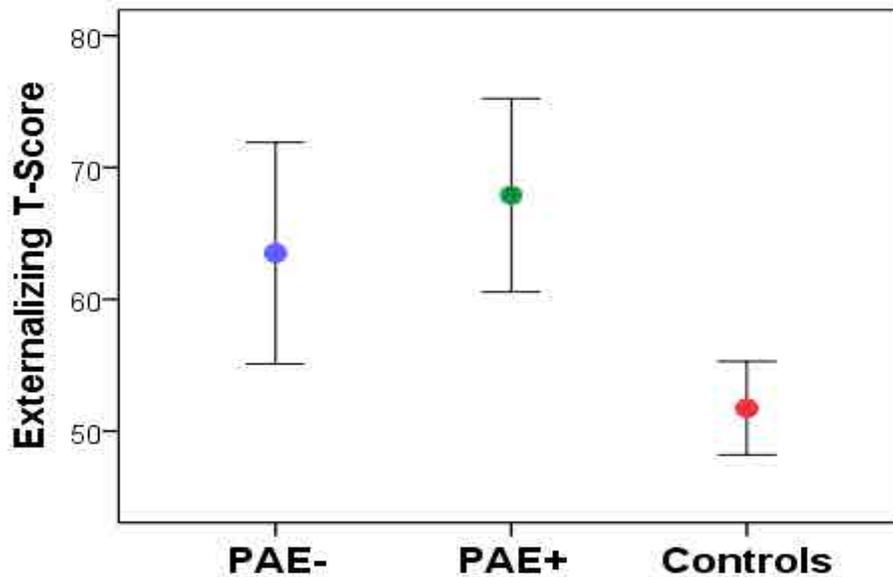


Cortical Development in FASD

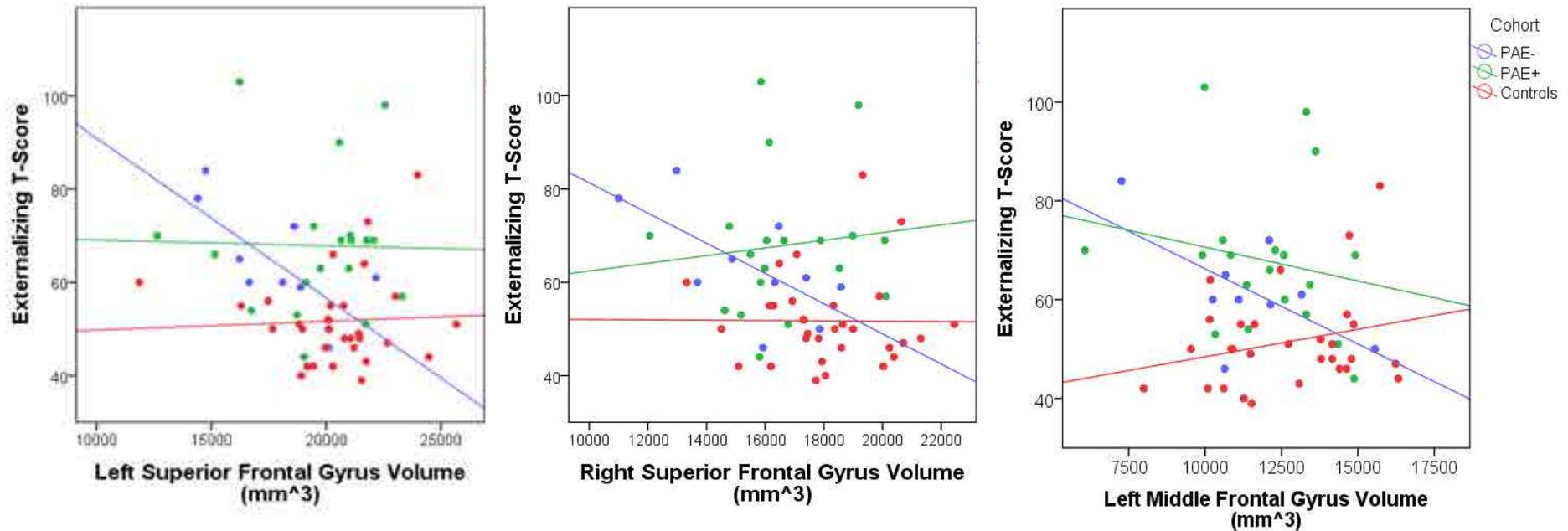


Lebel et al.,
J Neurosci, 2012

Mental Health Symptoms in Youth



Brain Structure – Mental Health Relationships



Brain Findings in PAE

- Higher FA in young children
- Lower FA in youth (moderated by postnatal exposures)
- Suggests altered development trajectories
 - Premature development with early plateau?
- Related to mental health symptoms dependent on postnatal exposures

Implications for Policy & Practice

Implications for Assessment

- Multiple exposures beyond PAE are common and important.
- Heterogeneity of exposure and outcome requires assessment across functional areas in development, behavior and mental health.
- Diagnostic processes must take into account other relevant exposures and a comprehensive multidimensional exposure review is required.

Implications for Assessment

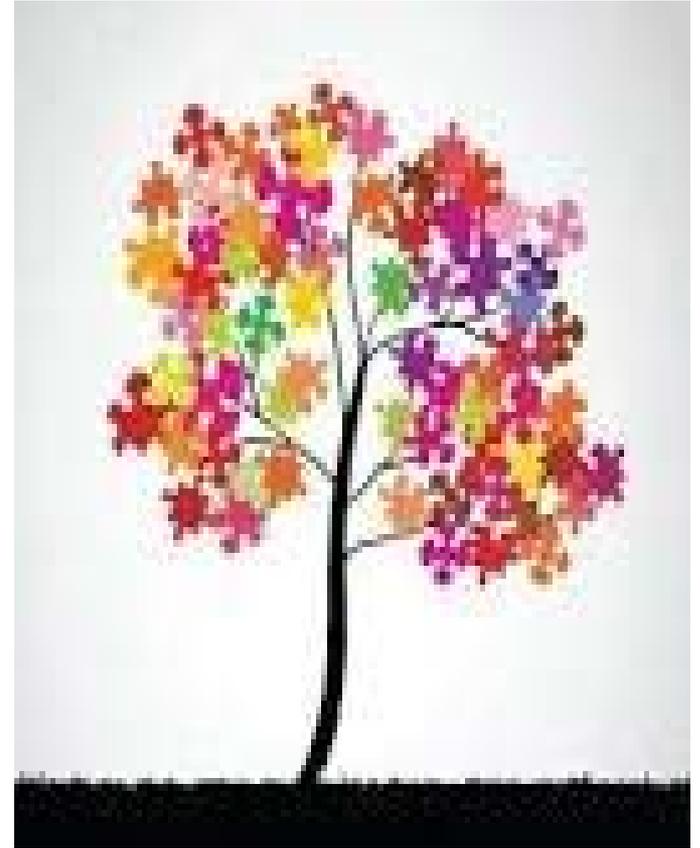
- Clinicians must expect complexity regarding exposures and associated outcomes, but also tolerate ambiguity as to which factors explain outcomes.
- Collaboration between clinicians is key to integrate assessment findings related to individual profiles of risk, protective factors and outcomes.
- Collaboration with other information sources such as Child Welfare will better inform the process.
- Recommendations must be individualized to the child/youth's personal story.

Implications for Assessment

- Recognize the priority for functional / developmental and mental health assessment.
- Acknowledge individual multiple exposure profiles, and the effect that other adverse exposures together have on child outcomes.
- Acknowledge the service need intensity for this population.
- Disseminate findings to all child-serving sectors to enhance understanding and service provision.
- Importance of knowledge translation to inform funding and policy.

Summary

- PAE matters
- Other prenatal and postnatal exposures matter
- The mental health story matters
- Environment matters
- Resilience matters



*Ask more questions, gather more information,
more fully tell the story, improve outcomes*

Upcoming Project

- CIHR-funded project to support continued research collaboration
- Mental health and brain abnormalities in youth with FASD
 - 120 FASD, 120 controls across Alberta
 - Comprehensive mental health and neurocognitive assessments
 - Structural and functional MRI scans
 - Recommendations for provision of care

More Info

- Posters:
- P02: The relationship between brain structure and mental health problems in children and adolescents with prenatal alcohol exposure
- P22: White matter microstructure in young children with prenatal alcohol exposure
- P39: The impact of placements on mental health outcomes in children exposed to alcohol prenatally

Acknowledgments

- Preeti Kar
- Quinn Andre
- Chantel Ritter
- Natalia Kruger
- Cumulative Risk Diagnostic Clinic
- Alberta Ministry of Children's Services



“The answers you get depend on the questions you ask!”

- Thomas Kuhn



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