UNDERSTANDING THE NEURODEVELOPMENT CONSEQUENCES OF PRENATAL ALCOHOL EXPOSURE (PAE)

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JULIE A. KABLE, PHD
GEORGIA PSYCHOLOGICAL ASSOCIATION ANNUAL MEETING, APRIL, 2016
AUGUSTA, GA
AAP and the ABA Statements

RESOLVED, That the American Bar Association urges attorneys and judges, state, local, and specialty bar associations, and law school clinical programs to help identify and respond effectively to Fetal Alcohol Spectrum Disorders (FASD) in children and adults, through training to enhance awareness of FASD and its impact on individuals in the child welfare, juvenile justice, and adult criminal justice systems and the value of collaboration with medical, mental health, and disability experts.

FURTHER RESOLVED, That the American Bar Association urges the passage of laws, and adoption of policies at all levels of government, that acknowledge and treat the effects of prenatal alcohol exposure and better assist individuals with Fetal Alcohol Spectrum Disorders (FASD): WHAT YOU NEED TO KNOW TO HELP YOUR CLIENTS

Presented by
The American Bar Association
Section of Litigation
and the ABA Center for Continuing Legal Education
OUTLINE OF TODAY’S WORKSHOP: LEARNING OBJECTIVES

Participants will:

1. understand the neurodevelopmental consequences of prenatal alcohol exposure.

2. be familiar with the empirical evidence supporting the FASD diagnoses, including ND-PAE (Neurodevelopmental Disorder-Prenatal Alcohol Exposure) and how to apply these to their diagnostic assessment of alcohol-affected individuals across the lifespan.

3. Understand treatment approaches used for habilitative care of alcohol-affected individuals.
OUTLINE FOR THE WORKSHOP: SCHEDULE

• 2:00 PM-Introduction
• 2:10 PM- Understanding the Neurodevelopmental Effects of Prenatal Alcohol (and other drug) Exposure
• 2:45 PM- Questions and Discussion
• 3:00 PM- The Psychologist’s Role: Diagnosing Behavioral Effects of PAE, including ND-PAE
• 3:25 PM- 15 minute Break
• 3:40 PM- Diagnostic Domains over the lifespan
• 4:00 PM-Treatment Approaches
  • The ENEC Clinic Approach, Differential Diagnosis and Medication management
  • MILE-Academics and Behavior for School Aged children
  • Go-FAR- A promising approach for Reducing Disruptive Behavior
• 4:45 – Questions and Discussion
Teratogen

“Substance causing fetal malformation or monstrosities.”

THERE ARE MANY TERATOGENS

Known Teratogens include:

• Diseases (CMV, Toxoplasmosis, rubella)
• Environmental Toxins (Lead, Mercury)
• Prescription Medications (Thalidomide, Warfarin, Accutane)
• Drugs of Abuse (Alcohol)

Here is a picture of a child with microcephaly associated with the Zika Virus.
FASDS HAVE BEEN AROUND FOREVER...

1751 by English artist William Hogarth

1725 the College of Physicians in London warned the British House of Commons that alcohol is "too often the cause of weak and feeble, distempered children"

Book of Judges (13: 3,4)

The Anatomy of Melancholy (Burton, 1621), in which he is apparently quoting verbatim statements from ancient Greek and Roman writers which imply more than a rudimentary awareness of alcohol-related birth defects.

Burton appears to quote, e.g. the Roman miscellanist, Aulus Gellius (b. 125 ad) (‘if a drunken man get a childe, it will never likely have a good braine’)
ABOUT THE DISCOVERY OF FASD


IF WE KNOW THAT ALCOHOL USE IN PREGNANCY CAUSES FASD, WHY DOES IT CONTINUE?

• 50% of all pregnancies in the US are unplanned.
• 70% of women of child bearing age drink alcohol;~30% drink during pregnancy; 3% drink at risky levels.
• Alcoholism is an addiction—a mental health disorder with a biological basis
• 10% of Americans have a problem with alcohol
• Our society has chosen not to address these problems adequately.
ENVIRONMENTAL FACTORS: EFFECTS OF SUBSTANCE ABUSE ON CARETAKING

• Death of parent
• Loss of custody
• Depressed mother
• Neglect / Abandonment
• Abuse
• Inconsistent parenting
• Failure of attachment
• Failure to use social / medical services
HOW IS FASD DIAGNOSED?

- Alcohol Exposure
- Face
- Growth
- Brain
  - Developmental Disabilities
  - Learning Problems
  - Behavior Problems
DIAGNOSTIC CHECKLIST FOR CRITERION 1

- Alcohol Exposure: ____________________________ Yes [ ]
  - Maternal report…………………………………….. [ ]
  - Urine toxicology screen from birth/hospital records…… [ ]
  - DFCS Home study reports……………………………. [ ]
  - Maternal drug/alcohol treatment……………………. [ ]
  - Alcohol-related medical problems ........................ [ ]
  - Legal problems associated with alcohol use…………… [ ]
  - Reliable report of a consistent pattern of alcohol use .... [ ]
  - “Registered alcoholic” from Russia…………………….. [ ]

- Note: The list does not include “suspected” alcohol use because:
  - The woman used drugs including marijuana.
  - Someone thinks that she drank but never observed it themselves.
  - There is a legal battle going on over custody.
  - There is a general suspicion about the woman’s character and behavior.
  - The child has behavioral characteristics that some people associated with alcohol exposure.
  - The child was adopted internationally.
CRITERION 2: GROWTH DEFICIENCY (<10TH %)

• **Growth Deficiency:** Yes [ ]

  • Birth weight percentile (<10th %) ........ [ ]
  • Birth length percentile (<10th %) ........ [ ]
  • Current weight percentile (<10th %) ....... [ ]
  • Current height percentile (<10th %) ....... [ ]

• **Birth Records:**
  • weight, length, head circumference
  • Percentiles
  • Gestational Age

• **Current Growth:**
  • weight, length, head circumference
  • Percentiles

• Identifying any other factors that may account for growth failure rather than alcohol exposure.
  • Neglect
  • Feeding disorders
  • Medical conditions
CRITERION 3: DYSMORPHOLOGY

- **Checklist Score:** Yes [ ]

- **Dysmorphia Score:** [ ]
  (Scores greater than 10 suggest alcohol effects.)

- **Narrative disqualifier:**
  (This is used if we think that the score is not measuring alcohol pathology but is the result of other factors.)
DOSE/RESPONSE RELATIONSHIP BETWEEN DYSMORPHIA SCORES AND OZ AA/WK

Lynch, et al., 2004
CRITERION 4: NEURODEVELOPMENTAL

CNS Damage: [ ]

- CATEGORY 1:
  - Birth Head circumference percentile (< 2 yrs)...... [ ]
  - Head circumference Percentile.............................. [ ]
  - CT/MRI Abnormality Past...................................... [ ]
  - CT/MRI Present.................................................... [ ]
  - Cognitive/Intellectual Ability.............................. [ ]
  - Visual-spatial Ability........................................... [ ]

- CATEGORY 2:
  - Graphomotor Skills............................................ [ ]
  - Math Skills....................................................... [ ]
  - Executive Function Skills...................................... [ ]
  - Working Memory.................................................. [ ]
  - Processing Speed............................................... [ ]
  - Memory Organizational Skills.............................. [ ]
  - Learning/Encoding Deficit..................................... [ ]
  - Other (list:______________________________________) [ ]

Narrative disqualifier:

(This is used if we think that the score is not measuring alcohol pathology but is the result of other factors.)
SPECTRUM OF EFFECTS OF PRENATAL ALCOHOL EXPOSURE

- Fetal Alcohol Spectrum Disorders (IOM, CDC)
  - Fetal Alcohol Syndrome (FAS)
  - Partial FAS
- Alcohol Related Neurodevelopmental Disorder (ARND)
- Neurodevelopmental Disorder-Prenatal Alcohol Exposure (ND-PAE) *

FAS- (Alcohol Exposure), Face, Growth, Cognition & Behavior

pFAS-Alcohol Exposure, Cognition/Behavior and one of Face or Growth

ARND-Alcohol Exposure and Cognition

ND-PAE-Alcohol Exposure, Cognition, Behavior and Adaptive

*Source: ND-PAE-DSM-V, 2013
THE TIP OF THE ICEBERG
Fetal Alcohol Spectrum Disorders (FASDs)

FAS
1 per 1000

Partial FAS
5 per 1000

Alcohol-related Birth Defects
1 per 100

Alcohol-related Neurobehavioral Effects

73,000 Alcohol-Affected Georgia Citizens, 0 to 21 years
DIAGNOSES FOR FASD

• The IDC code used is specific to the discipline. That is, physicians can use medical codes (i.e., Q86.0). Psychologists and other practitioners of “behavioral health” have to use “behavior” codes.
• The only FASD specific behavioral code is 315.8-ND-PAE
• Other conditions can be diagnosed in addition those that are alcohol-specific, e.g.,
  • Intellectual Disability (F70, 71, 72, 73)
  • Global Developmental Delay (F88), Language Dx (F80.9), et
  • Learning Disorders (e.g, with math impairment, F81.2)
  • All kinds of behavior disorders
OF SPECIAL INTEREST TO PSYCHOLOGISTS
PAE AND NEUROBEHAVIOR

Diagnosis
• Are there Specific Domains that reflect the effects of exposure?
• How to discriminate the effects of the teratogen from other environmental and familial factors that may affect outcomes (and why do you need to?)
• “Standards of care”

Treatment
• Medication Effects in FASD?
• Supplements?
• Specific Behavioral Methods that are effective?
• Educational interventions that are effective?
Children with FASD may have problems in the following areas through out their lives:

**Physical/Health/Motor**
- Vision
- Heart Defects
- Neurology
- Gross and Fine Motor
- Feeding issues
- Sleep problems
- Immune System

**Developmental/Cognitive**
- Global Developmental and cognitive deficits
- Specific learning deficits
- (Nonverbal learning Disability)
- Executive Functioning DX
- Visual/Spatial Deficits

**Behavioral/Social**
- Arousal Dysregulation
- Disruptive Behavior DX
- Dx of Self Regulation
- Depression
- Secondary Behavior Disorders

**Academic/Vocational**
- Academic Difficulties
- Specific Math Disability
- Vocational underachievement

How does PAE affect the individual?

- Academic Difficulties
- Specific Math Disability
- Vocational underachievement

- Executive Functioning DX
- Visual/Spatial Deficits
DAMAGE TO THE CNS IS THE BASIS FOR BEHAVIORAL EFFECTS OF FASD

• Reduction in overall brain volume
• Malformations and reduction of volume of grey and white matter
• Thin or missing corpus callosum
• Alteration in brain activation
• Alterations in functional connectivity
CORTEX AND CEREBELLUM VOLUME IN ALCOHOL AFFECTED ADULTS AND TWO CONTROL GROUPS (N=78)

In Cerebral Cortex, Dysm<Controls, Left, p<.008; Right, p<.05, no other groups are significantly different.

Brain Volume Loss in Alcohol Exposed Individuals. Reflected in Microcephaly

Coles, Li, et al. 2008
In Cerebral Cortex, both alcohol groups differ from both control groups and not from each other.

Specific White Matter Volume Loss in both PAE groups

Coles, Li, et al. 2008
DTI STUDIES

- **White matter integrity** - Using Diffusion Tensor Imaging (DTI), identify effects of PAE in corpus callosum

- Assumption, there are specific effects on White Matter integrity in brain
Segmentation of the corpus callosum (A), in which some portions (1, 4 and 5) exhibited the general PAE effect (B). 1: Anterior, 2: Mid-Anterior, 3: Central, 4: Mid-Posterior, 5: Posterior.

OVERALL CONCLUSIONS:
PRENATAL ALCOHOL EXPOSURE

• Evidence for persistent, global deficits even when SES and postnatal environment accounted for.

• In addition to global deficits, there may be specific cognitive problems in the following areas: Motor functioning, visual spatial skills, math, memory.

• MRI (and fMRI) suggest neurological basis for behavioral findings.
DIAGNOSING BEHAVIORAL EFFECTS OF PAE INCLUDING ND-PAE

Julie A. Kable, PHD
WHY IS A DSM-5 DIAGNOSIS NEEDED FOR INDIVIDUALS WITH AN FASD?

- Currently there is no specific mental health code that adequately documents the cognitive and mental health impact of PAE.
- The existing diagnostic codes do not adequately capture their mental health needs.
- Children with FASD may not respond to treatment regimens developed using the existing codes similarly, which may lead to inappropriate treatments.
- **When seeking mental health care (assessments or interventions), providers and families often struggle with obtaining appropriate reimbursement for habilitative care**.
Need to advance the science so it is accepted completely as a disorder and receives its own unique code 315.81
NEUROBEHAVIORAL DISORDER ASSOCIATED WITH PRENATAL ALCOHOL EXPOSURE

History of More than Minimal Levels of PAE*

Domain: Neurocognitive Impairment
• Global IQ (IQ < 70)
• Executive function impairment
• Learning impairment
• Memory impairment
• Visual spatial reasoning impairment

Domain: Impairment in Self-regulation
• Impairment in mood or behavioral regulation
• Attention deficits
• Impairment in impulse control

Domain: Deficits in Adaptive Functioning Skills
• Communication deficit
• Social impairment
• Daily living skills impairment
• Motor impairment

ND-PAE

>13 drinks per month or more than 2 on one occasion

*Symptoms

Global IQ (IQ < 70)
Executive function impairment
Learning impairment
Memory impairment
Visual spatial reasoning impairment
Impairment in mood or behavioral regulation
Attention deficits
Impairment in impulse control
Communication deficit
Social impairment
Daily living skills impairment
Motor impairment
• History of More than Minimal Levels of PAE

- Amount not specified in actual criteria but guidelines are in the supporting text
  >13 drinks per month or more than 2 on one occasion
- If child meets criteria for full FAS then ND-PAE can be diagnosed without documented exposure
- Documentation can be from maternal self-report, medical and other records, or clinical observation
B. Neurocognitive impairment, as evidenced by 1 (or more) of the following:

- **Global intellectual impairment** (i.e., IQ of 70 or below, or a standard score of 70 or below on a comprehensive developmental assessment).
- **Impairment in executive functioning** (e.g., poor planning and organization; difficulty changing strategies or inflexibility; difficulty with behavioral inhibition).
- **Impairment in learning** (e.g., lower academic achievement than expected for intellectual level; requires special education services; specific learning disability).
- **Impairment in memory** (e.g., problems remembering information learned recently; repeatedly making the same mistakes; difficulty remembering long verbal instructions).
- **Impairment in visual spatial reasoning** (e.g. disorganized or poorly planned drawings or constructions; problems differentiating left from right; problems aligning numbers in columns).
EXECUTIVE FUNCTION IMPAIRMENTS IN FASD

- Individuals with FASDs demonstrate difficulties:
  - Regulating basic attention
  - In planning and organization
  - Mentally manipulating information
  - In changing strategies or thinking about things in more than one way
  - In abstract reasoning
  - Problems generalizing or applying knowledge to new situations
VISUAL SPATIAL IMPAIRMENTS

• Visual memory
• Visual perception
• Visual-motor integration
• Spatial memory

Everyday Symptoms:
• Disorganized or poorly planned drawings or constructions
• Perceptions of time, size, distance, or intensity (quantity)
• Problems differentiating left from right;
• Problems aligning numbers in columns
C. Impairment in self-regulation in 1 (or more) of the following:

- Impairment in mood or behavioral regulation (e.g., mood lability; negative affect or irritability; frequent behavioral outbursts).
- Attention deficit (e.g., difficulty encoding new information; difficulty shifting attention; difficulty sustaining mental effort).
- Impairment in impulse control (e.g., difficulty waiting turn; difficulty complying with rules; confabulating; taking possessions of others).
Early Signs of Dysregulation

- Greater stress reactivity
- Sleep disruption
- Negative affectivity
A Comparison of Children Affected by Prenatal Alcohol Exposure and Attention Deficit, Hyperactivity Disorder

Claire D. Coles, Kathleen A. Platzman, Cheryl L. Raskind-Hood, Ronald T. Brown, Arthur Falek, and Iris E. Smith

Patterns of neuropsychological impairments in children with FASD and ADHD. Note that domains listed for each group name have been directly compared. See text and Table 1 for details and related references.

An Event-Related Potential Study of Response Inhibition in ADHD With and Without Prenatal Alcohol Exposure


Fetal alcohol spectrum disorders: neuropsychological and behavioral features.

Maltson SN*, Crocker N, Nguyen TT.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dysfunction</th>
<th>Differences</th>
<th>Stimulus changes needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>Easily over aroused</td>
<td>Downward shift in need for central stimulation or reduced ability to modulate or habituate stimulus input</td>
<td>Reduce sensory input</td>
</tr>
<tr>
<td>ADHD</td>
<td>Under aroused</td>
<td>Shift in level of central stimulation found to be optimal from inadequate neurotransmission of incoming stimulation</td>
<td>Respond to stimulant medications and increases in arousal</td>
</tr>
<tr>
<td>FAS</td>
<td>Arousal dysfunction</td>
<td>Slower gating of incoming stimulation and reduced capacity to inhibit attending to distracting stimuli</td>
<td>Respond to simplification of sensory input (fewer distracters and slower presentation)</td>
</tr>
<tr>
<td>Cocaine Exposure</td>
<td>Heightened arousal responses</td>
<td>Over aroused by stimulation and difficulties returning to baseline levels. Also has difficulties with maintaining inhibitory control</td>
<td>Monitoring of arousal level so stimulus input can be modified when too high. Longer periods allowed for recovery of functioning</td>
</tr>
</tbody>
</table>
SELF-REGULATION IMPACT ON LEARNING: DEFICITS IN AFFECTIVE SHIFTING

- Children and adults with FASDs have been found to have particular difficulties with reversal shift learning (also called affective shifting) (Chasnoff, et al., 2010; Coles, Platzman, et al., 1997; Kerns, et al., 1997; Kodituwakku, et al., 1995), which involves incorporation of feedback during stimulus-reward association.
SELF-REGULATION IMPACT ON LEARNING: COPING WITH NEGATIVE FEEDBACK OF FAILURE

Individuals diagnosed with FASD deteriorates under conditions of negative feedback during reward protocols and that this deterioration is predictive of parent-rated behavioral problems (Kodituwakku, May, Clericuzio, & Weers, 2001)

Emotion-related learning in individuals prenatally exposed to alcohol: an investigation of the relation between set shifting, extinction of responses, and behavior

Piyadasa W. Kodituwakku a,*, Philip A. May a, Carol L. Clericuzio b, David Weers c

a Center on Alcoholism, Substance Abuse, and Addiction, University of New Mexico, Albuquerque, NM 87106, USA
b Department of Pediatrics, University of New Mexico, Albuquerque, NM 87106, USA
c Department of Psychology, University of New Mexico, Albuquerque, NM 87106, USA

Received 31 December 1999; received in revised form 1 December 2000; accepted 14 December 2000

Abstract

The association between deficits in emotion-related learning, conceptual set shifting, and behavioral problems was investigated in individuals with substantial prenatal alcohol exposure. Twenty subjects with confirmed prenatal alcohol exposure (10 of whom were diagnosed as having Fetal Alcohol Syndrome) and 20 normal controls matched for age, gender, and ethnic background participated. The two groups were administered a battery of tests including two tests of emotion-related learning (visual discrimination reversal and extinction of reward–response associations), tests of conceptual set shifting and intellectual ability, and behavioral measures. The alcohol-exposed group made fewer reversals than the control group in visual discrimination reversal and exhibited more variability in extinction. These group differences remained significant after controlling for intellectual ability and conceptual set shifting. Variability in extinction and two measures of set shifting, perseverative errors on the Wisconsin Card Sorting Test and omission errors on reversal learning, were found to be robust predictors of parent-rated behavioral problems. © 2001 Elsevier Science Ltd. All rights reserved.
Children’s Go/No-Go performance was event-rate dependent, with the ADHD-Combine group being affected in the slow condition and the ADHD-Inattentive and FASD groups having problems with the fast condition.
KEY QUESTIONS TO DIFFERENTIATE ADHD AND CHILDREN WITH SELF-REGULATION PROBLEMS

• Does the child have frequent meltdowns or temper tantrums?
• Does the child have more levels of disturbance under high or low levels of stimulation?
• How does the child deal with negative feedback while learning?
• Does the child take extremely long periods of time to recover from being upset?
D. Deficits in adaptive functioning as manifested in 2 (or more) of the following, including at least 1 of (1) or (2):

- **Communication deficit** (e.g., delayed acquisition of language; difficulty understanding spoken language; difficulty using language to express self so that the listener understands).
- **Social impairment** (e.g., overly friendly with strangers; difficulty reading social cues; difficulty understanding social consequences; acting too young).
- **Impairment in daily living** (delayed toileting, feeding, or bathing; problems following rules of personal safety; difficulty managing daily schedule).
- **Motor impairment** (e.g., poor fine motor development; delayed attainment of gross motor milestones or ongoing deficits in gross motor function; problems in coordination and balance).
IMPAIRMENTS IN ADAPTIVE COMMUNICATION
IMPAIRMENTS IN INDEPENDENT LIVING SKILLS
IMPAIRMENTS IN ADAPTIVE SOCIAL FUNCTIONING
PROGRESSIVE ADAPTIVE FUNCTIONING IMPAIRMENTS

Using a sample recruited from San Diego, Crocker, Vaurio, Riley, & Mattson (2009) found that adaptive behavior impairments persisted even when compared to an IQ-matched reference sample and became more severe with age.

Table 2. Mean (±SD) Standard Scores on the Vineland Adaptive Behavior Scale for Children With Heavy Prenatal Alcohol Exposure (ALC), Children With Attention-Deficit/Hyperactivity Disorder (ADHD), and Typically Developing Controls (CON).

<table>
<thead>
<tr>
<th>Domain</th>
<th>ALC</th>
<th>ADHD</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>77.23 (22.89)</td>
<td>87.61 (18.79)</td>
<td>103.25 (11.73)</td>
</tr>
<tr>
<td>Daily living skills</td>
<td>69.41 (19.83)</td>
<td>81.13 (19.31)</td>
<td>98.15 (13.02)</td>
</tr>
<tr>
<td>Socialization</td>
<td>81.50 (20.85)</td>
<td>83.83 (16.14)</td>
<td>102.45 (10.75)</td>
</tr>
</tbody>
</table>

Fig. 1. Scatterplots illustrating the relationship between age and standard scores on the 3 adaptive behavior domains for children with heavy prenatal alcohol exposure (ALC), children with attention-deficit/hyperactivity disorder (ADHD), and typically developing controls (CON).
• E. **The onset of the disturbance** (symptoms in Criteria B, C, and D) is before 18 years of age.

• F. **The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.**

• G. **The disturbance is not better explained by the direct physiological effects associated with postnatal use of a substance** (e.g., medication, alcohol or other drugs), a general medical condition (e.g., traumatic brain injury, delirium, dementia), **other known teratogens** (e.g., Fetal Hydantoin syndrome), **genetic condition** (e.g., Williams syndrome, Down syndrome, Cornelia de Lange syndrome), or **environmental neglect and/or abuse.**
CLASSICAL CRITERIA FOR PSYCHIATRIC DIAGNOSIS
(BLASHFIELD & DRAGUNS, 1976)

• **Predictive validity** - refers to the category being able to effectively predict the individual’s responsiveness to different treatments.

• **Coverage** - the criteria being able to capture all individuals with the condition

• **Descriptive validity** - refers to the homogeneity within the symptom categories but not necessarily across the symptom categories/domains

• **Reliability** - see the same child/information and the diagnosis is made consistently by different clinicians
  
  • Team reports and independently reviewing by clinicians to get an estimate of reliability in making the diagnosis
  
  • Compare experienced vs non-experienced (related to FASD) mental health professionals in making the diagnosis
PROGRESS IN VALIDATING THE DISORDER

Samples Studied

- **MILE Cohort** - A sample of children between 3-10 years of age who had been identified as having FAS or pFAS and had enrolled in math intervention study Funded by a CDC Cooperative agreement # U84-CCU320162-02 and this analysis was carried out with the support of the National Institute of Alcohol Abuse and Alcoholism subcontract #10313752 to grant # U01 AA019879-01.

- **CIFASD** - A multi-site sample of children who had a history of PAE recruited from FAS diagnostic clinics or the community to evaluate alcohol exposed children and youth ages 5 to 17 years in comparison to appropriate contrast groups to identify alcohol-specific teratogenic effects on cognition Funded by the support of support of the National Institute of Alcohol Abuse and Alcoholism subcontract #10313752 to grant # U01 AA019879-01 and U01 AA014834 (Mattson) /Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD).

- **CoFASP** - A multi-site sample of children who enrolled into a study designed to **establish the prevalence of FASD in school-aged children** Funded by the support of support of the National Institute of Alcohol Abuse and Alcoholism subcontract #10313752 and U01 AA019879 (Chambers) and U01X (May)/ The Collaboration on FASD Prevalence (CoFASP).
INTERNAL VALIDITY:
LATENT TRAIT OF DISEASE SEVERITY

- Individuals with a history of PAE are anticipated to have variability in ND-PAE symptomatology allowing for a comparison of cohesiveness and necessity of each item to identify the latent trait of disorder severity.
SYMPTOM MAPPING

- This involves delineating how to positively endorse symptoms (code yes or no)
- In a clinical context, symptoms are either present or absent based on history or data available from standardized testing
- Existing databases can be used to assess the validity of the diagnosis with test results and data serving as symptom indicators
- Deciding what the threshold is for clinical significance?
  - 2.0 STD Units—probably too restrictive
  - 1.5 STD Units
  - 1.0 STD Units
- Is the more restrictive criteria for adaptive functioning deficits needed?
  - AF 2 of 4—Need two symptoms with one from social or communication adaptive deficits
  - AF-1—Only need one symptom with no restrictions on which one

<table>
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<tr>
<th></th>
<th>AF 2 of 4</th>
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<tr>
<td>1.0 Cut-off</td>
<td>Model 1</td>
<td>Model 3</td>
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<td>1.5 Cut-off</td>
<td>Model 2</td>
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• DAS IQ
• KBIT COMPOSITE
• CBCL Attention
• Medical Dx or ADHD medications
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<tr>
<th>Domain</th>
<th>Symptom</th>
<th>Specific Measure</th>
<th>% Positive Endorsement (1.5 SD)</th>
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<td>60.7</td>
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<td>25.0</td>
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<td>KEYMATH TOTAL SS</td>
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<td>TERA SS</td>
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<td>Impairment In Learning</td>
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<tr>
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<td>WISC-3 Spatial Span Forward</td>
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<td>33.9</td>
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<td>K-BIT Matrices</td>
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<td>Specific Symptom</td>
<td>% Positive Endorsement (1.5 SD)</td>
<td>% Positive Endorsement (1.0 SD)</td>
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<td>64.3</td>
<td>83.9</td>
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<td>Self-Regulation</td>
<td>Impairment In Mood and Behavioral Regulation</td>
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<td>Impairment In Impulse Control</td>
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### Overall Domain and Diagnostic Endorsement

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptoms</th>
<th>% Positive Endorsement (1.5 SD)</th>
<th>% Positive Endorsement (1.0 SD)</th>
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<tr>
<td>Neurocognitive</td>
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<td>92.9</td>
<td>96.4</td>
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<tr>
<td>Self-Regulation</td>
<td>1 symptom</td>
<td>94.6</td>
<td>96.4</td>
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<tr>
<td>Adaptive Functioning</td>
<td>1 symptom</td>
<td>83.9</td>
<td>94.6</td>
</tr>
<tr>
<td>Adaptive Functioning</td>
<td>2 of 4 symptom</td>
<td><strong>60.7</strong></td>
<td>85.7</td>
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<tr>
<td>ND-PAE Diagnosis</td>
<td>3 Symptoms (1 AF)</td>
<td>82.1</td>
<td>89.3</td>
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<tr>
<td>ND-PAE Diagnosis</td>
<td>3 Symptoms (2 of 4 AF)</td>
<td><strong>60.7</strong></td>
<td>83.9</td>
</tr>
</tbody>
</table>

Breadth of coverage is good but not when 1.5 cut-off used with 2 of 4 AF symptoms.
### Phi Coefficients of Specific ND-PAE Symptoms with Domains of Impairment and Diagnosis (1.5 SD)*

<table>
<thead>
<tr>
<th></th>
<th>NI_1</th>
<th>NI_2</th>
<th>NI_3</th>
<th>NI_4</th>
<th>NI_5</th>
<th>SR_1</th>
<th>SR_2</th>
<th>SR_3</th>
<th>AF_1</th>
<th>AF_2</th>
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<td>.36</td>
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<td>.21</td>
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<tr>
<td>Dx_AF2/4</td>
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<td>.15</td>
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<td>.29</td>
<td>.03</td>
<td>.75</td>
<td>.62</td>
<td>.63</td>
<td>.27</td>
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</table>
INTERNAL CONSISTENCY OF 12 SYMPTOMS - CRONBACH’S ALPHA

- 1.5 Cut-off: 0.77
- 1.0 Cut-off: 0.74
# Predictive Validity

<table>
<thead>
<tr>
<th>Item</th>
<th>ND-PAE</th>
<th>No ND-PAE</th>
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<tr>
<td>Yes</td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td>No</td>
<td>False negative</td>
<td>True Negative</td>
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</table>

Sensitivity - true positive/all positives  
Specificity - true negative/all negatives
Sensitivity: true positive/all positives

1 - Specificity: true negative/all negatives
Receiver Operative Curve Area Under the Curve Analysis by Cut-off Values Used on Standardized Measures

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Threshold 1.5 Symptoms (AF1)</th>
<th>Threshold 1.5 Symptoms (AF2 of 4)</th>
<th>Threshold 1.0 Symptoms (AF1)</th>
<th>Threshold 1.0 Symptoms (AF2 of 4)</th>
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<tr>
<td></td>
<td>Area</td>
<td>Std. Error</td>
<td>Asymptotic Sig.</td>
<td>Area</td>
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<td>.080</td>
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<td>.683</td>
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<td>ni_2</td>
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<td>.076</td>
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<td>.664</td>
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<td>ni_3</td>
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<td>ni_4</td>
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<td>.073</td>
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<td>.705</td>
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<td>ni_5</td>
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<td>.693</td>
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<td>sr_1</td>
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<td>.644</td>
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<td>sr_2</td>
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<td>.615</td>
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<td>sf_5</td>
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<td>af_2</td>
<td>.830</td>
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<td>af_3</td>
<td>.733</td>
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<td>af_4</td>
<td>.646</td>
<td>.087</td>
<td>.152</td>
<td>.630</td>
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</table>
RELATIONSHIP OF SUM OF SYMPTOMS TO PARTICIPANT CHARACTERISTICS

• The sum of symptoms was not different between males and females using both cut-off values but did differ by race with more symptoms reported for African American children when using the 1.0 SD cut-off value.

• The number of symptoms was not related to the child’s level of dysmorphia, number of custody placements, child protective services involvement, years of education, and household income.

• The number of symptoms was positively related to the child’s age for both cut-off values (1.5 SD: r=.37, p < .006; 1.0 SD: r=.42, p < .001).
CIFASD SAMPLE

• AE Group: Prenatal alcohol exposure (PAE) with or without FAS (n=151)

• CON Group: non-exposed typically developing (IQ>88, no ADHD) controls (n=143)

• ExpCON Group: non-exposed including: (n=268)
  • CON Group (IQ>88, no ADHD)
  • ADHD Contrast Group (with ADHD)
  • Low IQ Contrast Group (IQ scores 54-88)

• (from Dr. Sarah Mattson)
### RATES OF IMPAIRMENT

#### Overall Domain and Diagnostic Endorsement

<table>
<thead>
<tr>
<th></th>
<th>MILE % Positive Endorsement (1.5 SD)</th>
<th>CIFASD % Positive Endorsement (1.5 SD)</th>
<th>MILE % Positive Endorsement (1.0 SD)</th>
<th>CIFASD % Positive Endorsement (1.0 SD)</th>
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<tr>
<td><strong>Neurocognitive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 symptom</td>
<td>92.9</td>
<td>79%</td>
<td>96.4</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Self-Regulation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 symptom</td>
<td>94.6</td>
<td>85%</td>
<td>96.4</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Adaptive Functioning</strong></td>
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<td></td>
</tr>
<tr>
<td>1 symptom</td>
<td>83.9</td>
<td>75%</td>
<td>94.6</td>
<td>89%</td>
</tr>
<tr>
<td>2 of 4 symptom</td>
<td>60.7</td>
<td>47%</td>
<td>85.7</td>
<td>68%</td>
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<tr>
<td><strong>ND-PAE Diagnosis</strong></td>
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<tr>
<td>3 Symptoms (1 AF)</td>
<td>82.1</td>
<td>62%</td>
<td>89.3</td>
<td>79%</td>
</tr>
<tr>
<td>3 Symptoms (2 of 4 AF)</td>
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ACCURACY OF ND-PAE (AE V. EXPCON @ 1.5 SD)

**AF Criteria: 2 of 4 symptoms, with 1 being either communication OR social impairments**

ND-PAE ‘AUC’ = .658 (poor)

Slide prepared by Dr. Mattson
<table>
<thead>
<tr>
<th>Domain (1.0 SD)</th>
<th>AF Original</th>
<th>AF Revised</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>.62</td>
<td>.79</td>
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<tr>
<td>Specificity</td>
<td>.76</td>
<td>.63</td>
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<tr>
<td>Positive Predictive Value</td>
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<td>.55</td>
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<td>Negative Predictive Value</td>
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<td>.84</td>
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<td>AUC (ND-PAE)</td>
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<td>.831</td>
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<table>
<thead>
<tr>
<th>Domain (1.5 SD)</th>
<th>AF Original</th>
<th>AF Revised</th>
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<tbody>
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<td>Sensitivity</td>
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<td>.62</td>
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<tr>
<td>Specificity</td>
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<td>.80</td>
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<tr>
<td>Positive Predictive Value</td>
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<td>.64</td>
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<tr>
<td>Negative Predictive Value</td>
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<td>.79</td>
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<tr>
<td>AUC (ND-PAE)</td>
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<td>.711</td>
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*SUMMARY OF PROPOSED AF REVISION*

AE v. expCON

Slide prepared by Dr. Mattson
EPIDEMIOLOGICAL SAMPLES

- San Diego (n=934)
  - 59 Participants excluded b/c no adaptive measure/12 SR/1NI
- New Mexico/South Dakota (n=589)
  - 98 participants missing for AF

ND-PAE Risk
- Mothers reported drinking more than 2 drinks on one occasion or greater than 13 drinks a month at any point in the pregnancy
- Presence of alcohol-related dysmorphia (shortened (<10th) palpebral fissure, smooth philtrum, and thin upper vermillion) 2/3 and growth less than 10th percentile

Controls
- Mothers denied any alcohol consumption in pregnancy
- Children have no alcohol related dysmorphia (shortened (<10th) palpebral fissure, smooth philtrum, and thin upper vermillion) and growth was above the 10th percentile
DISCRIMINATIVE VALIDITY

Percentage Meeting Criteria for ND-PAE by Diagnostic Model

<table>
<thead>
<tr>
<th>Diagnostic Model</th>
<th>NDPAE RISK</th>
<th>CONTROLS</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>1.0_AF1-YES</td>
<td>32.1</td>
<td>19.5</td>
<td>x=3.8, p &lt; .052</td>
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<tr>
<td>1.0 AF2/4_YES</td>
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<tr>
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<td>3.8</td>
<td>x=8.9, p &lt; .003</td>
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<tr>
<td>1.5 AF2/4_YES</td>
<td>5.7</td>
<td>0</td>
<td>x=10.6, p &lt; .001</td>
</tr>
</tbody>
</table>
INTERNAL CONSISTENCY OF 12 ND-PAE SYMPTOMS ACROSS SAMPLES

MILE n=56; San Diego n=854; May ND-PAE Risk n=48; May Control n=137
Results indicate that the ND-PAE criteria are useful in identifying affected children - adequate breadth of coverage

Results are limited to children with known exposure history at this point

Criteria had good internal validity, especially after modifying AF criteria - homogenous symptoms across 3 samples

Diagnosis occurs more often in those identified as ND-PAE RISK relative to controls - discriminative validity

Using a 1.0 SD cutoff and the revised AF criteria yielded the strongest model (AUC = .831), although specificity was higher when using the 1.5 SD cutoff - discriminative validity

Additional modifications to the criteria (e.g., changing general cognitive cutoff to 1.5 SD?) should be tested
ALCOHOL AFFECTED ADULTS

• This is truly an “Undiscovered Country”.
• There are only a few studies of adults with FASD.
• There are no specific clinical programs in the United States (there are some in Canada).
• Several Longitudinal Exposure Studies have followed individuals from birth through young adulthood.
• Questions remain about health, mental health, and cognition.
• There is no information about Middle Age and Beyond.
• Searching with the term “fetal alcohol syndrome” = 2,047 hits.
• Searching with the term “fetal alcohol” = over 4,500 hits.
• Restricted to humans aged 19 and over = 709 hits, and fewer than 25 articles dealt with physical, cognitive, or behavioral outcomes.

Although FASDs have lifelong effects, and most children diagnosed with an FASD will grow into adulthood, we know almost nothing about the long-term behavioral and health consequences of this disorder.
WHY BE CONCERNED?

There is no empirical information to guide diagnosis and treatment of adults with fetal alcohol spectrum disorders (FASD).

But....

Nearly all publications on the effects of prenatal alcohol exposure note that the consequences are profound, and have life-long implications for the affected individual, the family and society.
LONG-TERM HEALTH EFFECTS?

• *Determine the long-term health consequences* of prenatal alcohol exposure. Popova et al. (2016) identified 428 comorbid conditions co-occurring in individuals with FASD.

• Animal data point to an increase in negative health outcomes, and a fetal programming model (Hellemans et al., 2010; Zhang et al., 2005) provides one explanation about how prenatal exposure to alcohol might impact long-term health and behavior.

• *It is critical to see if results based on animal data can be replicated in humans.*
ATLANTA ADULT ASSESSMENT PROJECT (AAAP)

• 236 Young Adults, including Alcohol Exposed, SES Controls and Disability Controls.

• Identified Prenatally from 1980 to 1986

• Maternal Alcohol and Drug Use was ascertained from Birth Mothers during pregnancy.

• Recruited from Inner City Public Hospital with predominantly African-American population.

• Children were tested in infancy, at 7 years, at 14 years and at 22 years.

• At 22 years, measured Cognitive, Neuropsychological status, Emotional/Social, Adaptive Functioning, Substance Use, Life Stress, Physical Health (Growth, etc), Medical History and carried out Imaging Studies with MRI.
MEASURES FROM ATLANTA ADULT ASSESSMENT PROJECT

Cognition
- Wechsler Abbreviated Scale of Intelligence (WASI)*
- Mazes (WISC-III-PI)
- Dichotic Listening
- Visual Alexia*

Attention
- VIGIL-Auditory and Visual Sustained Attention*
- 2’s and 7’s-Attention

Achievement
- Woodcock-Johnson Achievement Tests (Selected)*
- EC 301 Calculation and Number Processing*

Memory
- Wechsler Memory Scale (WMS)*
- Verbal and Spatial Selective Reminding Tasks*
- Subject Ordered Pointing

Motor*
- Finger Localization
- Perdue Pegboard

Risk Taking
- Gambling Task
- Balloon Task

*Shows Alcohol Effects
MEASURES FROM ATLANTA ADULT ASSESSMENT PROJECT

Emotion and Behavior
- Adult Self Report
- Adult Behavior Checklist (Collateral)
- Composite International Diagnostic Interview (CIDI-SF)

Independent Living Skills
- Adaptive Behavior Assessment System (Collateral)*
- DEX Self-Rating
- DEX Independence Rating

Social Behavior
- Social Contacts Form and Social Activities Scale
- Lifestyle Interview
- Lifestyle Interview (Collateral)

Substance Use/Abuse
- Addiction Severity Index (ASI)*
- Drug Checklist*
- SASSI
- Lab Test*

Life Stress
- Life Stressors and Social Resources Inventory (LISRES-A)

Health
- Hearing and Vision Screens
- Physical Examination
- Asthma Questionnaire
- Health/Medical History
- Reproductive Questionnaire

*Shows Alcohol Effects
IN SUMMARY: ADULTS

• Criteria that define the disorder—Physical features, Growth, Cognitive Deficit—appear to be persistent into adulthood and can be thought of as the Direct Teratogenic effects of the exposure. (Primary Effects)

• Social and Emotional outcomes appear to be determined by a developmental psychopathology process rather than a strictly teratogenic process. That is, they are determined by the impact of multiple risk factors on the developing child. (Indirect or Secondary Effects)

• Therefore, to understand them, assessment them and provide interventions, you have to understand these risk factors and their effects on development.
APPROACHES TO TREATMENT

ENEC MILE GOFAR

CLAIRE D. COLES AND JULIE A. KABLE, PH.D.
WHY DO WE NEED TARGETED TREATMENT AND HABILITATIVE CARE FOR CHILDREN WITH FASD?

- Understanding the Occurrence of Secondary Disabilities in Clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE)-Final Report August 1996 (n=415/90)

94% Mental health problems
45% Inappropriate sexual behavior
43% Disrupted school experience
42% Trouble with the Law
Among Adults (>21)
80% Dependent living situation
80% Problems with employment
FAS INTERVENTION RESEARCH

Although the research on the teratogenic effects of prenatal alcohol exposure began in the 1970’s, treatment research in this area is in its infancy.

Without an “Evidence Base”, it is very difficulty to argue for targeted treatment for FASD.
Prospective human studies and animal studies converge on evidence regarding the teratogenic effects of prenatal alcohol.

Identification of FAS: 1973
- Jones & Smith; Jones, Smith, Uleland, & Streissguth

Teratology Research:
- 1995-Seattle
- 1996-Atlanta-Marcus

Diagnostic Clinics:
- 1995-Seattle
- 1996-Atlanta-Marcus

1996 Institute of Medicine Report-calling for clinical services and the Streissguth's report on Secondary disabilities

Targeted Intervention Research

2013 DSM-V ND-PAE (315.8)

2012 ABA and AAP Statement
Interventions and “the Burden of Care”

Children with FASD may have problems in the following areas through out their lives:

Physical/Health/Motor
- Eye exams
- Cardiology
- Neurology
- Physical therapy
- Feeding issues
- Developmental pediatric care

Developmental/Cognitive
- Developmental/cognitive assessments
- Individual speech and occupational therapy
- Child cognitive habilitation

Behavioral/Social
- Parent education and training/therapy
- Child therapy
- Psychiatry care
- Social skills training
- Social supports and assistance with linking to community resources

Academic/Vocational
- Psychoeducational assessments
- Special education or modified educational programs
- Tutoring services
- Parent training to “partner with the schools”
THE INSTITUTE OF MEDICINE (1996) RECOMMENDED THAT EACH STATE HAVE A “FAS CLINIC” WHERE INDIVIDUALS COULD BE REFERRED FOR DIAGNOSIS AND RECOMMENDATIONS

- Because of the many possible effects, a Multidisciplinary team was best to make the diagnosis.
- Specialized knowledge was necessary for differential diagnosis.
- Children and Families had many social factors that needed to be addressed as well as the direct effects of the drug.
- FASD Centers could serve as sites for evaluation of novel interventions.
- Centers for Prevention and Training of professionals-physicians, psychologists, allied health professionals.
- Having a “home” would allow families to receive consistent care and be followed over time.
The Emory Neurodevelopment and Exposure Clinic (ENEC) serves children with prenatal exposure to alcohol, drugs, or other substances. As part of the Division of Child, Adolescent and Young Adult Psychiatry, we provide:

- Differential diagnosis of effects of prenatal exposure
- Referrals and consults
- Behavioral and educational intervention with children and families
- Medication Management

ENEC is the only multidisciplinary center of its kind in the Southeast. We were formerly known as the Fetal Alcohol and Drug Exposure Clinic.

Phone: 404 712 9810
email: fasclinic@emory.edu
RESEARCH ON SPECIFIC FASD INTERVENTIONS
<table>
<thead>
<tr>
<th>Author</th>
<th>Skill</th>
<th>Sample</th>
<th>Treatment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kable &amp; Coles,</td>
<td>FAS Caregiver Advocacy and Behavioral</td>
<td>Children with FASD</td>
<td>Comparison of parent training via workshop or on-line program</td>
<td>Both methods of information deliver were well received and improved</td>
</tr>
<tr>
<td>2012</td>
<td>regulation</td>
<td></td>
<td></td>
<td>knowledge but better behavioral change was obtained via workshops</td>
</tr>
<tr>
<td>Fisher</td>
<td>FAS training for parents and teachers</td>
<td>Case studies of families who attended</td>
<td>Curriculum Delivered in Group Sessions with Manuals-TRIUMPH</td>
<td>Parents reported training effective and maintained knowledge over 6-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trainings at Double ARC/NODAS Ohio</td>
<td></td>
<td>months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Skill</td>
<td>Sample</td>
<td>Treatment</td>
<td>Result</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kable, Coles, &amp; Taddeo, 2007 &amp; Coles, Kable, &amp; Taddeo, 2009</td>
<td>Behavior and math functioning using metacognitive training techniques</td>
<td>61 US Children between, 3-10 years</td>
<td>Socio-cognitive habilitation</td>
<td>Improved behavior and math knowledge</td>
</tr>
<tr>
<td>Carmichael-Olsen et al (in Bertrand et al., 2009)</td>
<td>Parental stress and child behavioral functioning</td>
<td>52 US Children between 5-11 years</td>
<td>Positive behavioral support/parent training</td>
<td>Parents reported greater met needs, improved parental efficacy, and reported reduced problem behaviors for child</td>
</tr>
<tr>
<td>Kerns et al., 2010</td>
<td>Attentional control</td>
<td>10 Canadian children between 6-15 years</td>
<td>Computerized Attentional Control Training- CPAT</td>
<td>Improved sustained attention and selective attention</td>
</tr>
<tr>
<td>Wells et al, 2012</td>
<td>Self-regulation</td>
<td>78 US Children between 6-11 years</td>
<td>Alert Program</td>
<td>Improved Executive function skills and emotional problem-solving skills</td>
</tr>
<tr>
<td>Nash et al, 2014</td>
<td>Self-regulation</td>
<td>25 Canadian Children between 8-12 years</td>
<td>Alert Program</td>
<td>Improvements in inhibitory control, emotional regulation and social cognition</td>
</tr>
<tr>
<td>Coles, Kable, Taddeo, &amp; Strickland, 2015</td>
<td>Self Regulation and Adaptive Behavior</td>
<td>30 Children between 5 and 10</td>
<td>Metacognitive Training with GoFAR Game and Parent Training and Direction intervention</td>
<td>Improved self regulation and sustained attention.</td>
</tr>
</tbody>
</table>
BEHAVIORAL REGULATION TRAINING

Incorporates typical behavioral management training principles into the context of dealing with how the neurodevelopmental damage associated with prenatal alcohol exposure interferes with learning and compliance.

A key component of BRT training is learning how to teach the child affective regulation.

KEY MODULES:
What are social learning principles?
How do I modify my child’s level of arousal?
How do I modify my child’s world to prevent problematic situations?
How do I get my child to comply?
**INTERVENTIONS TARGETED TO IMPAIRMENTS IN SELF-REGULATION**

- Neurocognitive habilitation for children with fetal alcohol spectrum disorders (Ira Chasnoff’s group: Published in Bertand, 2009)
- MILE Program (Kable, Coles, & Taddeo, 2007; Coles, Kable, & Taddeo, 2009)
  - Behavioral regulation training for parents
  - Metacognitive technique entitled FAR that improved math learning
- GoFAR Program (Coles, Kable, Taddeo, & Strickland, Kable, Taddeo, Strickland & Coles, 2015)
<table>
<thead>
<tr>
<th>Timler, 2005</th>
<th>Social skills/communication</th>
<th>Case study of 1</th>
<th>2 1-hour individual sessions &amp; 4 2-hour group sessions</th>
<th>Increased strategies on how to behave in social situations and increased number of mental state verbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor et al., 2006</td>
<td>Social skills</td>
<td>100 US children 6-12</td>
<td>Bruin Buddies social skills training program</td>
<td>Improved social skills and reduced behavior problems via parental report</td>
</tr>
<tr>
<td>O’Connor et al., 2012</td>
<td>US children 6-12</td>
<td>Bruin Buddies social skills training program</td>
<td>Improved social skills and self-concept</td>
<td></td>
</tr>
</tbody>
</table>
## VIRTUAL REALITY: PERSONAL SAFETY

<table>
<thead>
<tr>
<th>Study</th>
<th>Topic</th>
<th>Participants</th>
<th>Virtual reality game to teach</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padgett, Strickland, &amp; Coles, 2006</td>
<td>Child fire safety</td>
<td>5 US Children 4-7</td>
<td>teach fire safety skills</td>
<td>All children able to perform skills in analog setting</td>
</tr>
<tr>
<td>Coles, Strickland, Padgett, &amp; Belmoff, 2007</td>
<td>Child fire and street safety</td>
<td>32 US Children 4-10 years of age</td>
<td>teach fire and street safety skills</td>
<td>Greater knowledge gains for fire and street safety immediately but only fire after 1 week post-test</td>
</tr>
</tbody>
</table>
## BUILDING ACADEMIC SKILLS

<table>
<thead>
<tr>
<th>Author</th>
<th>Skill</th>
<th>Sample</th>
<th>Treatment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Lapadat, 2000</td>
<td>Reading and spelling</td>
<td>One adolescent child with FAS</td>
<td>One-on-one tutoring,</td>
<td>Improved standardized test scores for reading and spelling</td>
</tr>
<tr>
<td></td>
<td>achievement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porter-Larson, 2000</td>
<td>Reading</td>
<td>3rd grade male who probably had FAS</td>
<td>Reading tutoring program</td>
<td>Improved standardized reading scores</td>
</tr>
<tr>
<td>Adnams in Riley et al., 2007</td>
<td>Language and literacy</td>
<td>65 South African Children, 9-10 years</td>
<td>Language and literacy intervention</td>
<td>Improved phonological awareness and early literacy. No difference in general achievement</td>
</tr>
<tr>
<td>Kable, Coles, &amp; Taddeo, 2007/</td>
<td>Behavior and math</td>
<td>61 US Children between, 3-10 years</td>
<td>Socio-cognitive habilitation</td>
<td>Improved behavior and math knowledge</td>
</tr>
<tr>
<td>Coles, Kable, &amp; Taddeo, 2009</td>
<td>functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kable, J. A., Taddeo, E.,</td>
<td>Math functioning</td>
<td>US Children between, 3-10 years</td>
<td>Socio-cognitive habilitation MILE/FAR</td>
<td>Improved math skills</td>
</tr>
<tr>
<td>Strickland, D., &amp; Coles, C. D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Although the primary focus was to improve math functioning, interactive learning or metacognitive strategies were used to improve learning.
### MATH OUTCOMES

<table>
<thead>
<tr>
<th>Percentage with Clinically Significant Gain</th>
<th>Psychoed. Contrast</th>
<th>Math Tutoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post 1 Gain(^1)</td>
<td>23.1%</td>
<td>58.6%</td>
</tr>
<tr>
<td>Post 2 Gain(^2)</td>
<td>38.5%</td>
<td>64.3%</td>
</tr>
</tbody>
</table>

Kable, Coles, & Taddeo, 2007; Coles, Kable, & Taddeo, 2009

Community Translation Study-Positive relationship between change in math scores and fidelity to using the FAR methodology (KeyMath Total SS: \(r=.48, p < .02\); TEMA-3 Total SS: \(r=.45, p < .04\)).

Kable, Coles, Taddeo, and Strickland, 2015
Child’s age-6 years, 4-months at 1st post-test
GoFAR: Affective and Cognitive Training in the Context of Learning Adaptive Living Skills

The general goal of this study is the development of a novel and effective intervention method for children with the neurodevelopmental deficits associated with prenatal alcohol exposure by targeting the affective and cognitive control deficits (ACCD) common in this population using a combination of “serious” computer games and experiential learning.
### Adaptive Skills

Please choose five ([5]) items from the following list and rank them from 1 to 5. This way we can tailor the BAT-sessions to make them most relevant for you and your child.

<table>
<thead>
<tr>
<th>Helping around the house</th>
<th>School</th>
<th>Social Interactions</th>
<th>Animal care</th>
<th>Animal Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make the bed</td>
<td>Getting ready for school</td>
<td>Inviting a friend</td>
<td>Feeding the dog</td>
<td>Playing with the dog</td>
</tr>
<tr>
<td>Put away toys/books</td>
<td>Prepare lunch</td>
<td>Planning what to do with a friend</td>
<td>Feeding the cat</td>
<td>Playing with the cat</td>
</tr>
<tr>
<td>Put away clothes</td>
<td>Homework folder signed</td>
<td>Sharing toys</td>
<td>Washing the dog</td>
<td></td>
</tr>
<tr>
<td>Help doing the laundry</td>
<td>Organizing the back pack</td>
<td>Visiting a friend</td>
<td>Walking the dog</td>
<td></td>
</tr>
<tr>
<td>Bake a cake/cookies</td>
<td>Waiting for the bus</td>
<td>Sleep over at a friend’s house</td>
<td>Cleaning the litter box</td>
<td></td>
</tr>
<tr>
<td>Set the table</td>
<td>Doing homework</td>
<td>Planning a birthday party</td>
<td>Cleaning the fish bowl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attending a birthday party</td>
<td>Cleaning the rabbit/hamster cage</td>
<td></td>
</tr>
</tbody>
</table>

#### At home
- **Nighttime**
  - Bedtime routine
  - Brushing teeth
  - Putting P.J.s on

- **Morning time**
  - Getting out of bed
  - Brushing teeth/showering
  - Getting dressed
  - Choosing clothes
  - Breakfast

- **Behavior**
  - Playing quietly when caregiver is busy

#### Going to the store
- Make a shopping list
- Getting things in the store
- Waiting in line at the check-out

#### Going to a restaurant
- Ordering food
- Waiting for the food
- Eating a meal

- **Parent selected**
- **Multi-step Skill building**
- **Mental Containment Games**
Outcomes

1. Parental Knowledge and Satisfaction


3. Child Behavioral Functioning:
   - Overall Problem Behavior: Achenbach Child Behavior Checklist and Teacher Report Form
   - Negative Affectivity/Effortful Control-Rothbart Questionnaire
   - Frequency of Problem Behavior: Disruptive Behavior Checklist
Disruptive Behavior Record Form

Study ID: ____________________________ Date Completed: ____________

Week Represented: ___________________

Circle One: Pre-treatment Mid-Treatment Post-treatment

<table>
<thead>
<tr>
<th>Daily Count:</th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of temper tantrums or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>emotional meltdowns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weekly Assessment of Negative Behaviors

<table>
<thead>
<tr>
<th>Problem Behaviors</th>
<th>Score (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Displays a low tolerance for frustration</td>
<td>0-never 1-sometimes (1-3 times/wk) 2-fairly often (4-6 times/wk) 3-often (daily) 4-always (several times daily)</td>
</tr>
<tr>
<td>Acts aggressively towards others</td>
<td>0-never 1-sometimes (1-3 times/wk) 2-fairly often (4-6 times/wk) 3-often (daily) 4-always (several times daily)</td>
</tr>
<tr>
<td>Responds impulsively when attempting something</td>
<td>0-never 1-sometimes (1-3 times/wk) 2-fairly often (4-6 times/wk) 3-often (daily) 4-always (several times daily)</td>
</tr>
<tr>
<td>Behaves destructively</td>
<td>0-never 1-sometimes (1-3 times/wk) 2-fairly often (4-6 times/wk) 3-often (daily) 4-always (several times daily)</td>
</tr>
<tr>
<td>Difficulties with maintaining sustained mental effort or attention</td>
<td>0-never 1-sometimes (1-3 times/wk) 2-fairly often (4-6 times/wk) 3-often (daily) 4-always (several times daily)</td>
</tr>
</tbody>
</table>
Outcomes

Executive Functioning:

• BRIEF (parental report)
• TOVA-Test of Variables of Attention + Physiological regulation (HR and Vagal tone)
• Leiter Attention Sustained Task
• Draw the Line Slowly Task
• NEPSY-2 Statue, Comprehension Instructions, Inhibition, Visuomotor Precision, Speeded Naming, Auditory Attention and Response set, Tower, Word Generation
<table>
<thead>
<tr>
<th></th>
<th>CONTROL (n=10)</th>
<th>FACELAND (n=10)</th>
<th>GOFAR (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s Age (years)</td>
<td>7.0 (1.6)</td>
<td>6.8 (1.3)</td>
<td>7.5 (1.4)</td>
</tr>
<tr>
<td>Child’s Gender-% Male</td>
<td>70.0%</td>
<td>40.0%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Child’s Race % Caucasian/African American/Mixed Race</td>
<td>50.0%/40.0%/0.0%</td>
<td>50.0%/40.0%/10.0%</td>
<td>40.0%/10.0%/40.0%</td>
</tr>
<tr>
<td>% in Adopted Home or Legal Guardianship</td>
<td>100%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Number of Child Placements</td>
<td>1.9 (1.1)</td>
<td>2.0 (1.1)</td>
<td>3.3 (2.7)</td>
</tr>
<tr>
<td>Child Protection Involvement</td>
<td>54.5%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Child’s Birth Head Circumference(^1)</td>
<td>32.1 (2.3)</td>
<td>30.4 (3.4)</td>
<td>32.3 (4.9)</td>
</tr>
<tr>
<td>Child’s Birth Weight (grams)(^2)</td>
<td>2444.5 (790.5)</td>
<td>2268.3 (638.8)</td>
<td>2837.0 (1308.8)</td>
</tr>
<tr>
<td>Child’s Pedscore(^3)</td>
<td>15.8 (7.0)</td>
<td>17.0 (4.1)</td>
<td>20.0 (3.6)</td>
</tr>
<tr>
<td>Child’s DAS(^4): General Conceptual Ability</td>
<td>87.7 (11.3)</td>
<td>81.6 (19.5)</td>
<td>89.3 (11.3)</td>
</tr>
<tr>
<td>Caregiver’s Age in Years</td>
<td>51.5 (11.1)</td>
<td>46.8 (10.0)</td>
<td>49.6 (7.0)</td>
</tr>
<tr>
<td>Caregiver Gender-% Female</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Caregiver Education Years</td>
<td>13.9 (1.7)</td>
<td>13.8 (5.1)</td>
<td>14.5 (1.8)</td>
</tr>
<tr>
<td>Combined Household Income (6=35,000-49,999)</td>
<td>5.8 (1.9)</td>
<td>6.0 (2.4)</td>
<td>7.4 (1.7)</td>
</tr>
<tr>
<td>Number of Adults in Household</td>
<td>1.8 (.79)</td>
<td>1.8 (.63)</td>
<td>2.2 (.42)</td>
</tr>
<tr>
<td>Number of Children in Household</td>
<td>2.4 (1.9)</td>
<td>1.5 (1.8)</td>
<td>1.6 (1.5)</td>
</tr>
</tbody>
</table>
GOFAR INTERVENTION STUDY

Parent Behavioral Regulation Training
Child GOFAR Computer GAME
Behavioral Analog Therapy Sessions

Parent Behavioral Regulation Training
Child FACELAND Computer Game
Behavioral Analog Therapy Session

Mid-treatment Assessment

GOFAR

FACELAND

CONTROL

POST-TEST

POST-TEST

POST-TEST
PARENTAL ENGAGEMENT AND MID-TREATMENT OUTCOME

• Improvements in the child’s ability to regulate attention was related to the therapist’s ratings of achievement of therapy goals across the sessions (r = -0.70, p < .001) and trended towards a relationship with parental completion of homework during the sessions (r = -0.44, p < .059).

• A trend was also found between therapist ratings of the parent’s achievement of therapy goals and reductions in children’s destructive behavior (r = 0.39, p < .10).

• A significant univariate treatment group effect was found on change in sustained mental effort (F (1, 17) = 5.85, p < .027, partial eta-squared= .26) with those in the GOFAR group demonstrating greater reductions in problems in this area than those in the FACELAND group but not a significant multivariate group effect.
ASSESSMENT OF LEARNING FROM THE FAR COMPUTER GAME

• After one session, 57.1% of the participants were able to identify the elements of FAR

• After the fifth session 85.7% were able to do this
### BAT SESSION - THERAPY PROCESS OUTCOMES

<table>
<thead>
<tr>
<th>ITEMS</th>
<th>FACELAND (n=10)</th>
<th>GOFAR (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Session Time (minutes)</td>
<td>53.9 (6.6)</td>
<td>56.4 (4.6)</td>
</tr>
<tr>
<td>Average Treatment Goals Achieved Per Session</td>
<td>4.5 (0.8)</td>
<td>3.9 (0.7)</td>
</tr>
<tr>
<td>Average Rating of Goal Achievement(^1)</td>
<td>3.3 (0.6)</td>
<td>3.9 (0.3)*</td>
</tr>
<tr>
<td>Average Rating of Therapist Fidelity for FAR method</td>
<td>21.6 (1.6)</td>
<td>22.2 (1.1)</td>
</tr>
<tr>
<td>Average Rating of Parent Fidelity for FAR method</td>
<td>14.1 (4.2)</td>
<td>15.8 (2.5)</td>
</tr>
</tbody>
</table>
Change in Negative Behavior over the Course of Treatment by Group Status

- **Control**
- **Faceland**
- **GOFAR**

Pretest, Mid-Treatment, Post-Treatment
## Changes in TOVA Performance

<table>
<thead>
<tr>
<th>TOVA Variable</th>
<th>GOFAR Pretest</th>
<th>GOFAR Post-test</th>
<th>FACELAND Pretest</th>
<th>FACELAND Post-test</th>
<th>CONTROLS Pretest</th>
<th>CONTROLS Post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD Index</td>
<td>-3.48*</td>
<td>-0.81</td>
<td>-5.11*</td>
<td>-3.67</td>
<td>-3.15</td>
<td>-2.90</td>
</tr>
<tr>
<td>Response Time</td>
<td>-0.74*</td>
<td>0.07</td>
<td>-1.65</td>
<td>-1.11</td>
<td>-0.82</td>
<td>-0.68</td>
</tr>
<tr>
<td>Response Time Variability</td>
<td>-2.38*</td>
<td>-1.10</td>
<td>-3.30*</td>
<td>-3.18</td>
<td>-2.47</td>
<td>-2.31</td>
</tr>
<tr>
<td>D-Prime</td>
<td>-2.12</td>
<td>-1.57</td>
<td>-2.86</td>
<td>-2.33</td>
<td>-2.74</td>
<td>-2.13</td>
</tr>
</tbody>
</table>

### Attention Performance Index

The Attention Performance Index of -2.26 is in the range of individuals independently diagnosed with ADHD.

Note: This finding alone is not sufficient to establish a diagnosis of ADHD. The clinician needs to consider additional sources of information, such as Comparison to the Normative Sample (see above), as well as history and collateral information (such as behavior rating scales).
CHANGES IN DOMESTIC LIVING SKILLS

Domestic Raw Score on VABS

- Pretest
- Post-test

Graph shows changes in domestic living skills across three groups: GoFAR, Faceland, and Control. Scores increase from pretest to post-test for all groups, with the Control group showing the most improvement.
SUMMARY

- Learning FAR regardless of how (computer vs. BATs) resulted in improvements in the child’s disruptive behavior as rated by parents.
- Children who received the GoFAR game as opposed to the Faceland game demonstrated greater gains in sustained mental effort at mid-treatment.
- Parents were able to learn the FAR methodology over the course of BATS sessions.
- Children in both the GoFAR and Faceland groups both demonstrated reductions in negative affectivity.
- Children in both the GoFAR and Faceland groups demonstrated improvements in sustained attention skills (TOVA ADHD Index).
- Children in both the GoFAR and Faceland groups demonstrated improvements in their adaptive domestic living skills.
- Relative gains of GoFAR vs the Faceland group may be limited by the small sample size.
Sample size is small and many trends. Need to replicate findings in a larger sample.

Are the BATs necessary? Contrast those who received PT and GoFAR program only to those who received full treatment (+BATS).

What is the neural basis of the change? Neuroimaging to capture the brain-based changes associated with treatment outcome.

What is the long-term effect of the intervention?
KEY FEATURES NEEDED TO IMPROVE LEARNING

• Appropriate environment
• Simplified learning environment
• Reduce chances of failure or making wrong choices
• Monitor arousal and teach in “calm alert states”
UNPUBLISHED AND RUMOR...

- Project Step Up-16-18 year-olds
- Partners for Success-16-25 year-olds
- MILE in the School System-Rasmussen
- Sensorimotor Training to Affect Balance, Engagement and Learning in Children with FASD (McCoy, Jirikowic)
- Fostering Self-Regulation in Infants and Toddlers with FASDs (Paley)
NOVEL APPROACHES TO INTERVENTIONS WITH FASD

Service dog clinical case report: Fry-Johnson, Powell, & Winokur, 2009

Hyperbaric Oxygen Therapy case report-40 treatments resulted in improved computer test scores; 33 more continued gains
Stoller, 2005
Pediatrics, 116(4), pp e586-e5911

Cost=Service Dog $10,000-15,000; HBOT=$100-300 per treatment
HUMAN CHOLINE SUPPLEMENTATION STUDIES

• **Prenatal Supplementation**
  Ongoing study in the Ukraine with pregnant women
  PI: Christina Chambers

• **Postnatal Supplementation**
  Protocol for delivering the supplement to children postnatally is being delivered and piloted
  PI: Jeffrey Wozniak
Correlations between cardiac OR outcomes and choline and its metabolites

<table>
<thead>
<tr>
<th></th>
<th>Visual Habituation/Dishabituation Paradigm</th>
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<tbody>
<tr>
<td></td>
<td>Habituation Average HR$^1$ Δ</td>
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<tr>
<td>ΔCholine$^2$</td>
<td>.19*</td>
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<td>ΔBetaine$^2$</td>
<td>.18$^T$</td>
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<tr>
<td>ΔDMG$^2$</td>
<td>.23*</td>
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</tbody>
</table>

* indicates significance at the 0.05 level
$^T$ indicates trend at the 0.10 level
ns indicates no significant difference
What about the future of interventions?

• Improving access to care
• Timeline from bench to bedside
• Continue to develop targeted behavioral interventions
• Develop targeted pharmaceutical interventions
• Develop innovative methods for assessing treatment effects
• Develop mechanisms for multi-site clinical trials
• Develop standardized methodology and protocols for evaluating treatments
BURDEN OF CARE

• If the outcome of children with a history of prenatal alcohol exposure is altered as a function of their postnatal environmental experiences and exposure to targeted interventions, then there is an increased “burden of care” associated with parenting such a child. This impacts:
  • Decisions about who can be the child’s caregiver as he or she should have the capacity to meet the child’s need
  • Supports that should be available to the child and their families to access needed services
Prospective human studies and animal studies converge on evidence regarding the teratogenic effects of prenatal alcohol.

Identification of FAS
1973
Jones & Smith; Jones, Smith, Uleland, & Streisguth

Teratology Research

Diagnostic Clinics
1995-Seattle
1996-Atlanta

1996 Institute of Medicine Report—calling for clinical services

Targeted Intervention Research
2000-
Functional Neuroimaging in the Examination of Effects of Prenatal Alcohol Exposure

Claire D. Coles · Zhihao Li

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Abstract Functional neuroimaging offers the opportunity to understand the effect of prenatal alcohol exposure on the activities of the brain as well as providing a window into the relationship between neural activation and the behavioral outcomes that have been described in affected individuals. Several different methodologies have been used to examine the neurophysiological signal changes associated with different brain functions in prenatally exposed individuals and those diagnosed with fetal alcohol syndrome (FAS) or other fetal alcohol spectrum disorders (FASD). These include electroencephalography (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). These studies demonstrate that it is feasible to use these technologies with this clinical population and that the damage to the central nervous system associated with prenatal alcohol exposure has widespread functional implications; however, currently, the literature in these areas is limited and unsystematic. Functional MRI with this clinical population has just begun to explore the implications of prenatal alcohol exposure with the first paper published in 2005. Other methodologies are similarly limited in scope. Nonetheless, these functional neuroimaging studies suggest that prenatal alcohol exposure, or a diagnosis of FAS, may lead to restrictions in neural efficiency or a global decrement in processing resources.

Keywords Prenatal alcohol exposure · EEG · PET · SPECT · fMRI · Review

Introduction

Alcohol is a potent teratogenic agent that affects the development of the brain in individuals exposed prenatally. Neurodevelopmental consequences have been documented through behavioral studies of exposed children and young adults since the fetal alcohol syndrome (FAS) was first described in the 1970’s (Jones and Smith 1973). Both individuals who meet criteria for FAS and those who fall on what is called the fetal alcohol spectrum (fetal alcohol spectrum disorders: FASD) show numerous behavioral alterations and cognitive deficits. Microcephaly is used as a diagnostic criterion for FAS. Human (Spadoni et al. 2007) and animal studies (Sulik et al., this volume) have documented both global and specific alterations in brain anatomy. For instance, alcohol exposure is often associated with smaller intracranial volume as well as volume deficits in specific brain regions over and above those accounted for by small intracranial volume (Archibald et al. 2001; Chen et al. 2011). Given this evidence of neurological and neurobehavioral impact, it is highly probable that functional neuroimaging, which enables observation and recording of brain activation in human samples, also will identify alterations associated with prenatal alcohol exposure whether or not accompanied by structural differences. A
second finding may be the demonstration of relationships between functional alterations and observable cognitive deficits or behavioral abnormalities, which could have diagnostic implications. Finally, investigation of such relationships can add significantly to our general understanding of the relationship between brain and behavior over development. This paper will review what is still a limited body of research that has used functional neuroimaging to examine the nature and extent of alcohol’s effects on the developing brain. In addition, we will note the constraints that currently exist on interpretation of these results and indicate directions for future research.

Methods for Functional Neuroimaging

Functional neuroimaging includes those techniques that measure the neurophysiological signal changes associated with different brain functions. These signal changes are usually caused by performing a specific task or by switching between different task states, but recordings can also be made during sleep or during what is called “resting state” when no specific task is occurring. The results are thought to provide information about the neuromechanisms underlying the brain functions that are associated with various sensory and cognitive activities. A number of functional neuroimaging approaches have been used in studies of the effects of prenatal alcohol exposure. These include electroencephalography (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Each of these techniques has its own advantages and limitations and these are summarized in the next section.

Electroencephalography (EEG) uses scalp electrodes to detect and measure gross field potentials caused by synchronized synaptic activities in the brain (Nunez and Srinivasan 2006). Thus, unlike other imaging methods, EEG provides relatively direct measurement of electric neuronal activity and it offers the best temporal resolution (~microsecond) among functional neuroimaging approaches. However, as the neuronal activation sources are usually separated from the electrodes by inactivated tissues, like cerebrospinal fluid, skull and scalp, the spatial resolution of EEG is relatively low in relation to other neuroimaging approaches. In addition, due to scalp recording and noise, there are limitations in the brain regions that can be measured, especially for those sources deep within the brain (Whittingstall et al. 2003). EEG is the oldest of the modern functional brain imaging techniques. As a result it is probably the best understood in terms of its relationship with behavioral correlates. For example, early ERP (event-related potential) components, like P1—a positive voltage deflection around 100 ms after stimulus onset, usually represent perceptual responses while late ERP components, like P3, usually represent attention-demanding cognitive processing. Besides the early and late components, two negative components—N2 and ERN, appearing around 200 ms, are often reported in studies of cognitive functions. N2 reflects conflict monitoring and executive control while ERN is related to error detection. A general introduction to various ERP components and associated brain processes can be found in (Fabiani et al. 2000).

Single-photon emission computed tomography (SPECT) is a nuclear medical tomographic technique that uses gamma rays to evaluate blood flow or concentration of various neurotransmitters. Following injection of a radioisotope, a gamma camera is used to acquire, from different angles, 2D projections of a 3D distribution of radioactive tracers. These 2D projections are fed into a subsequent algorithm of 3D reconstruction to produce 3D images. As blood flow is coupled to metabolic activity, SPECT can be used to evaluate brain metabolism regionally. As a well-established technique, SPECT is widely available and used with inexpensive radio tracer. However, low image resolution, signal attenuation and non-quantifiable blood flow measure are its traditional disadvantages.

Positron emission tomography (PET) also relies on radioactive materials and gamma ray detection. However, instead of direct gamma radiations, PET tracers emit positrons that annihilate with electrons thus generating two gamma photons travelling in opposite directions. A PET scanner detects these emission “coincidences” that can provide images in a higher resolution than SPECT (Wernick and Aarsvold 2004). PET is often used to quantitatively evaluate glucose metabolism and blood flow that is associated with brain activity. In addition, it is possible to radiolabel compounds that bind selectively to specific neurotransmitters (e.g., dopamine and serotonin receptors); therefore, metabolic activity of many neurotransmitters can be examined by PET as well. PET and SPECT are widely used to measure changes of blood flow and brain metabolism; but due to the reliance on radioactive materials, both are considered “invasive” approaches and are more often used in clinical samples than for research purposes.

Functional magnetic resonance imaging (fMRI) is now commonly used in the study of human brain function. This specialized form of magnetic resonance imaging was developed in the early 1990’s. Employing the different magnetic susceptibility of oxygenated and deoxygenated hemoglobin and the concentration changes caused by local neural activation (Cohen and Bookheimer 1994), most fMRI studies measure blood oxygen level dependent (BOLD) magnetic resonance signals. Specifically, local neural activation is associated with increased consumption of energy and increased blood oxygen levels; and oxygenated hemoglobin has a different MR signal from that
produced by deoxygenated hemoglobin. The BOLD fMRI signal is often termed the hemodynamic response. This response is characterized by an initial delay of a few seconds, a peak over 4–6 s and then a signal recovery over more than 10 s. Compared with other volumetric functional imaging techniques, fMRI is fast in imaging speed. The acquisition of a $3 \times 3 \times 3$ mm$^3$ resolution brain volume regularly only takes 2–3 s (typical fMRI scan needs repetitive volume measurements and takes several minutes). Besides BOLD fMRI, there are also other fMRI approaches. For instance, arterial spin labeling can directly measure cerebral blood flow (CBF) and provide similar information to PET but without the disadvantage of using radioactive materials (Aguirre et al. 2005; Feng et al. 2004).

There are several advantages to fMRI over other forms of functioning imaging. In addition to its high availability and its noninvasive nature, is the high spatial resolution that can distinguish brain structures at millimeter scale. Further, with this technique it is possible to examine the whole brain area as it is engaged with a particular task. With these advantages, fMRI has become the primary tool in volumetric functional neuroimaging and its application has exhibited a increasing trend in studies of prenatal drug exposure (Derauf et al. 2009; Norman et al. 2009).

While being the most effective neuroimaging approach currently available, fMRI does have limitations. In contrast to EEG, which has a high temporal resolution, the relatively slow hemodynamic response limits its capability in capturing fast changes in temporal domain. Its spatial specificity is subject to distribution of local vascular structure and susceptibility artifacts. Most importantly, the BOLD response is only a surrogate signal of local neuronal activations; that is, it is an indirect assessment of neuronal activity. Other limitations of fMRI include the complexity of experiment designs required as well as data interpretation when such designs are used. Finally, this methodology is sensitive to motion artifacts that can limit the use of the technique with children and clinical populations. More details about advantages/disadvantages of fMRI and about how to use this technique appropriately in basic neuroscience research are reviewed extensively by Logothetis (2008).

**Functional Imaging to Study Fetal Alcohol Spectrum Disorders and Effects of Prenatal Alcohol Exposure**

Early applications of functional neuroimaging studies in samples of children exposed to alcohol due to maternal use during gestation were carried out with EEG, SPECT and PET (see Table 1). With SPECT, differences in cerebral blood perfusion were reported in the temporal (Bhatara et al. 2002) as well as parieto-occipital and prefrontal (Riikonen et al. 1999) regions of alcohol-affected subjects. A SPECT study also showed a group difference in medial-frontal serotonin transporter binding and increased striatal dopamine transporter binding in alcohol-exposed individuals (Riikonen et al. 2005). With PET, differences associated with alcohol exposure were found in the regional cerebral metabolic rates in thalamus and basal ganglia (Clark et al. 2000). However, though they employed functional neuroimaging approaches, all of these early SPECT and PET studies simply focused on the “resting-state” brain. As a result, they do not provide direct insights into the effects on specific behavioral deficits (e.g., attention deficit or memory problems) that have been found to be associated with prenatal exposure or with the diagnosis of FAS. In addition, compared with recent studies, some of these early studies have methodological issues that may limit interpretation. These issues include relatively small sample sizes and less sophisticated methods for data handling than are used currently (e.g., data simply being visually inspected).

**EEG Studies of FASD** also revealed alterations associated with prenatal alcohol exposure (D’Angiulli et al. 2006). The earliest work, carried out in the 1970’s and 1980’s, used exposure samples rather than the clinically identified samples that have characterized much later work. Exposure samples are composed of individuals identified through maternal drinking, usually during the prenatal period, and followed longitudinally. These early studies focused on outcome in infancy, particularly on arousal regulation, sleep and sensory processing (see Table 1). Studies of older children and adolescents, discussed below, have examined attention and cognition and have identified reductions in mean power of alpha frequencies (Kaneko et al. 1996; Mattson et al. 1992).

EEG studies of the impact of prenatal alcohol exposure on sleep during infancy (Chernick et al. 1983; Havlicek et al. 1977; Ioffe et al. 1984) found that, in comparison to non-exposed infants, infants of drinking mothers showed generalized EEG hypersynchrony in all stages of sleep. In at least one longitudinal study, these power increases were found to be correlated with later developmental outcomes in the same children (Ioffe and Chernick 1990) with those showing increased EEG power having lower motor and mental development scores. In another sample, alcohol-exposed infants were found to have more disturbed sleep and more frequent arousals (Scher et al. 1988) than unexposed controls. Studies of sensory processes (that is auditory, visual and somatosensory evoked potentials) in alcohol exposed and affected children have also been done using EEG responses to specific stimuli (Church and Gerkin 1988; Olegård et al. 1979; Pettigrew and Hutchison 1984; Rössig et al. 1994; Scher et al. 1998). Auditory brainstem responses (ABR) are used to evaluate initial sensory processing of auditory stimuli and in studies using this methodology, alcohol exposure is associated with slower perception of auditory information (that is with prolonged...
# Table 1

Function studies using EEG, SPECT and PET to evaluate effects of prenatal alcohol exposure (PAE) and FASD diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Brain function</th>
<th>Subjects (mean age)</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havlicek et al. 1977</td>
<td>EEG</td>
<td>Sleep studies</td>
<td>26 newborn infants of alcoholic mothers and healthy term controls</td>
<td>• EEG hypersynchrony in 3 sleep stages (quiet, indeterminate, REM) and increased EEG power</td>
</tr>
<tr>
<td>Chernick et al. 1983</td>
<td>EEG</td>
<td>Sleep studies</td>
<td>17 Alcohol exposed neonates; plus infants of matched smoking controls and unexposed controls</td>
<td>• EEG hypersynchrony in alcohol exposed newborns during 3 sleep stages, with greatest increase during active sleep. No differences were seen in other groups. Authors suggest that this indicates persistent neurological changes as a result of prenatal alcohol exposure.</td>
</tr>
<tr>
<td>Ioffe et al. 1984</td>
<td>EEG</td>
<td>Sleep studies</td>
<td>42 neonates, 11 preterm infants of alcoholic mothers +11 matched controls +10 healthy preterms and 10 matched controls</td>
<td>• Infants of alcohol mothers had elevated EEG power (hypersynchrony) relative to controls. No differences were seen in other groups. Authors suggest that this indicates persistent neurological changes as a result of prenatal alcohol exposure.</td>
</tr>
<tr>
<td>Spohr and Steinhausen 1987</td>
<td>EEG</td>
<td>Developmental follow-up</td>
<td>Prospective clinical sample of FASD</td>
<td>• EEG pathology in younger children resolved over development.</td>
</tr>
<tr>
<td>Ioffe and Chernick 1990</td>
<td>EEG</td>
<td>Sleep studies and developmental follow up</td>
<td>1988: 441 newborns, gestational ages from 30 to 40 weeks, tested within 48 h of birth. 1990: 38 infants with alcohol exposure; tested at 40 wks GA; follow-up 1 1/2 and 10 month</td>
<td>• REM and quiet sleep EEG power at birth inversely related to Bayley developmental outcomes.</td>
</tr>
<tr>
<td>Scher et al. 1988</td>
<td>EEG</td>
<td>Sleep studies and arousal</td>
<td>55 neonates exposed to a range of alcohol and marijuana</td>
<td>• First trimester alcohol exposure associated with sleep disruptions and more arousals.</td>
</tr>
<tr>
<td>Mattson et al. 1992</td>
<td>EEG and structural MRI</td>
<td>Resting state</td>
<td>2 PAE children (13 and 14)</td>
<td>• PAEs showed abnormalities of the corpus callosum and volume reductions in the basal ganglia and thalamic structures</td>
</tr>
<tr>
<td>Kaneko et al. 1996</td>
<td>EEG</td>
<td>Resting state</td>
<td>18 matched triads of FAS, Down syndrome and normal controls, 4–15 years (9.1)</td>
<td>• Moderate abnormality in EEG of PAEs</td>
</tr>
<tr>
<td>Burden et al. 2009</td>
<td>EEG</td>
<td>Go/No-Go</td>
<td>7 PAE (11.5) vs. 6 control (12.1)</td>
<td>• Significant reductions in mean power of the alpha frequencies in PAEs and Down syndrome children</td>
</tr>
<tr>
<td>Burden et al. 2010</td>
<td>EEG</td>
<td>Go/No-Go</td>
<td>78 young adults (19.4) including:</td>
<td>• Down syndrome children showed diffuse EEG slowing while PAEs did not</td>
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<td></td>
<td>32 PAE−/ADHD−, 16 PAE+/ADHD−, 15 PAE−/ADHD+, 15 PAE+/ADHD+</td>
<td>• Down syndrome children showed alpha power decrease in posterior cortical regions, whereas PAE children were more affected in the left hemisphere.</td>
</tr>
<tr>
<td>Burden et al. 2011</td>
<td>EEG</td>
<td>Go/No-Go/ continuous recognition memory</td>
<td>139 Inuit children (11.3) including 39 ALC and 101 control</td>
<td>• No significant group difference on behavior performances</td>
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<td></td>
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<td></td>
<td></td>
<td>• PAEs showed slower P2 latency and smaller P2 amplitude suggesting inefficient early visual processing</td>
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<td></td>
<td>• PAEs showed decreased N2 amplitude suggesting less controlled and coherent strategy in response inhibition/execution</td>
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<td></td>
<td>• Regardless of PAE, ADHD is associated with less accuracy at inhibiting responses</td>
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<td>• Only ADHD group without PAE showed a diminished P3 difference between the Go and No-go condition</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Comparable Behavioral Performance</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• PAEs showed decreased P2 latencies on Go/NO Go suggesting inefficient early visual processing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Decreased FN400 amplitude and P3 amplitude on memory task</td>
</tr>
</tbody>
</table>
latencies) (Church and Gerkin 1988; Kable et al. 2009; Pettigrew and Hutchinson 1984). Similarly, visual processing was assessed by Scher et al. (1998) who found that certain wave latencies (i.e., N1, P1, at 1 month, and N2, at 4 months) were prolonged early in infancy in a manner suggesting developmental delays.

Studies of older children and adults with FASD using EEG have focused on attention and cognitive function. Kaneko et al. (1996) used an evoked-potential, oddball paradigm that was passive in nature; that is, it did not require an active response, and found that at least half of the alcohol-affected children tested had EEGs that could be classified as “abnormal”. This was one of the only studies to compare alcohol-affected children to both unexposed controls and another clinical group, those with Down syndrome. FASD diagnosis was found to be associated with slower P3 latencies than were shown by either contrast group. However, in this sample of older children, the N1 wave, noted to be altered by Scher et al. (1998) in infants, did not discriminate alcohol exposed from the other groups. Both N1 and P3 are believed to be associated with attentional responses.

Several recent studies also employed event-related potential (Burden et al. 2009, 2010, 2011). Two of these studies examined the effect of alcohol exposure on inhibitory control with similar task paradigms (Go/No-Go) administered to two samples recruited from Cape Town, South Africa and Detroit, Michigan. The Cape Town sample, whose mean age was 11.7 years (Burden et al. 2009), had a much higher level of prenatal alcohol exposure than the Detroit sample. The Cape Town sample used alcohol 42.8% of days during the month in contrast to the 13.6% in Detroit. In addition, in Cape Town, the mean ounces of absolute alcohol consumed per day (oz AA/dy) was 2.9 (SD=3.0) versus 0.3 (SD=0.7) in Detroit. In this Cape Town sample, prolonged latency of P2, and diminished Go vs. No-go amplitude difference of P2 and N2 components were observed in the alcohol-exposed children. These alterations reflect inefficient visual processing (prolonged P2), impaired early discrimination between conditions (P2 amplitude), and less controlled response inhibition (N2 amplitude).

In addition, the exposed group showed a long lasting P3 component, suggesting increased cognitive effort (Fig. 1). The data from the less heavily alcohol-exposed Detroit sample (Burden et al. 2010), who were adolescents rather than school-aged children, did not replicate these alcohol-related difference in group response suggesting that there may be more evidence of effects of exposure with higher doses. However, the focus of the Detroit study was a comparison of the characteristics of alcohol-exposed children with and without attention deficit hyperactivity disorder (ADHD). Responses of participants with ADHD were found to be uniquely associated with diminished P3 component to the “Go” and “No-Go” condition. Such diminished response was not associated with alcohol exposure. P3 is believed to reflect both response inhibition and persistent cognitive effort and often is found to be

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Brain function</th>
<th>Subjects (mean age)</th>
<th>Major findings</th>
</tr>
</thead>
</table>
| Riikonen et al. 1999 | Structural MRI and SPECT | Resting state | 11 PAE (8.6) vs. 6 control (16) | • Morphological anomalies (e.g. cortical atrophy) shown in patients’ MRI  
• SPECT showed mild hypoperfusion of the left hemisphere (especially in parietooccipital and frontal regions) in PAEs  
• Only 1 MRI was found to be abnormal in the subject with the lowest IQ  
• Decreases in relative regional cerebral metabolic rates were found in 5 brain regions comprising thalamus and basal ganglia |
| Clark et al. 2000 | Structural MRI and PET | Resting state | 19 PAE (20.6) vs. 15 control (22.8) | • MRI revealed several microcephaly, agenesis or hypoplasia of corpus callosum and agenesis of hippocampal commissure  
• SPECT revealed at least 25% CBF reduction in the temporal region relative to the cerebellum  
• Significant brain volume reduction in PAEs |
| Bhatara et al. 2002 | Structural MRI and SPECT | Resting state | 5 PAE (6–29) vs. 2 control (29, 35) | • Reduced serotonin transporter binding in the medial frontal cortex and increased striatal dopamine transporter binding in PAEs |
| Riikonen et al. 2005 | Structural MRI and SPECT | Resting state | 12 PAE (10.5) vs. 10 (for MRI, 10.8) +10 (for SPECT, 9.8) control | • There were unusable subjects due to reasons of severe head motion, poor behavior performance, participant refusal, disease affecting cerebral perfusion or technical issues |

a There were unusable subjects due to reasons of severe head motion, poor behavior performance, participant refusal, disease affecting cerebral perfusion or technical issues.
diminished in individuals with attentional disorders. The investigators interpreted this result as suggesting that alcohol-affected individuals and those with ADHD, though sharing similar symptomatology, are different in certain aspects of their neural basis. In a third study (Burden et al. 2011), these investigators carried out a large scale EEG study in Inuit children, mean age 11.3 years, using the same Go/No-Go paradigm as well as a measure of continuous recognition memory. Maternal binge drinking during pregnancy was found to be associated with alterations in EEG responses, with the alcohol-exposed group showing slower P2 latencies on the inhibition task, suggesting slower visual processing, and reduced amplitudes on the memory protocol in components associated with item familiarity and retrieval. It is of interest that, when behavior was measured, both accuracy and reaction time on these tasks were equivalent for both groups despite differences in EEG response. The authors of these papers interpreted all of these results in light of the “dose” of alcohol associated with each group to suggest that more extensive exposure had more comprehensive effects on EEG results.

Review of these EEG studies indicates that there are alterations in response associated with alcohol exposure but that outcomes may be affected by dose, comorbidity and development changes that make effects more or less apparent as individuals grow older. Changes over age in EEG results in alcohol-affected samples were noted previously by Spohr and Steinhausen (1987) and are reviewed by D’Angiulli et al. (2006).

Functional MRI is the technique most commonly employed in functional neuroimaging studies of the effects of prenatal alcohol exposure, although the body of research in this area remains limited. The first research paper using this methodology appeared in 2005 (Maliszka et al. 2005) and there are currently nine published papers in this area (See Table 2). Of these, four concerned working memory, one verbal paired associate learning, two math processing, one inhibitory control and one visual sustained attention. Of those that have examined working memory, two focused on spatial memory (Maliszka et al. 2005; Spadoni et al. 2009), one on verbal working memory (O’Hare et al. 2009) and one on facial recognition (Astley et al. 2009). A review of these papers (below) suggests that there is a variety of outcomes found whose results cannot be easily synthesized. For this reason, the information from these studies is provided followed by a discussion of the challenges associated with research in this area with reference to the cited studies.

Maliszka et al. (2005) used clinically recruited samples of both children and adults to examined spatial working memory function. Their hypothesis was that, using fMRI, differences would be noted in brain regions associated with working memory performance, particularly in frontal areas, which support efficient working memory. No structural MR (or brain volume) differences were found in either children or adults although there were behavioral differences on cognitive task performance. The fMRI results were complex. BOLD activation was found to be affected by group status (FASD versus controls), age, and task difficulty. In the FASD group, there was increased activation in the inferior and middle frontal regions during spatial memory tasks. In controls, more parietal activation was observed. Different patterns of outcomes were found in children and
Table 2  Function studies using fMRI to evaluate effects of prenatal alcohol exposure (PAE) and FASD diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Brain function</th>
<th>Subjects (mean age)</th>
<th>Major findings</th>
</tr>
</thead>
</table>
| Malisza et al. 2005 | fMRI          | Spatial working memory          | 14 children (7–12) +10 adults (18–33) PAE vs. 15 children +10 adults Control (age matched ±1 yr.) | • Generally impaired behavior performances in PAEs  
• PAE children showed greater inferior-middle frontal activity, while control children showed greater superior frontal and parietal activity  
• Control children showed an overall increase in frontal activity with increasing task difficulty, but PAE children showed decreased activity  
• PAE adults demonstrated less brain activity overall, but greater inferior-middle frontal activity during the simpler tasks  
• Control adults demonstrated greater inferior frontal activity with increasing task difficulty, while this pattern was not consistently observed in PAE adults. |
| Fryer et al. 2007 | fMRI          | Go/No-Go                        | 13 PAE (14.5) vs. 9 control (14.5)                                                | • Similar task performance between group  
• PAEs showed greater BOLD response across prefrontal cortical regions and less right caudate nucleus activation |
| Sowell et al. 2007 | fMRI          | Verbal paired associate learning | 11 PAE (10.7) vs. 16 control (10.8)                                                | • Behavior performance not recorded during scan  
• PAEs showed less activation in left medial and posterior temporal regions and more activation in right dorsal frontal cortex |
| Li et al. 2008    | fMRI and structural MRI | Sustained visual attention | 7 PAE (20.4) vs. 7 control (21.3). Adults                                         | • Generally impaired behavior performances in PAEs  
• Significant white and gray matter volume reduction in the occipital-temporal area of PAEs  
• PAE’s activation resided more superiorly than that of controls resulting in reduced activation in the ventral occipital-temporal area  
• The location of PAE functional abnormality approximately matches that of the significant structural reduction |
| Astley et al. 2009 | fMRI          | Face working memory             | 16 FAS/Partial FAS (13.3) +22 Static Encephalopathy/Alcohol Exposed (12.4) +20 Neurobehavioral Disorder/Alcohol Exposed (12.5) +13 Control (12.9) | • Generally impaired behavior performances in PAEs  
• 1-back activation was comparable across all study groups  
• 2-back activation was significantly lower in exposed group in extended prefrontal and parietal regions  
• Control group could increase brain activation with increasing memory load while exposed group could not |
| O’Hare et al. 2009 | fMRI          | Verbal working memory           | 20 PAE (10.7) vs. 20 Control (10.9)                                                | • Insignificant group difference in behavior performances  
• PAE subjects showed increased activation versus controls in the left dorsal frontal, left inferior parietal, and bilateral posterior temporal regions |
| Spadoni et al. 2009 | fMRI          | Spatial working memory          | 10 PAE (14.7) vs. 12 Control (13.6)                                                | • Groups did not differ on task performances in the memory condition, but controls had faster reactions during the vigilance condition  
• PAE subjects showed greater BOLD response in frontal, insular, superior, middle temporal, occipital, and subcortical regions. |
| Santhanam et al. 2009 | fMRI          | Arithmetic processing           | 19 dysmorphia (23.3) +18 non-dysmorphia (23.2) +17 control (23.0).Adults           | • PAEs exhibited lower accuracy but comparable reaction time as compared with controls |
adults. In children, the control group showed increased frontal lobe activity as the task difficulty increased while those with FASD showed an opposite effect. That is, they showed increased activation relative to controls on easier tasks but reduced response on more difficult cognitive tasks. In the adults (age range: 18–33 years), the FASD group generally showed less brain activation than the controls. With increasing task difficulty, both the child and adult controls, exhibited increasing brain activation in frontal regions, but the children and adults with FASD did not. The authors suggest that alcohol diagnosis is associated with “improper” functioning in the prefrontal areas of the brain that affects working memory skills.

Another fMRI study focused on spatial working memory in clinically-recruited children and adolescents (mean age 13.6–14.7 years) (Spadoni et al. 2009). Data analysis was restricted to those participants who were able to perform behavioral tasks within the scanner to acceptable criteria (total accuracy 69–100%). In this study, as well, overall brain size did not differ between groups. The authors reported that, for the FASD group, greater frontal BOLD response was noted during the spatial working memory tasks but not during the simple vigilance task. That is, this study observed “greater-activations” in the alcohol group in extended brain regions during the spatial working memory task (Fig. 2). In an analysis comparing brain activation with task efficiency, greater activation in right middle frontal gyrus (Brodmann Areas 8 & 6), medial frontal and superior frontal gyri were found to be related to a shorter reaction time in task for the contrast group but not for the alcohol-affected group. The authors suggest that findings may indicate a delay in achieving mature information processing by the alcohol-affected children.

Interpretation of results can be difficult as inconsistencies in study results could be due to a number of factors, including the experimental group difference on behavior performance. In the study of Maliszsa et al., the exposed group was generally impaired in behavioral performance while in that of Spadoni et al. the group difference was not significant. However, differences in results could also be related to a number of other sources of variability including task characteristics (that is, difficulty), ability differences (IQ), or comorbid psychiatric conditions. Variations in brain structure can also affect activation (see Bookheimer and Sowell 2005 for a commentary on these issues).

In addition to spatial working memory, fMRI has been used to examine working memory for verbal information (O’Hare et al. 2009) and faces (Astley et al. 2009). For verbal working memory, O’Hare and colleagues, reported increased brain activation in the alcohol group (mean age 10.7 years) in the left dorsal frontal, left inferior parietal and bilateral posterior temporal regions even when behavioral performance did not differ. This increase in activation is consistent with the findings of this group in their study of spatial working memory discussed above (Spadoni et al. 2009).

In a study that used working memory for facial recognition, Astley et al. (2009) reported lower brain activation in the exposed group in extended prefrontal and parietal regions, particularly in the right hemisphere and particularly on tasks requiring more “mental effort”. Participants were clinically identified children with FASD and controls (age range: 8–15.9 years) and neuroactivation was assessed in seven brain regions include anterior cingulate, anterior and posterior parietal lobes and several frontal regions, including dorsolateral prefrontal, inferior frontal, middle frontal and precentral regions. During an

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Brain function</th>
<th>Subjects (mean age)</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meintjes et al. 2010</td>
<td>fMRI</td>
<td>Number processing</td>
<td>15 PAE (10.4) vs. 18 Control (10.1)a</td>
<td>• Dysmorphic PAEs showed significantly lower activation in regions known to be associated with arithmetic processing, including left superior and right inferior parietal regions and medial frontal gyrus • Nondysmorphic PAEs showed generally intermediate but not significantly different from controls • Insignificant group difference in behavior performances (inside scanner) • During Proximity Judgment, exposed children recruited additional parietal pathways • During Exact Addition, exposed children exhibited more diffuse and widespread activations</td>
</tr>
</tbody>
</table>

a There were unusable subjects due to reasons of severe head motion, poor behavior performance, participant refusal, disease affecting cerebral perfusion or technical issues.
“N-back” facial recognition task, the right inferior frontal gyrus, right posterior parietal lobe, right dorsal lateral prefrontal cortex, and right middle frontal gyrus, were found to exhibit greater activation by controls but not by those most affected by alcohol exposure. On an easier version of this task (1-back versus 2-back), there were no group differences in activation.

Inconsistency can be noticed between the findings of these two studies of working memory with the exposed group showing generally higher activation in the verbal study but generally lower activation in the face study. Certainly, differences may be the result of differences associated with task difficulty; however, group difference on behavior performance may contribute to these results, as well. In the face recognition study, those in the FASD group showed impaired behavior performances as well as IQ scores that are significantly lower than those in the control group while in the verbal memory study, those in the alcohol group performed at a comparable level on the in-scanner task although they also had lower mean ability scores than the controls.

Two recent fMRI studies examined functional alterations associated with number processing (Meintjes et al. 2010; Santhanam et al. 2009) based on behavioral research that suggests that number processing and math are areas of specific deficit in alcohol-exposed individuals (Kable and Coles 2004). Using a subtraction task, with a sample of prenatally exposed young adults and controls (Mean age: 23.2 years) with similar ability level and demographic characteristics, Santhanam and colleagues (2009) reported lower activation by alcohol-affected individuals in parietal and prefrontal regions known to be involved in arithmetic processing (Dehaene et al. 2004). In this study, which employed a longitudinal cohort identified prenatally, whole brain size was significantly smaller in alcohol-exposed adults. To reduce potential distortions associated with normalization of brain images to standardized templates, ROIs were defined in the standard space (template) but back-projected into the native space of each individual. Activation intensity and number of activated voxels of each ROI then were calculated in native space. In addition, activated voxel numbers for each ROI were individually normalized to the size of the ROI mask for each individual. This approach makes the group comparison less sensitive to normalizing distortions than typical procedures. In this study, behavioral performance on the subtraction task also was poorer in the alcohol groups but these results were not correlated with activation outcomes.

Fig. 2 Functional brain activation differences (bottom frame) between the prenatal alcohol exposed (top-left frame) and control (top-right frame) subjects in a spatial working memory task. The exposed group exhibited greater activation in extended brain regions. This figure is adapted from (Spadoni et al. 2009) with permission.
Meintjes and colleagues used tasks of exact addition and proximity judgment to examine brain activation associated with number processing (Meintjes et al. 2010). Participants were school-aged South African children (8–12 years) who had been exposed prenatally to heavy alcohol use. Control children were born to nonusers or to women drinking fewer than 7 drinks a week. Behavioral performance in the scanner was equalized by controlling task difficulty and excluding the data of children who could not meet accuracy criteria (for proximity judgment, 8 of 15 participants in the FASD group were excluded); more exacting neuropsychological tasks performed outside the scanner did show significant differences with the group heavily exposed to alcohol performing more poorly. Functional MRI results indicated additional or more widespread activation by the exposed group rather than activation that was specific to the regions that were identified as active in math processing. In contrast, such specific activation was characteristic of the controls.

Functional MRI was used in three other studies examining brain alterations associated with inhibitory control (Fryer et al. 2007), verbal paired associate learning (Sowell et al. 2007) and sustained visual attention (Li et al. 2008). As the research designs and experimental tasks varied significantly, they must be considered separately.

Executive functioning has been identified as an area of concern in alcohol-affected individuals and inhibitory control is considered a major component of the behavioral pathology reported in individuals with FASD. To study inhibitory control, Fryer and colleagues (2007) used a “Go/No-Go” task with clinically identified children and adolescents (ages: 8–18) and controls. In this sample, brain size did not differ and there was similar behavioral performance between the alcohol group and the controls. However, greater BOLD response was noted in the alcohol group versus the control group in the left medial and right middle frontal gyri with less activation in the right caudate nucleus. The authors attribute these results to altered frontal-striatal activation patterns in the alcohol group that may require greater activation of frontal regions during inhibition.

To study verbal paired associate learning, Sowell et al. compared clinically diagnosed children, ages 8–13, with a contrast group (Sowell et al. 2007). Both groups had mean ability (IQ) scores in the average range but there remained a 20 point IQ differences between these two groups. A paired association task was done during the scan but behavioral performance was not recorded to avoid motion artifacts associated with a verbal response. The imaging finding was that the FASD group showed less activation in the left medial and posterior temporal regions but more activation in the right dorsal frontal cortex. The areas of underactivation relative to controls are those usually thought to be associated with memory function.

The single study of sustained visual attention (Li et al. 2008) focused on the occipital-temporal region, which resides at the receiving end of attention modulation. The adult participants in this study were members of a longitudinal cohort identified prenatally. Alcohol-exposed participants showed both impairments of sustained attention on the behavioral task as well as structural volume reduction in the occipital-temporal region. Examination of white matter alterations in this area and of functional activation associated with this task indicated correspondence between the two measures. The authors hypothesized that, in the alcohol-exposed participants, functional activation patterns were altered due to structural impairment in this region.

These functional neuroimaging studies suggest that prenatal alcohol exposure and FASD diagnosis are associated with alterations in brain function in widespread cortical and subcortical regions. In addition, there are suggestions of a general association between functional brain activation and behavioral outcomes. In some cases, these functional alterations have been correlated with impairments in several different cognitive and behavioral outcomes. It is apparent, however, that there are a number of factors that affect the specific patterns of both behavior performance and BOLD activation across these studies. Results can vary depending not only on experimental group differences but also due to subject characteristics and task parameters.

Methodological Issues for Functional Neuroimaging Studies of FASD

The brief review of fMRI studies presented above does not provide a clear and consistent pattern associated with FASD or prenatal alcohol exposure. We suggest that, in addition to the general limitations that affect the interpretation of functional imaging studies, there are also specific issues associated with the study of FASD that should be noted.

Artifact/inaccuracy in image registration due to microcephaly generally affects the results of fMRI studies. To perform group analysis, fMRI data usually requires spatial normalization of each individual’s structural and functional images so that anatomical variability across different brains can be minimized. This spatial normalization is achieved by warping individual brain images to match a standard template in stereotaxic space (Friston et al. 1995). However, as the widely-available and commonly-used templates (e.g., ICBM452) are all built from brains of healthy adults, using these templates may introduce systematic bias in the results of group comparison (Bookheimer and Sowell 2005). Such bias is particularly likely in the case of FAS where severely affected individuals typically have smaller brain size than non-exposed controls or those representing the spectrum of alcohol effects (FASD);
therefore, a different amount of image deformation and intensity modulation may be introduced into the data of these groups. Although quantitative assessment of the normalization-induced group difference has not yet been reported in studies of prenatal alcohol exposure, data from pediatric studies (which are complicated by a similar situation of smaller brain size in children) do suggest extra caution in interpreting imaging results with a biased normalization template (Wilke et al. 2002, 2003; Yoon et al. 2009). For future functional and structural studies of FASD, using a customized template with contributions from both the exposed and control sample would be preferable. Alternatively, using local structural measurements (e.g., gray matter volume) as covariates in statistics of group comparison can also provide effective control of this normalization bias (Oakes et al. 2007).

Group difference of cognitive ability level is a specific challenge for all kinds of functional neuroimaging studies of FASD. Due to the neurodevelopmental compromise, exposed and affected individuals often have lower ability levels (IQ) and widespread neuropsychological deficits. Such deficits are required for the diagnosis of FAS or associated disorders, which are a prerequisite to inclusion in most clinical studies. Thus, the individuals being studied tend to show reduced behavioral performances relative to controls in the experimental tasks that are required for functional neuroimaging. This can be the case even when controls are matched for socioeconomic status (SES) and other relevant factors. Different behavioral performance between groups may complicate the interpretation of functional imaging data. Even when there is no clinical condition, activation difference can be observed between groups of healthy subjects who show different behavior performance (Grabner et al. 2007). Thus, in a particular research paradigm, observed brain activation difference could either reflect neuronal alterations associated with alcohol exposure, or reflect results associated with the ability differences between groups. To deal with this issue, some of the cited studies matched behavioral performance between groups (Burden et al. 2009; Fryer et al. 2007; Meintjes et al. 2010; O’Hare et al. 2009) either by using a easy experimental task (so that both group can perform fairly well), or by a post-hoc select-and-match of subjects based on their performance. Obviously, both strategies limit the generalizability of the results: the former strategy by restricting the kinds of cognitive tasks and the performance range that can be examined and the latter, by excluding the most affected individuals from participation.

An alternative approach to minimizing this effect of ability difference is to parametrically manipulate the task difficulty in the experiment (Amaro and Barker 2006; Kotsoni et al. 2006). With this design, brain activations do not need to be directly compared between groups at any specific level of task difficulty; instead, researchers can examine how brain activation changes with difficulty, and it is this change that will be compared between groups. For example, in a working memory study, the memory load can be parametrically manipulated to require subjects to perform the task at different levels of difficulty. With increasing task difficulty, control subjects may show increasing brain activation in memory-related regions, but individuals with FASDs may exhibit limited increment of this brain activation in the same regions. This approach was used by Sowell et al. (2007) in their study of verbal learning.

Developmental outcomes of prenatal alcohol exposure have not been directly examined by functional neuroimaging. The majority of the studies reviewed were carried out in children of late school age or adolescence. This age group is probably being studied most commonly because of access to samples and because children at that age are more cooperative with experimental protocols. However, development of cognition and behavior proceeds throughout the lifespan and as we know from functional neuroimaging studies of typical individuals and from other clinical groups, there are significant changes throughout the lifespan in brain function. When there are “developmental” delays or deficits, it can be difficult to understand whether these are truly delays and, therefore, eventually resolvable or whether these are deficits and represent permanent alterations in function. Currently, the functional neuroimaging studies of the effects of prenatal alcohol exposure that have been done are limited in number and in terms of the ages of the individuals who have been included in these studies. Thus, interpretation of “developmental” effects of prenatal alcohol exposure on brain function cannot be done as yet.

Sample characteristics and conditions of comorbidity vary between studies. Using samples drawn from populations with different characteristics may produce different results. In this literature, there are two methods commonly used to identify effects of alcohol exposure. The first is to identify women who use alcohol in pregnancy and to examine their offspring, in comparison with a non-exposed group whose mothers did not use alcohol. The second method is to recruit from clinical settings where alcohol-exposed individuals may apply for care and to compare their behavior or other characteristics to that of a contrast group. However, longitudinally followed alcohol-exposed individuals and individuals applying for mental health services usually have different characteristics. Clinical samples, in fact, represent a subset of the exposure population. When samples are recruited from clinical populations, as must often be the case, it is difficult to avoid questions about the effects of social and other factors that have brought them to the attention of clinicians. One paper (Spadoni et al. 2009) in discussing potential study limitation commented on the questions inherent in studying a sample recruited from a clinical population. As these authors noted, “Because of the
high incidence of psychiatric co-morbidities in individuals with prenatal alcohol exposure, excluding medicated subjects would limit the generalizability of ...results. (p. 2074)

However, it also seems likely that including subjects medicated with stimulants and antipsychotics, two common prescriptions for older children identified with alcohol-related behavioral disorders and FASD (Frankel et al. 2006; O’Malley and Nanson 2002), may also affect outcomes of activation studies. Similarly, when using adolescent and adult populations, controlling for alcohol and other drug use by participants may be important to avoid effects of concurrent exposure.

Discussion

Studies of functional neuroimaging suggest that prenatal alcohol exposure, or a diagnosis of FAS, may lead to a general decrease in neural efficiency or a global decrement in processing resources. Depending on the task requirements, compensation mechanisms may be needed for the exposed individuals to achieve a behavioral performance comparable to their peers. This view is supported by fMRI studies that report comparable behavioral performance (Fryer et al. 2007; Meintjes et al. 2010; O’Hare et al. 2009; Spadoni et al. 2009) and show increased activation in the task-associated brain regions. However, there may be conditions under which such “compensation” cannot occur, when the task is particularly challenging, or when exposure level was higher. Studies reporting impaired behavioral performance (Astley et al. 2009; Malisza et al. 2005; Santhanam et al. 2009) support such an argument as they show decreased activation in the associated brain regions. EEG studies also suggest a dose/response gradient (Burden et al. 2009, 2010, 2011).

Most of the currently available neuroimaging studies have used a “regional” approach to show which part of the brain is activating differentially between the groups during task performance. With increasing imaging data available on whole brain that can describe alterations of neural activation, future studies of functional neuroimaging in alcohol-exposed populations will progress by applying knowledge available from previous studies of neuropsychology and functional neuroimaging to the understanding of functional networks. For example, recent fMRI studies have shown that besides functional activations, attention-demanding tasks usually also induce deactivation in several brain regions termed as the “default mode network (DMN)”. This network includes brain regions active when the individual is awake and alert but not focused on external stimuli or tasks (Raichle and Snyder 2007). Typically comprising the anterior and posterior cingulate as well as bilateral inferior parietal cortices (Fig. 3), the DMN should be considered in future studies of prenatal alcohol exposure due to its significant relevance to attention/arousal regulation (Sonuga-Barke and Castellanos 2007), which are known being impaired in FASD (Mattson et al. 2006). Interactions of the DMN with task-positive brain networks should be of interest to most researchers as in many other psychiatric situations (Buckner et al. 2008) including prenatal cocaine exposure (Li et al. 2010) and attention deficits/hyperactivity disorder (Liddle et al. 2010).

Similarly, it would be valuable to explore brain networks beyond the prefrontal-parietal system that has received the bulk of experimental attention. The published functional neuroimaging studies so far focus on functions that are cognitively demanding (working memory, attention, number processing and inhibitory control), largely involving the prefrontal-parietal executive system (Jones and Smith 1973). However, the completion of a complex cognitive task requires cooperative effort across different neural networks and impaired behavioral outcome may reflect not only functional changes in the executive system but also in neural networks that processing information at relatively early stages (e.g., visual system). Comprehensive understanding of the impact of prenatal exposure needs imaging data from both aspects.

Finally, in examining functional outcomes, connectivity is of prime importance as different brain regions do not work in isolation. With fMRI, neural connections can be examined through two different aspects, functional and effective connectivity. Functional connectivity measures temporal signal correlations between regions and effective

Fig. 3 The default mode brain network (the blue regions) shown in lateral (top) and midsagittal (bottom) view. This figure is adapted from (Buckner et al. 2008) with permission.
connectivity measures causal influence exerted by one region over another. Both approaches have made exceptional contributions to studies in populations with different pathologies (Whittingstall et al. 2003) and it is likely that this approach will be equally fruitful in future studies of effects of alcohol exposure. A recent example of this approach used “resting-state” data and found lower inter-hemispheric functional connectivity between para-central regions in the exposed group (Wozniak et al. 2011). Future studies will benefit from joint use of activation and connectivity approaches to examine the effects of prenatal alcohol exposure on both the nodes and margins of brain networks.

References


Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE): Proposed DSM-5 Diagnosis

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Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE): Proposed DSM-5 Diagnosis

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Abstract Over the past 40 years, a significant body of animal and human research has documented the teratogenic effects of prenatal alcohol exposure (PAE). Neurobehavioral Disorder associated with PAE is proposed as a new clarifying term, intended to encompass the neurodevelopmental and mental health symptoms associated with PAE. Defining this disorder is a necessary step to adequately characterize these symptoms and allow clinical assessment not possible using existing physically-based diagnostic schemes. Without appropriate diagnostic guidelines, affected individuals are frequently misdiagnosed and treated inappropriately (often to their considerable detriment) by mental health, educational, and criminal justice systems. Three core areas of deficits identified from the available research, including neurocognitive, self-regulation, and adaptive functioning impairments, are discussed and information regarding associated features and disorders, prevalence, course, familial patterns, differential diagnosis, and treatment of the proposed disorder are also provided.

Keywords ND-PAE · Fetal alcohol spectrum disorders · Prenatal alcohol exposure · Psychiatric diagnosis

The Diagnostic and Statistical Manual, 5th edition, from the American Psychiatric Association now includes in its nomenclature “Neurobehavioral Disorder associated with Prenatal Alcohol Exposure (ND-PAE)” [1]. ND-PAE was listed in the Conditions for Further Study and also given as an example under “Other Specified Neurodevelopmental Disorder (315.8).” This paper presents research supporting ND-PAE diagnostic criteria. In addition, interactive effects of adverse psychosocial influences, relation to other DSM-5 diagnoses, culture influences, prevalence, developmental course, family patterns and treatment considerations are briefly described.

A large body of evidence from experimental animal research, longitudinal prospective human studies, and clinical research documents the teratogenic effects of prenatal alcohol exposure (PAE) on fetal growth and development, central nervous system (CNS) function, and behavior throughout the lifespan [2]. Extensive research on the effects of PAE supports the existence of a spectrum of diagnostic conditions as described by the Institute of Medicine in 1996 (IOM) [3]. Accordingly, these conditions are collectively referred to as Fetal Alcohol Spectrum Disorders (FASD), a non-diagnostic umbrella term accepted in 2004 by consensus of governmental, research and advocacy organizations [4].

The diagnostic coding schema put forth by the IOM has been useful in delineating variation in physical characteristics associated with PAE. However, this schema does not adequately describe the significant neurodevelopmental and mental health symptoms often associated with PAE. Without a diagnostic schema that fully captures these
symptom patterns, service needs of many individuals affected by PAE are often not identified or appropriately treated by mental health professionals. The diagnostic term “ND-PAE” was proposed to encompass the range of neurodevelopmental disabilities that can be associated with PAE and can be diagnosed either in the presence or absence of physical effects of PAE. For example, individuals with an ND-PAE diagnosis may also be diagnosed with Fetal Alcohol Syndrome (FAS) or partial FAS.

**Diagnostic Features**

Confirmed gestational alcohol exposure is required for diagnosis of ND-PAE. Although both animal and human studies have documented adverse effects with low levels of drinking [5, 6], identifying a threshold of PAE remains challenging. Current data suggest that a history of *more than minimal* gestational alcohol exposure (e.g., light drinking) prior to pregnancy recognition and/or following pregnancy recognition should be required. Light drinking has been defined as 1 to 13 drinks per month, with no more than 2 drinks per drinking occasion [7]. Confirmation of *more than minimal* gestational alcohol exposure may be obtained from: maternal self-report of alcohol use in pregnancy; a spouse/partner, relative, or friend who observed the biological mother drinking alcohol during pregnancy; and/or documentation in medical or other records.

Although these criteria provide general guidelines to define confirmed *more than minimal* gestational alcohol exposure, questions regarding how much alcohol is needed to impact neurodevelopmental outcome remain unanswered. The impact of low levels of PAE remains controversial [8, 9]. Consumption levels may vary on a daily and weekly basis, even among heavy alcohol users [10]. Dosage level interacts with period of fetal development, maternal and fetal genetics, and maternal physical status and metabolic systems [11]. Maternal characteristics such as older age at delivery, smoking, certain obstetric problems and medical conditions (especially liver disease) all increase the probability of bearing affected offspring [12]. Despite extensive research, no specified “safe” level of drinking during pregnancy has been identified. Public health recommendations in multiple countries are that women should not drink when planning pregnancy or throughout pregnancy to prevent teratogenic effects, including those that may be more subtle [13–15].

Clinicians may be uncomfortable with asking patients and their families about gestational alcohol exposure histories but this is a necessary criterion for making the diagnosis. Guidelines as well as professional training programs to facilitate asking about gestational alcohol exposure have been developed [16, 17] and have been found to increase the clinicians’ comfort and skill at asking these questions. Clinicians should not make a diagnosis of ND-PAE if they are not confident in the validity of information they obtain documenting *more than minimal levels* of gestational alcohol exposure.

Although ND-PAE diagnostic guidelines do not require evidence of structural brain damage, a diagnosis of ND-PAE indicates potential underlying brain alterations. Extensive research data support the presence of changes to both structural and functional integrity of the brain [18, 19] in individuals with PAE. Consistent with the extensive data on the mechanisms of alcohol as a potent neurobehavioral teratogen [20], these alterations can result in a range of neurodevelopmental outcomes with wide individual variation. The criteria for ND-PAE encompass these outcomes. For purposes of diagnosis, symptoms have been clustered into three domains: neurocognitive functioning, self-regulation, and adaptive functioning. Table 1 outlines these three domains and symptoms associated with each. The diagnosis of ND-PAE does not rely on the specificity of any one domain, but on the intersection of these three domains of impairment, which potentially result in a lifetime of behavioral and mental health problems and adverse impact to quality of life.

**Impairment in Neurocognitive Functioning**

Evidence of CNS dysfunction may be revealed through global intellectual deficits (or clear evidence of significant, global developmental delay in very young children), or by a profile of impairments in specific areas of neurocognitive functioning. Psychometric data from direct child testing, and standardized parent or teacher questionnaires, are both useful as evidence of CNS dysfunction and can effectively aid diagnosis. Judgments according to psychometric data, systematic clinical observations and focused interview are the basis for diagnostic guidelines used in research definitions of this set of conditions and in multidisciplinary clinics specializing in diagnosing conditions associated with PAE. A diagnosis of ND-PAE requires at least one symptom indicating impairment in the area of neurocognitive functioning, in concert with deficits in the two additional domains.

**Global Intellectual Deficits**

Global intellectual deficits, or significant developmental delay among young children, are possible neurodevelopmental outcomes of PAE. However, accumulating evidence highlights that many individuals with conditions related to PAE do not meet criteria for intellectual disability [21].

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Scores ranging from severe intellectual deficiency to average levels of functioning are found in reviews of clinical research, with mean group performance in the borderline to mildly intellectually deficient range [22].

Impairments in Executive Functioning

Individuals with PAE have been described as showing impairments in complex information processing or executive functions (EF) [23, 24], including difficulties in planning, organization, and problem-solving skills. Animal models of PAE have also found deficits in EF [25] that persist into adulthood. Individuals with PAE show repetitive errors and deficits in overall performance on progressive planning tasks [26], suggesting difficulties incorporating feedback. Response perseveration has also been found in animal models of PAE [27]. Individuals with PAE have shown trouble learning to shift during problem-solving tasks, particularly when making reversal shifts [28], which has also been found in animal models of PAE [29]. In clinical terms, individuals with PAE demonstrate difficulties in planning and organization, or cognitive inflexibility as evidenced by difficulties in changing strategies or thinking about things in more than one way. Notably, EF problems have been found to be greater than expected based on IQ scores among these individuals [30], and impairment in some aspects of EF may become more pronounced with age [31].

Learning Problems

Among those with a history of PAE, academic achievement problems are greater than expected for general intellectual level, and there is a high incidence of special education services [32] and poorer educational attainment [33]. Deficits in math achievement have regularly been identified in both longitudinal and clinical studies of individuals with PAE [32, 34] and linked to alterations in brain structure in this population [34, 35]. Repeating grades, school failure, and school drop-out have all been identified as negative outcomes commonly seen among individuals with PAE [36]. Of course, these school outcomes are ultimately determined by complex interactions between the neurodevelopmental status, environmental supports, and emotional and behavioral functioning of the individual with PAE.

Memory Deficits

Research data reveal significant, persistent difficulties in memory among those with PAE, including verbal and visual-spatial memory. Deficits in organizational or metamemory strategies for encoding and retrieving information have been identified among children with PAE [37]. However, strategies to support memory can be helpful and retrieval or retention of learned material may be less affected than encoding [38]. Animal models of PAE have also detected memory impairments [39, 40].

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**Table 1** Core symptoms of neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)

<table>
<thead>
<tr>
<th>1. Neurocognitive impairment (1 or more)</th>
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<tbody>
<tr>
<td>1. Global intellectual impairment (i.e., IQ or global developmental score below 70)</td>
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<tr>
<td>2. Impairment in executive functioning (e.g., poor planning and organization; difficulty changing strategies or inflexibility; difficulty with behavioral inhibition)</td>
</tr>
<tr>
<td>3. Impairment in learning (e.g., lower academic achievement than expected for intellectual level; requires special education services; specific learning disability)</td>
</tr>
<tr>
<td>4. Impairment in memory (e.g., problems remembering information learned recently; repeatedly making the same mistakes; difficulty remembering long verbal instructions)</td>
</tr>
<tr>
<td>5. Impairment in visual spatial reasoning (e.g., disorganized or poorly planned drawings or constructions; problems differentiating left from right; problems aligning numbers in columns)</td>
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<th>2. Impairment in self-regulation (1 or more)</th>
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<tbody>
<tr>
<td>1. Impairment in mood or behavioral regulation (e.g., mood lability; negative affect or irritability; frequent behavioral outbursts)</td>
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<tr>
<td>2. Attention deficit (e.g., difficulty encoding new information; difficulty shifting attention; difficulty sustaining mental effort)</td>
</tr>
<tr>
<td>3. Impairment in impulse control (e.g., difficulty waiting turn; difficulty complying with rules; confabulating; taking possessions of others)</td>
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<tr>
<th>3. Deficits in adaptive functioning (2 or more with at least 1 of the first two symptoms)</th>
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<tr>
<td>1. Communication deficit (e.g., delayed acquisition of language; difficulty understanding spoken language; difficulty using language to express self so that the listener understands)</td>
</tr>
<tr>
<td>2. Social communication and interaction impairment (e.g., overly friendly with strangers; difficulty reading social cues; difficulty understanding social consequences; acting too young)</td>
</tr>
<tr>
<td>3. Impairment in daily living (e.g., delayed toileting, feeding, or bathing; problems following rules of personal safety; difficulty managing daily schedule)</td>
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| 4. Motor impairment (e.g., poor fine motor development; delayed attainment of gross motor milestones or ongoing deficits in gross motor function; problems in coordination and balance) |
hippocampal volume have been linked to functional memory impairments in human neuroimaging studies [41, 42] and animal models [39, 43].

Active working memory, which involves the capacity to store and process meaningful units at a given moment in time, has been found to be deficient in individuals with PAE, particularly for tasks involving multiple-step instructions [31]. Deficits in the ability to manage goals in working memory are thought to represent a central underlying mechanism in the neurocognitive problems seen in individuals with PAE [44]. Clinical observations suggest that alcohol-exposed individuals have problems remembering information learned recently, require frequent reminders, have difficulty remembering lengthy verbal instructions, and lose or misplace possessions.

Visuospatial Processing

Evidence for specific deficits in visual/spatial perception [45] has been found, including deficits in visual memory [46], visual perceptual skills [47], visual-motor integration [46] and spatial memory [48]. Alterations associated with PAE in the microstructural characteristics of white matter have been further linked to deficits in visual-motor integration [49] and deficits in visual perception [50]. Clinically, these symptoms may be expressed as disorganized or poorly planned drawings or constructions, problems differentiating right from left, and difficulties using spatial cues.

Impairments in Self-Regulation

Difficulties in self-regulation among individuals with PAE have been reported in research findings, are commonly reported by parents and professionals [51] and may be observable even among infants and young children [52]. A diagnosis of ND-PAE requires at least one symptom indicating impairment in the area of self-regulation, in concert with deficits in the two additional domains.

Mood or Arousal Regulation

Deficits in arousal among individuals with PAE are well documented [53]. Among young children affected by PAE, disturbances may be seen in physiological processes and regulatory capacity in day and nighttime functioning. Clinically, significant sleep problems are present with high frequency [54]. Greater stress reactivity has been found among infants [55] and in animal models of alcohol effects [56, 57]. Children with PAE have also been described as showing a central problem in ‘negative affectivity,’ which includes internal feelings of distress and anger and negative engagement with others [58]. Other significant mood symptoms are commonly reported, including mood lability, frequent behavioral outbursts, irritability, and over-reaction to environmental stressors [51]. Individuals are often described clinically as easily overwhelmed by typical environmental experiences and as showing perseverative responses, rather than being responsive to environmental feedback when trying to learn a new task. Abnormal sensory encoding or sensitivities are commonly reported by parents [53].

Attentional and Impulse Control Problems

Problems in shifting attention and sustaining mental effort to complete tasks [59, 60] and inhibit impulses [60, 61] have been described in this population and have been replicated in animal models [62]. Because of problems with impulse control, individuals with PAE are often clinically described as breaking rules or cheating at games, confabulating or telling lies, or stealing. Importantly, this may be due more to underlying cognitive and behavioral regulation impairment than to actual conduct problems.

Impairments in Adaptive Functioning

Accumulating research data support significant adaptive function deficits among individuals with PAE [63]. Such deficits are persistent, becoming more evident in later childhood and beyond. Notably, adaptive behavior deficits cannot be fully explained by decrements in IQ or a history of environmental disruption [64]. Children with PAE have been found to show delayed adaptive function even compared to those with Attention Deficit, Hyperactivity Disorder (ADHD), with socialization and communication impairments increasing with age [65]. Compared to healthy controls, young children with PAE need more intensive levels of adaptive support from parents and teachers [66]. A diagnosis of ND-PAE requires at least two symptoms indicating impairment in the area of adaptive functioning, in concert with deficits in the two additional domains. At least one area of deficit must be in either communication or social functioning.

Deficits in Communication

Deficits in all areas of language and communication appear common among children affected by PAE. These have been explained as resulting from the impact of PAE on overall intellectual level [67], yet this is not always the case [68]. While the specific nature of language and communication deficits in this clinical population is highly variable, deficits may often be apparent in the pragmatic or
integrative use of language. Individuals may have trouble understanding figurative language, using abstract and decontextualized language, and coordinating increasingly complex messages [69]. Clinically, these difficulties may be observed as excessive talkativeness, an overtly passive communication style, a tendency to make many comments that seem off topic or inappropriate for the communicative context, and/or conversation that is disorganized and difficult for a listener to follow.

**Deficits in Social Skills**

Although individuals with PAE may appear quite sociable, social skills deficits are actually common [70]. Further, they show greater interpersonal impairment when compared with developmentally delayed, non-exposed children with similar deficits in verbal IQ [71]. Clinical observations reveal symptoms such as being overly friendly with strangers, socially immature, having difficulty understanding social consequences or reading social cues, or being naive and gullible. Individuals with PAE have difficulty making and keeping friends, or have superficial friendships, often choosing unsuitable peers as friends. Difficulties in emotion and social information processing are seen, suggesting problems with the social cognitive processes underlying successful peer social interaction [67].

**Deficits in Activities of Daily Living**

Young children with PAE show problems in activities of daily living, such as dressing and bathing, toileting and feeding [66]. Clinical observations and parent reports reveal problems understanding the rules of personal safety and safety awareness [72]. They often appear trusting of strangers and, coupled with a tendency toward socially indiscriminate behavior, are at risk for placing themselves in unsafe situations. Clinical observations reveal that older individuals with PAE have problems telling time and organizing their daily schedules [21]. Along with problems in mathematics and abstract reasoning [32], they have been described as having problems managing their finances. Finally, because many individuals with PAE continue to need adult supervision and adaptive support, they often have difficulty securing and maintaining independent employment [36].

**Deficits in Motor Functioning**

Children with PAE show deficits in adaptive motor functioning starting in infancy [73] that persist into later life [74]. Descriptive studies of individuals with full FAS often note deficits in motor skills and coordination [75], including delayed attainment of gross motor milestones or ongoing deficits in motor function. Among children with PAE, deficits in visual-motor integration [68] and fine-motor strength and coordination are often noted [76, 77]. Also seen are deficits in overall balance [78], motor clumsiness [47], delayed motor responsiveness [79], abnormalities in peripheral nerve conduction [80], abnormal gaits [81], and tremors [74]. Animal models of PAE have also replicated deficits in motor functioning [82].

**Interaction with Negative Psychosocial Influences**

The relationship between PAE and later behavioral outcomes is clearly affected by negative psychosocial influences commonly experienced by individuals with PAE. These influences contribute to problematic outcomes, especially in the domain of behavioral regulation [52]. Adverse circumstances can include parental substance abuse and mental health problems, child neglect or maltreatment, disruption in placement or exposure to familial violence. A history of PAE increases the risk for maltreatment [83]. Moreover, these factors appear to have a compounding effect [84] even in studies using animal models [57, 85].

**Interactions with Other Drugs**

Children with ND-PAE may also have prenatal exposure to other drugs that influence their neurodevelopmental status. For example, prenatal exposures to nicotine [86], cocaine [87], and crystal methamphetamine [88] have been found to disrupt behavioral regulation. Interestingly, these have not been associated with the same degree of neurocognitive deficit as PAE [89]. In addition, women who use prescription medications, which may be harmful to the fetus, are also more likely to drink in pregnancy [90]. Nevertheless, the majority of studies that closely control for exposure to other drugs continue to find the largest teratogenic effects are attributable to PAE. Clinicians are encouraged to take a thorough history of other prenatal exposures and consider their known effects when formulating their conceptualization and treatment plans for individuals with ND-PAE.

**Relationship with Other DSM-5 Diagnoses**

Many individuals with PAE have global intellectual deficits, which should be appropriately diagnosed when present. However, many are not considered intellectually disabled, with only 20–50 % of those with FAS attaining IQ scores <70 [91].
Although mental health disorders are not a criterion for the proposed diagnosis of ND-PAE, co-occurring difficulties in mental health have been identified in as many as 90% of participants in studies of this clinical population [36, 92, 93]. Suicidal ideation and attempts are among the most serious of these potential problems [94]. Symptoms of depression and mania [95] have been reported in both children and adults, and an increased incidence of somatoform disorder, substance dependence or abuse disorders, and paranoid, passive-aggressive, and antisocial personality disorders have been found among adults with PAE [96, 97].

In the presence of PAE, disorders to carefully evaluate are oppositional defiant disorder (ODD), conduct disorder (CD), and ADHD. Research reveals that children with PAE show a high incidence of symptoms thought to describe ODD and CD [95]. Importantly, clinicians rendering a dual diagnosis of ND-PAE and ODD or CD should evaluate whether symptoms apparently associated with ODD and CD are primarily a manifestation of the neurocognitive deficits that define ND-PAE. For example, a clinician should clarify whether noncompliant behavior actually arises from poor comprehension of what was requested, whether lying is actually confabulation, or whether what appears to be stealing actually results from poor understanding of ownership.

ADHD is the most common mental health diagnosis given to individuals with PAE [98]. Although early research identified similarities between the two disorders [99], more recent comparison studies suggest that individuals with ND-PAE and ADHD have some distinctive neuropsychological characteristics. A literature review [100] comparing children with PAE and those with ADHD concluded that children with PAE had greater impairments in problem-solving, overall IQ, shifting attention, verbal fluency, verbal encoding, daily living skills, and face and emotion processing than do children with ADHD. Adaptive behavior deficits observed in children with PAE grow increasingly more severe with age, suggesting a progressive decline in functioning over time relative to children with ADHD [65]. Children with PAE were also found to have more difficulties with conditions associated with over-arousal, whereas children with ADHD and no history of PAE demonstrated deficits in conditions of under-arousal [101]. Additional group differences have been reported in the pattern of neural processing using event-related potentials as outcome measures on an inhibition task [102] and in responses to a conditioned eye blink task, with longer latencies and poorly timed responses among those with PAE compared to those with ADHD [103]. In contrast, children with ADHD had more difficulties with basic motor control, focused attention, sustained attention, and information retrieval. Symptom overlap between the disorders was identified in the areas of set shifting, complex motor skills, static balance, social skills, communication skills, and parental report of behavioral problems [100]. It is important to note that most studies of ADHD do not inquire about PAE, so the ADHD literature may be affected by confounding prenatal alcohol-related effects.

Other Issues Related to Differential Diagnosis

Differential diagnosis includes several genetic (i.e., Cornelia de Lange Syndrome, Down Syndrome, and Dubowitz Syndrome) and teratogenic conditions (Fetal Hydantoin Syndrome, Maternal Phenylketonuria) that share some common features with ND-PAE. A careful review of prenatal exposure history is needed to clarify presence and extent of alcohol exposure. Individuals with extreme prematurity may have neurobehavioral profiles similar to those of individuals with ND-PAE, so it is important to establish levels of gestational alcohol exposure before rendering a diagnosis in these cases. A history of prematurity should not, however, be used as an exclusion criterion given that PAE is associated with an increased risk for extreme prematurity [104].

Evaluation by a pediatrician or clinical geneticist may be needed to distinguish genetic disorders with similar presentations from those sometimes seen among children with ND-PAE. Other considerations for differential diagnosis may include the direct physiological effects of current use or misuse of a substance such as medication, alcohol or other drugs, or problems attributed to a general medical condition such as traumatic brain injury or other neurocognitive disorders (i.e. delirium, dementia). A careful history of symptom onset and current substance use should aid in differentiating these conditions from ND-PAE. Of importance, in addition to ND-PAE, the presence of a diagnosis of FAS may also apply if the individual meets criteria for growth retardation, facial features as well as the neurocognitive deficits described by ND-PAE.

Specific Culture

There is widespread recognition of effects of PAE around the world and across ethnic groups [105]. In a variety of countries, the more widely-studied FAS has been identified more frequently among groups of lower socioeconomic status (SES) than among the more economically advantaged [10]. FAS has also been found more often within minority groups in the US [106]. It is important to note that SES or ethnic group may artificially mark different patterns of alcohol use, differences in genetic susceptibility to alcohol, and/or other environmental, social, or
psychological factors associated with poverty that may increase the risk for maternal drinking (e.g., lack of prenatal care, depression) or exacerbate the impact of the exposure (e.g., poor maternal nutrition). Various customs and practices around alcohol consumption also impact incidence of the disorder [107–110].

**Prevalence**

Prevalence rates of ND-PAE are currently unknown, but recent prevalence rates of conditions collectively known as FASD are estimated to be as high as 2–5% in the US using active case ascertainment [111, 112]. Estimates of FAS are much higher among certain countries and groups, depending on maternal drinking patterns and other factors [105, 107, 110, 113]. Given that nearly half of all US pregnancies are unplanned, with millions of fertile women sexually active while not using adequate contraception, many women are at risk for an alcohol-exposed pregnancy [114]. In the National Birth Defects Prevention Study, 8% of women reported the risky pattern of binge drinking in the first trimester of pregnancy [115]. Given the challenges of establishing accurate and timely prevalence information, the magnitude of neurobehavioral problems associated with PAE is likely even greater than indicated by current data.

**Life Course**

Among individuals with PAE, evidence of CNS dysfunction differs according to developmental stage. As clear deficits in many core domains may not be manifested early in life, diagnostic evaluation of infants, toddlers and preschoolers with PAE can be challenging. For young children, individually-administered developmental assessments and standardized parent questionnaires may provide evidence of impairment. Still, only about half of young children prenatally exposed to alcohol show marked developmental delay in the first 3 years of life, including those later diagnosed with FAS or partial FAS [58]. For young children with PAE, problems may occur in attention regulation, negative affectivity, sensory sensitivities, and physiological disturbance, such as disrupted sleep [116]. There may be delays or deficits in motor or oral-motor tone or skills, language acquisition, play skills, or social immaturity. Pairing of high physiological arousal and poor regulatory capacity may often occur [52]. Despite the challenges, diagnosis of young children is vital given the potential for change following early intervention, but may require specialized input or testing to capture early impairment.

When children affected by PAE reach school age, learning difficulties, executive function impairment and problems with integrative language functions usually emerge more clearly, as well as social skills deficits and challenging behavior. In particular, as school and other requirements become more complex, greater deficits are noted. Consequently, the school years are the period in which diagnosis of ND-PAE is most likely.

The CNS dysfunction seen among those affected by PAE often leads to adaptive behavior decrements and maladaptive behavior with lifelong consequences. Individuals affected by PAE have a higher prevalence of disrupted school experiences and, in adolescence and beyond, often have poor employment records, trouble with the law, confinement (legal or psychiatric), dependent living conditions, and other ‘secondary disabilities’ in lifestyle and daily function [91]. As discussed earlier, co-occurring psychiatric conditions and persistent psychopathology across the lifespan show increased prevalence in this population, shown in longitudinal clinical studies of individuals with PAE [93].

**Familial Pattern**

ND-PAE is a consequence of the teratogenic effects of PAE. However, different genetic variants may possibly influence fetal vulnerability to alcohol teratogenesis. Research has shown that teratogenic effects of PAE can be influenced by multiple maternal factors, including hormone status (particularly hormones of the HPA axis), nutrition, oxidative stress level, age, parity and years of drinking [117–120]. Genetic profiles of both mother and fetus may also alter the metabolism of alcohol and risk of physical birth defects, prenatal mortality, learning and other neurobehavioral deficits in the offspring [121–123]. Familial patterns of heavy drinking during pregnancy, which may be associated with family and cultural customs, may also result in an increased incidence of ND-PAE.

**Treatment**

Individuals with the disorder of ND-PAE present as complex cases with multiple, ongoing and costly service needs [124]. Recommendations for treatment approaches are available [58, 125] and existing treatment approaches have been critically reviewed [126]. Promising approaches to improvement of neurobehavioral outcomes are being explored in animal models and clinical samples.

Several lines of animal research suggest the promise of various prenatal and neonatal interventions, including prenatal and postnatal treatment with neuroprotective
peptides [127] and various nutrients [128–132]. Other research has demonstrated positive effects of neonatal handling, postnatal environment enrichment, and rehabilitative training on rats and mice with perinatal alcohol exposure [133].

Studies of treatments for children with PAE have targeted behavioral problems, cognitive and academic skills, and adaptive skills. Positive effects have so far been demonstrated in studies utilizing supportive behavioral consultation with parents [52, 134], socio-cognitive habilitation to improve math skills [135], language and literacy training [136], rehearsal training to improve working memory [137], computer-based interventions to increase fire and street safety skills [72] and attentional control [138], parent-assisted social skills intervention [139], and self-regulation training [140, 141].

Community and clinic-based surveys indicate that stimulants are commonly used for children with PAE [142], but clinical trials using standard ADHD medications have so far produced mixed results. Two crossover studies with small samples demonstrated positive effects of stimulants on hyperactivity symptoms but not on measures of inattention [143, 144]. Retrospective studies of medication response among individuals with PAE have also yielded mixed results, with some studies finding more positive responses to some stimulant medications than others [145–147]. Collectively, data so far suggest that although symptoms of hyperactivity seem to improve, inattentive symptoms may not be effectively ameliorated by psychostimulants among children with PAE. Psychostimulant medications have also not been found as beneficial as neuroleptics in facilitating response to cognitive behavioral treatments [148]. Clearly, larger samples and more intensive research attention are needed to establish effective pharmacological treatment approaches.

Animal models of PAE have suggested altered reactivity to methylphenidate in the postnatal period [149, 150], resulting in increased activity and decreased excitability of the dopamine neurons in the ventral tegmental area [151]. In contrast, reduced activity and improved performance on learning tasks have been found in response to choline supplementation delivered prenatally [152] or postnatally [153]. The use of fenofibrate, which is a lipid regulating agent that affects nuclear receptors (i.e., peroxisome proliferator-activated receptor-PPAR-alpha), has also been found to minimize symptoms of hyperactivity after PAE [154]. The impact of these substances among humans with PAE is not yet known, although clinical trials of some compounds are underway.

Individuals with ND-PAE may have complex medical problems and psychosocial issues that must also be addressed in ongoing developmental, educational and psychological treatment planning as these risk factors further disrupt their neurobehavioral functioning. Effective intervention requires that the needs and goals of caregivers, family members and the affected individual are all taken into account [155]. Family support, through both formal services (often including respite care) and peer support of other caregivers raising individuals with PAE, is essential. For some individuals with PAE with very complex needs, wraparound services may be required. Individualized educational programming and supportive therapies, caregiver behavior consultation and education, individual and family mental health services, recreational therapies and organizations, social skills and teen groups, and case management of social services are typically needed over time. In some instances, medication management, mentoring programs, substance use education and treatment, and/or legal and judicial assistance may be required. For older individuals, vocational services, alcohol-exposed pregnancy prevention, and requirements for long-term financial and lifestyle assistance should be considered. Indeed, a lifespan perspective on treatment needs and understanding that multimodal treatment [156] is required characterize the appropriate stance when working with individuals with ND-PAE and their caregivers [157].

**Summary**

The development of ND-PAE as a mental health diagnosis is an important step in the appropriate identification and treatment of individuals with a lifetime of behavioral and mental health problems associated with PAE. For the condition to be documented more fully as a unique psychiatric disorder, programmatic research is needed. Evidence supporting the presence of symptoms in the three domains comprising the criteria for ND-PAE is already substantial. However, further research is needed to determine the number and type of symptoms required within each domain to appropriately differentiate those affected by PAE from individuals with other mental health disorders. Specifically, discriminant validity studies using proposed ND-PAE criteria should be conducted at different developmental stages compared to specific disorders (i.e., ADHD, ODD, CD, and Bipolar and Related Disorder), given symptom overlap between ND-PAE and these diagnostic groups. In addition, discriminant validity studies using proposed criteria are needed at different developmental stages comparing those with ND-PAE to populations of children with developmental disabilities.

To date, assessments of individuals with PAE have been traditionally performed by specialized multidisciplinary clinics, developmental pediatricians/pediatricians, and geneticists. These specialized multidisciplinary assessments are very useful, when available. The development of
ND-PAE as a mental health diagnosis to characterize the neurobehavioral impact of PAE broadens diagnostic access. But this advance also means that a variety of mental health professionals, including psychiatrists, psychologists, counselors and social workers, must become familiar with standardized diagnostic criteria (listed on pages 798–801 of the complete DSM-5 manual). Field trials should be conducted to evaluate barriers to implementation of ND-PAE diagnostic criteria, including issues involved in documentation of PAE and assessment of each of the proposed diagnostic domains. Research clarifying the use of ND-PAE is a high priority, given the societal costs [124], caregiving burden and individual suffering of those affected by this mental health diagnosis.

References

Critical Review

Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span

Natasha Reid, Sharon Dawe, Douglas Shelton, Paul Harnett, Judith Warner, Eleanor Armstrong, Kim LeGros, and Frances O’Callaghan

Background: Individuals with fetal alcohol spectrum disorders (FASDs) can experience profound impairments and long-term adverse outcomes. This systematic review adopts a life span perspective providing an extensive analysis of the available literature.

Methods: Studies were identified from PsycInfo, PubMed, Scopus, Web of Knowledge, CINAHL, ERIC, The Cochrane Central Register of Controlled Trials, and gray literature. Two reviewers independently screened the title and abstract of each reference, and the methodological rigor of the included studies was assessed using the Effective Public Health Project assessment tool.

Results: Thirty-two studies met the inclusion criteria, of which the vast majority targeted early to middle childhood. Two studies focused on early intervention in the postnatal period, and 6 studies aimed to improve attention and/or self-regulation in childhood. Three of these provided promising evidence on improving self-regulatory difficulties for children with FASDs. Nine studies focused on improving specific areas of dysfunction. Six studies addressed social skills; 3 of these used an adaptation of a well-validated social skills program. Three studies provided promising initial evidence that parents and caregivers could benefit from support with child behavior and a further 4 studies provided education and advocacy for parents/caregivers, teachers, or child welfare workers. The final 2 studies were aimed at supporting parents who were themselves affected by prenatal alcohol exposure.

Conclusions: There is growing evidence for interventions that improve outcomes for early to middle childhood. However, a lack of research exists outside of this developmental period. This lack of research is concerning given the potential positive impact of early intervention, for individuals and, financially, for governments. In addition, the lack of interventions for adolescents and adults further highlights the widening developmental gap and the potential influence of secondary disabilities for this at-risk population.

Key Words: Fetal Alcohol Spectrum Disorders, Prenatal Alcohol Exposure, Systematic Review, Intervention, Treatment.
2009) evaluated the impact of pharmacological \((n = 2)\) and nonpharmacological \((n = 10)\) interventions for children. This review included randomized controlled trials (RCTs), quasi-RCTs, non-RCTs, and cohort studies with pre- and postintervention measurements. Meta-analysis was not possible because of the highly variable nature of the interventions, leading the authors to conclude that there was currently a lack of good-quality evidence for specific interventions for children with FASDs. Subsequently, there have been a number of narrative reviews of interventions for children and adolescents with FASDs (Kodituwakku, 2010; Olson et al., 2009b; Paley and O’Connor, 2011; Petrenko, 2015). Importantly, Kodituwakku (2010) and Olson and colleagues (2009b) proposed theoretical frameworks to guide the development of interventions. Olson and colleagues (2009b) integrated developmental and family systems theory, and Kodituwakku (2010) presented a neurodevelopmental framework in which it was proposed that early intervention in self-regulation and attention is likely to have more far-reaching effects than specific training in other domains. More recently, Petrenko (2015) has called for a unification of these conceptual frameworks and the inclusion of information from the lived experiences of parents and individuals with FASDs.

The current systematic review expands upon these previous reviews in 3 ways. First, we include intervention studies that were identified by Peadon and colleagues (2009) as in progress or recently completed at the time of their review. Second, we assess the methodological quality of interventions using a standardized assessment rating tool. Third, we take a life span developmental perspective, rather than restricting our focus to children. As the impact of PAE is lifelong, there is a growing consensus that the needs of individuals should be considered from such an approach in order to investigate the potential to ameliorate difficulties and to improve well-being for all individuals with FASDs.

**MATERIALS AND METHODS**

This systematic review has been reported in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA (Liberati et al., 2009; Moher et al., 2009). Details of the protocol for this systematic review were registered with PROSPERO (CRD42014015188).

**Inclusion Criteria**

Studies were considered for the review if (i) the target population consisted of individuals of any age with PAE that included FAS, pFAS, alcohol-related neurodevelopmental disorder (ARND), or PAE; (ii) the intervention could be classified as primarily focusing on improving well-being and functioning through the provision of behavioral treatment, advocacy, or support (thereby excluding pharmacological interventions); (iii) quantitative measures of functioning were reported in order that comparisons could be made about potential gains. No restrictions were placed on the type of outcomes or study design.

**Search Strategy and Study Selection**

Studies were identified during December 2014 from the following electronic databases: PsycInfo, PubMed, Scopus, Web of Knowledge, CINAHL, ERIC, and The Cochrane Central Register of Controlled Trials. Search terms were “fetal alcohol spectrum disorder” OR “fetal alcohol syndrome” OR “alcohol-related neurodevelopmental disorder” AND “intervention” OR “treatment” OR “therapy”. No date, document type, or language restrictions were placed on the searches. Forty FASD organizations were identified and webpages searched to locate non-peer-reviewed intervention trials that could be included (see Supporting Information for a complete list).

Two reviewers independently screened the title and abstract of each reference identified by the searches and determined the potential relevance of each article. For potentially relevant articles or, in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied.

**Study Quality Assessment**

The methodological rigor of the included studies was assessed using the Effective Public Health Project (EPHPP) assessment tool. The tool was developed to assess primary studies in public health (Thomas et al., 2004) and is based on guidelines set out by Jadad and colleagues (1996) and Mulrow and Oxman (1994). The EPHPP tool consists of 6 quality components: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. Each study was rated on these components as “strong,” “moderate,” or “weak” (see Table 1 for an overview of the EPHPP tool). Juni and colleagues (1999) recommend that relevant methodological aspects of studies should be individually assessed, and a total score should not be used. Therefore, an overall rating of the quality of the studies was not carried out. The quality assessment was undertaken independently by 2 reviewers, and any disagreements were resolved by discussion.

**Data Extraction and Synthesis**

Considerable heterogeneity in both the nature of the interventions and the measures used in the studies precluded the use of meta-analysis (Higgins and Green, 2011); therefore, a narrative synthesis method was used. Data were extracted systematically using a preformulated tool consisting of study design, sample size and population, intervention approach, and main results. The studies were subsequently grouped according to key outcome domains and reported within a life span perspective by looking first at those studies focusing on early infancy, then early to middle childhood and, finally, adolescence and adulthood.

**RESULTS**

**Study Characteristics**

The electronic database search located 2,962 citations (after duplicates were removed) which then underwent title and abstract screening. An additional 5 sources were included after an examination of reference lists, and another 2 reports were found from the Internet searches of relevant FASD organizations’ publication libraries. A full text review by 2 reviewers was undertaken for 51 studies; 29 met study inclusion criteria (see Fig. 1 for detailed information). An updated database search conducted prior to submission...
identified an additional 3 studies, resulting in a final total of 32 studies (Table 2).

The vast majority of studies investigated the effectiveness of interventions that targeted aspects of neurocognitive functioning. Of these, 2 studies aimed to improve developmental outcomes in infants. Six studies targeted underlying self-regulatory deficits, or attentional control. Nine studies focused on specific areas of dysfunction, such as math skills \((n = 3)\), language and literacy skills \((n = 2)\), fire/street safety skills \((n = 2)\), memory rehearsal \((n = 1)\), and motor skills \((n = 1)\). Six studies addressed social skills and 3 studies aimed to improve children’s behavior and reduce parental stress by providing structured parenting programs. A further 4 studies provided education and advocacy knowledge for parents and caregivers \((n = 2)\), teachers \((n = 1)\), and child welfare workers \((n = 1)\), and the final 2 studies were both aimed at supporting parents who were themselves affected by PAE.

**Quality Rating**

The details of the quality ratings for the included studies are shown in Table 3. It is notable that none of the studies received a rating of “strong” for the component of “selection bias” or “blinding.” Nineteen of the studies were rated “strong” in study design; this reflects the number of RCTs and controlled clinical trials (CCTs) in the identified studies. Twenty-seven of the studies, across all study design types, used measures that were reliable and valid. Seventeen studies reached the criteria to be scored as “strong” for withdrawal/dropouts.

**Efficacy of Interventions Targeting Individuals with FASD Across the Life Span**

**Developmental Outcomes in Infants.** Two studies (Kartin et al., 2002; Yazdani et al., 2009) primarily focused on helping mothers to provide an optimal environment to promote their infant’s development. Yazdani and colleagues (2009) found that following their home visiting service, children with PAE scored in the average range on developmental tests, which may be interpreted to suggest that deficits were ameliorated through an intensive early intervention service. However, in a study with a considerably stronger design, Kartin and colleagues (2002) found no effect of the home visiting service on the same measures of developmental outcome, with children scoring significantly below age-expected norms.

**Self-Regulation and Attentional Control.** A range of approaches and intervention studies aimed to improve cognitive functioning in early to middle childhood. Three studies investigated the effectiveness of ALERT (Williams and Shellenberger, 1996), a program specifically adapted for children with FASDs, and designed to improve executive functioning (EF). These studies were methodologically robust albeit with small sample sizes and limited follow-up data. Nonetheless, gains were made in all 3 studies (Nash et al., 2015; Soh et al., 2015; Wells et al., 2012) on measures of EF, such as parent report using the Behaviour Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 2000) and selected neuropsychological tests. Most recently, Soh and colleagues (2015) found changes in gray matter volume in critical regions for self-regulation in children in the immediate treatment group compared to children in the delayed treatment group who showed modest growth in one related area.

There is also some evidence that gains can be made on attention and that these gains can generalize to other areas. Kerns and colleagues (2010) found improvements in the immediate posttreatment assessment on measures of sustained and selective attention, and improvements also extended to math and reading fluency. In an unpublished thesis, Vernescu (2008) found that children showed significant improvements in auditory and visual sustained attention and on tasks assessing nonverbal reasoning. However, gains in cognitive functioning were not obtained in a pilot study by Adnams and colleagues (reported in Riley et al., 2003) using cognitive control therapy to enable children to learn metacognitive skills. This intervention was, however, limited by the small sample size, and the authors suggested that the duration was less than required.
Specific Skills. Nine studies focused on remediation of specific skills. Three demonstrated that children were able to benefit from a mathematical skills program specifically designed for children with FASDs. The first intervention trial carried out by Kable and colleagues (2007) found that 6 weeks of The Math Interactive Learning Experience (MILE) program resulted in significant gains in both math knowledge and parent reports of problem behavior, which were maintained at 6 months compared to control children (Coles et al., 2009). More recently, Kable and colleagues (2015) conducted a community translation of the MILE program and found that compared to a parent instruction group, children in the intervention groups (center-based or community-based) showed more positive gains in math skills immediately posttest. Finally, findings from a case study ($n = 5$) provide preliminary evidence for the use of components of the MILE program to improve nonverbal reasoning, reading comprehension, and mathematics reasoning in children and in adolescents aged 10 to 13 years (Millians and Coles, 2014).

Two studies (Coles et al., 2007; Padgett et al., 2006) demonstrated that children with FAS or pFAS were able to learn a sequence of safety commands after playing computer games designed to teach safety skills relating to either fire or street safety. Adnams and colleagues (2007) tested the effectiveness of a classroom-based literacy training intervention of 38 hours of therapy over a 9-month period. Children with FASDs improved in specific language and literacy skills, although no parallel improvements in general scholastic skills were found compared to control children.

Loomes and colleagues (2008) found short-term improvements in digit span in children receiving rehearsal training across 10 days, while Gryiec and colleagues (2004) found improvements in the number of words spelt correctly, following 6 weeks of practicing a “cover, copy, and compare” spelling procedure by a 7-year-old child. Finally, Keiver and
### Table 2. Intervention Studies Across the Life Span

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<td>Kartín and colleagues (2002) CCT</td>
<td>65 home visiting advocacy service, 31 controls; women reported heavy substance use during pregnancy. Recruited within 1 month of delivery; children tested at 3 years</td>
<td>3-year home visitation program to assist mothers with drug/alcohol treatment and support</td>
<td>No differences between the groups although all children performed below developmental age</td>
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<tr>
<td>Yazdani and colleagues (2009)</td>
<td>28 children primary PAE and 15 no alcohol use recruited. All mothers reported use of cocaine. Children tested at 2/3 years</td>
<td>Intensive home visiting program with liaison with ancillary services, addiction, parenting</td>
<td>No differences between groups. All children scored in normal range</td>
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<tr>
<td><strong>Self-regulation and attentional control</strong></td>
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<tr>
<td>Nash and colleagues (2010) CCT</td>
<td>14 treatment, 15 delayed; pFAS &amp; ARND; Canadian Guidelines or 4-digit code. Mean age 10 years (8 to 12 range)</td>
<td>ALERT program for self-regulation; 12 weeks; individual 1-hour sessions. Pre/post and 6-month follow-up</td>
<td>Significant improvement for treatment compared to delayed on the Inhibition-Naming &amp; Affect Recognition (NEPSY-II) and the BRIEF</td>
</tr>
<tr>
<td>Wells and colleagues (2012) RCT</td>
<td>40 treatment, 38 control; FAS or ARND; Canadian Guidelines or 4-digit code. Mean age 8 years (6 to 11 range)</td>
<td>ALERT; 12 weeks, 75-minute group sessions for children and parents run separately. Pre/post and 2/3-month follow-up</td>
<td>Treatment group showed significant improvement compared to control group on the BRIEF and the RATC</td>
</tr>
<tr>
<td>Soh and colleagues (2015) CCT</td>
<td>20 treatment, 18 delayed; 27 control FAS, pFAS, ARND; Canadian Guidelines or 4-digit code. Mean age 9 years (8 to 12 range)</td>
<td>ALERT 12 weeks; individual 1.5 hourly sessions; pre/post-testing; 2 weeks after treatment</td>
<td>Improvements on BRIEF and NEPSY-II for treatment group. Some evidence of increase in gray matter for treatment relative to delayed treatment</td>
</tr>
<tr>
<td>Kemn and colleagues (2010) Cohort</td>
<td>10 children previous diagnosis of FAS (diagnostic categories/criteria not stated). Mean age 12 years (8 to 15 range)</td>
<td>The Computerised Progressive Attention Program; 16 hours over 9 weeks at school; pre/post-testing</td>
<td>Significant decrease in reaction times and distractibility; significant improvement in auditory sustained attention and math and reading fluency</td>
</tr>
<tr>
<td>Vernescu (2008) CCT</td>
<td>10 treatment, 10 control; pFAS &amp; FAS; Canadian guidelines. Mean age 9 years (6 to 11 range)</td>
<td>Activities from the pay attention training protocol and additional visual search tasks; 12 daily individual 30-minutes sessions; pre/post-testing</td>
<td>Intervention group showed: Significant improvements in nonverbal reasoning, auditory and visual sustained attention. Trend for improved performance on alternating attention</td>
</tr>
<tr>
<td>Adnams et al. reported in Wells and colleagues (2012) CCT</td>
<td>5 treatment; 5 control; identified from previous study (n = 64) diagnosed with FAS criteria not stated. Mean age 8 years</td>
<td>Cognitive control therapy 1-hour session each week for 10 school-term months; pre/post-testing</td>
<td>Improvement in behavior ratings in intervention group. No differences on neuropsychological tests</td>
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<tr>
<td><strong>Specific skills</strong></td>
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<tr>
<td>Kable and colleagues (2007) CCT</td>
<td>28 treatment; 26 comparison. FAS or pFAS using IOM criteria or significant alcohol-related dysmorphology. Mean age 6 years (3 to 10 range)</td>
<td>All parents attended 2 × 2 hours workshops on FASD. All children received individual learning plan; treatment group received adapted tuition for maths MILE program. Preipost-testing</td>
<td>Significant gains in caregiver knowledge of FAS, behavior regulation and advocacy; decrease in problem behaviors. Significant higher gains found for intervention group on maths knowledge</td>
</tr>
<tr>
<td>Kable and colleagues (2015) CCT</td>
<td>20 centre-based treatment; 19 community treatment; 21 parent instruction group, FAS or pFAS; IOM criteria or significant alcohol-related dysmorphology. Mean age 6 years</td>
<td>All parents attended 2 × 2 hours workshops on FASD and provided manual on math learning (parent instruction group received no further intervention). Community translation of the MILE program expanded to 15 weeks and incorporated metacognitive control techniques. Preipost-testing</td>
<td>Participants in both the MILE groups showed greater gains in math skills at posttest compared to parent instruction group</td>
</tr>
<tr>
<td>Millians and Coles (2014) Case study</td>
<td>5; affected or suspected of PAE in foster care; 2 FAS; 1 no diagnosis, 1 deferred, 1 pFAS, IOM criteria. Ten to 13 years</td>
<td>Individualized interventions using the MILE program adapted for use with older children. Pre/post-testing</td>
<td>Participants in both the MILE groups showed greater gains in math skills at posttest compared to parent instruction group</td>
</tr>
<tr>
<td>Coles and colleagues (2007) CCT</td>
<td>16 children allocated to street safety and 16 to fire safety computer games, FAS or pFAS; IOM criteria. Mean age 7 years (4 to 10 range)</td>
<td>Played a virtual reality game of fire safety and street safety. Pre/post-testing and follow-up test at 1 week</td>
<td>Three of 5 adolescents made gains in 1 cognitive domain although these differed for each child. Two showed no changes</td>
</tr>
<tr>
<td>Cooper and colleagues (2016) Case study</td>
<td>2 FAS, 1 no diagnosis, 1 deferred, 1 pFAS, IOM criteria. Mean age 7 years (4 to 10 range)</td>
<td>Individualized interventions using the MILE program adapted for use with older children. Pre/post-testing</td>
<td>Three of 5 adolescents made gains in 1 cognitive domain although these differed for each child. Two showed no changes</td>
</tr>
<tr>
<td>Cables and colleagues (2017) Case study</td>
<td>5; affected or suspected of PAE in foster care; 2 FAS; 1 no diagnosis, 1 deferred, 1 pFAS, IOM criteria. Ten to 13 years</td>
<td>Individualized interventions using the MILE program adapted for use with older children. Pre/post-testing</td>
<td>Three of 5 adolescents made gains in 1 cognitive domain although these differed for each child. Two showed no changes</td>
</tr>
<tr>
<td>Kable and colleagues (2019) Case study</td>
<td>16 children allocated to street safety and 16 to fire safety computer games, FAS or pFAS; IOM criteria. Mean age 7 years (4 to 10 range)</td>
<td>Played a virtual reality game of fire safety and street safety. Pre/post-testing and follow-up test at 1 week</td>
<td>Three of 5 adolescents made gains in 1 cognitive domain although these differed for each child. Two showed no changes</td>
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### Table 2. (Continued)

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<th>Results</th>
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<tr>
<td>Padgett and colleagues (2006) Case study</td>
<td>5 children; FAS or pFAS; IOM criteria. Five to 7 years</td>
<td>Played a virtual reality game of fire/street safety. Pre/post-testing and 1-week follow-up</td>
<td>All 5 children reached 100% accuracy on the fire safety game; at 1 week posttest able to perform steps in the correct sequence</td>
</tr>
<tr>
<td>Adnams and colleagues (2007) CCT</td>
<td>18 exposed treatment; 18 exposed control; 23 nonexposed control; FAS pFAS or “deferred diagnosis category,” “revised IOM criteria. Mean age 10 years (9 to 10 range)</td>
<td>Language and literacy intervention, 1 hour per week in groups of 5 children; 38 hours of therapy over 9 months; pre/post-testing</td>
<td>Treatment group significant improved on preliteracy, reading, and spelling; no significant difference between intervention and control on general scholastic tests; scores of exposed children (intervention and control) remained lower than nonexposed children</td>
</tr>
<tr>
<td>Loomes and colleagues (2008) CCT</td>
<td>17 Experimental, 16 controls; previously diagnosed with ARND, neurobehavioral, or static encephalopathy. Mean age 7 years (4 to 11 range)</td>
<td>Experimental group-rehearsal training across 10 days. Pre/post-testing</td>
<td>Experimental group showed significant increase in digit span scores over the 3 sessions compared to the control group who showed no significant increase in number of words spelt correctly</td>
</tr>
<tr>
<td>Gryiec and colleagues (2008) Interrupted time series</td>
<td>1 child; 7-year-old girl; diagnosed with FAS (criteria not stated) and learning disabled</td>
<td>Cover, copy, and compare spelling procedure; 6 weeks with 2 to 3 sessions per week; 10 to 20 minutes per session; multiple baselines and measures at each session</td>
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<tr>
<td>Keiver and colleagues (2015) CCT</td>
<td>24 FASD, 32 control, ARND, pFAS &amp; FAS; 4-digit code &amp; Canadian Guidelines. Mean age 10 years (6 to 13 range)</td>
<td>FAST Club 8-week group motor skills intervention—Two 1.5-hour sessions per week for 8 weeks. Pre/post-testing</td>
<td>Cortisol levels were higher in children with FASD compared to control children in the afternoon and evening; the program did not significantly affect cortisol levels in children with FASD</td>
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<td>Social skills interventions</td>
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<tr>
<td>Timler and colleagues (2005) Case Study</td>
<td>1 child; girl aged 9 years 8 months, previous diagnosis of FASD (diagnostic category not stated); 4-digit code</td>
<td>Social communication intervention 6 weeks—2 weeks of individual sessions (1 hour each) and 4 weeks of group sessions with 2 peers (2 hours each). Pre/post-testing</td>
<td>Increased use of mental state verbs (e.g., know, thought). Increased knowledge of social script strategies that were used during the intervention (e.g., plan and take action)</td>
</tr>
<tr>
<td>O'Connor and colleagues (2006) CCT</td>
<td>51 treatment, 49 delayed, FAS, pFAS &amp; ARND, 4-digit code &amp; IOM criteria. Mean age 8 years (6 to 12 range)</td>
<td>CFT; 12 sessions, 90 minutes and separate concurrent parent sessions. Pre/post and 3-month follow-up</td>
<td>CFT group showed significant improvement in social skills and decreased problem behaviors compared to delayed CFT at posttreatment and follow-up</td>
</tr>
<tr>
<td>Keil and colleagues (2010) CCT</td>
<td>51 treatment, 49 delayed; FAS, pFAS or ARND; 4-digit code &amp; IOM criteria. Mean age 8 years (6 to 12 range)</td>
<td>CFT 12 sessions, 90 minutes, separate concurrent parent sessions. Pre/post and 3-month follow-up</td>
<td>CFT group made fewer hostile attributions in the peer group entry scenarios than delayed treatment group; maintained at follow-up</td>
</tr>
<tr>
<td>O'Connor and colleagues (2012) CCT</td>
<td>41 treatment, 44 standard care, PAE (n = 32) FAS, pFAS, ARND, 4-digit code &amp; IOM criteria; 53 control children without PAE. Mean age 8 years (6 to 12 range)</td>
<td>CFT in a community setting 12 sessions, 90 minutes, and separate concurrent parent sessions. Pre/post and 3-month follow-up</td>
<td>CFT group significant improvement on test of social skills knowledge and self-esteem compared to standard care. CFT equally effective for children with PAE as for those without</td>
</tr>
<tr>
<td>Meyer (1998) Case Study</td>
<td>4 children identified with FAE. Mean age 8 years</td>
<td>Required to imitate a 4-minute videotape of a block building task. Pre/post-observation</td>
<td>None of the children were able to imitate the block building task</td>
</tr>
<tr>
<td>Sparks-Keeney and colleagues (2011) Cohort</td>
<td>11 children with FASDs (diagnostic categories not stated); 4 digit code. Seven to 12 years</td>
<td>Community-based social skills group 90-minute sessions for 7 weeks, concurrent sessions with parents. Pre/post-testing</td>
<td>8 of the 11 children’s parents completed an adapted 25-item SSRS at pre- and post-testing. Of those, 7 showed improved ratings</td>
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<tr>
<td>Parenting skills</td>
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<tr>
<td>Olson et al. reported in Bertrand (2009) RCT</td>
<td>26 treatment; 36 standard care diagnosed with FASD (diagnostic categories not stated) 4-digit code, all had significant challenging behaviors. Five to 11 years</td>
<td>Families moving forward (FMF) behavioral consultation fortnightly sessions of 90 minutes for 9 to 11 months. Pre/post-testing</td>
<td>Improved parental self-efficacy, parental self-care, and parent report of child behavior problems in FMF compared to standard care; no differences in child-related parental stress</td>
</tr>
<tr>
<td>Gurwitch et al. reported in Bertrand (2009) RCT</td>
<td>23 treatment and 23 comparison; diagnosed with FASD (diagnostic categories not stated); modified IOM criteria and 4-digit code. Three to 7 years</td>
<td>Group adaptation of PCIT; Comparison—parent-only support and management; Both weekly 1-hour sessions x 14 weeks; pre-, mid- and post-testing</td>
<td>Approximately 50% attrition for both groups within the 14 weeks of treatment; No group differences observed, although reductions found across both groups on parenting stress and child behavioral problems</td>
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<table>
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<tr>
<td>Kable and colleagues (2012) CCT</td>
<td>24 community standard; 23 workshop; 29 Internet training parents of a child with FAS or pFAS; IOM criteria or significant alcohol-related dysmorphology. Mean age 7 years</td>
<td>Information only (community standard), workshop or Internet support 2 x 2 hour sessions covering behavior, information, and advocacy. Pre/post-testing</td>
<td>All groups reported improvement in knowledge of behavioral learning principles; Internet and workshop significant improvement in knowledge of FASD and parent advocacy; Some indication that significant differences reported on child behavior in community and workshop groups but not Internet group</td>
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<tr>
<td><strong>Support, education &amp; advocacy</strong></td>
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<tr>
<td>Leenaars and colleagues (2012) Retrospective case-file analysis</td>
<td>186 families parenting at least 1 child with FASD (diagnostic categories not stated); 4-digit code. Mean age 10 years (1 to 23 range)</td>
<td>Coaching families program provides support, education and advocacy for families with a child with FASD. Program length not stated. Pre/post-testing</td>
<td>Reduction in numbers of daily needs and parenting stress. Length of time in program associated with a greater reduction in needs and number of goals met</td>
</tr>
<tr>
<td>Pelech and colleagues (2013) Cohort analytic</td>
<td>98 intervention 84 comparison; out-of-home-care; diagnosed (categories or criteria not stated) or suspected (i.e., documented PAE). Mean age 11 years</td>
<td>Promising practices enhanced child welfare practices to improve placement stability. Tracked placement changes during 15-month period prior and compared to placement changes during project implementation</td>
<td>Significant decline in number of placement changes among children in the intervention group</td>
</tr>
<tr>
<td>Clark and colleagues (2014) CCT</td>
<td>6 teachers and 7 children treatment; 6 teachers and 6 children comparison group; and their classroom teachers; FAS, Gestalt diagnostic guidelines. Mean age 7 years (6 to 12 range)</td>
<td>Professional development for teachers focused on classroom environment. Over 1 school year. Included 2 full-day and 4 half-day workshops and weekly mentor-teacher meetings. Pre-, mid- and post-testing</td>
<td>Significant improvements in adaptive skills and significant decreases in school problems (both measured by the BASC-2 completed by teachers) reported for the intervention group; no significant changes found for the comparison group; no significant changes in academic achievement for intervention students</td>
</tr>
<tr>
<td><strong>Supporting parents who have FASD</strong></td>
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<tr>
<td>Hume and colleagues (2009) Cohort</td>
<td>81 parents/caregivers completed both intake and exit questionnaires; Families with children or youth with FASDs (diagnostic categories not stated); 0 to 19 years</td>
<td>“Key worker” program assist parents/caregivers and service providers understand child’s deficits and help develop environmental accommodations program length not stated. Pre/post-testing</td>
<td>Trends in direction of increased parenting confidence, parents experiencing less stress, reduction in parent/caregiver challenges, childcare were significant; changes reported in parent/caregivers’ ratings of child problem behaviors—overall no statistical difference from pre to post</td>
</tr>
<tr>
<td>Derys and colleagues (2011) Retrospective case-file analysis</td>
<td>24 Parents with FASD or suspected FASD (1 male, 23 female) (diagnostic categories/guidelines not stated). Mean age 30 years (19 to 47 range)</td>
<td>Step-by-step—3-year program; mentors work with families to help access support and services. Pre/post-testing</td>
<td>Significant reduction in client’s needs (e.g., housing, financial issues, mental health issues, addiction) significant increase in client’s goals (e.g., parenting, personal skills management, assessment, self-care and health)</td>
</tr>
<tr>
<td>Grant and colleagues (2004) Cohort</td>
<td>19: women diagnosed with or suspected FASDs; years enrolled in standard PCAP for women at risk of giving birth to a child with FASD with at least 1 year remaining in the program; 4-digit code. Mean age 22 years (14 to 36 range)</td>
<td>12-month pilot of PCAP-home visitation case management program modified to accommodate clients with FASDs. Pre/post-testing</td>
<td>Decreased alcohol and drug use. Increased use of contraception, medical, and mental health care services. Increases in obtaining stable housing</td>
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CCT, Controlled clinical trial; RCT, randomized controlled trial; FAS, fetal alcohol syndrome; pFAS, partial fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; BRIEF, Behaviour Rating Inventory of Executive Function; RATC, The Roberts Apperception Test for Children; MILE, Math Interactive Learning Experience; CFT, Children’s Friendship Training; FAE, fetal alcohol effects—child displays characteristics of FAS but not full syndrome; PCIT, parent-child interaction therapy; SSRS, Social Skills Rating System; BASC-2, Behaviour Assessment System for Children Second Edition; FASD, fetal alcohol spectrum disorder; IOM, Institute of Medicine; PAE, prenatal alcohol exposure; PCAP, parent-child assistance program.
colleagues (2015) embedded an evaluation of a motor skills program in a study of the regulation of the stress response in typically developing children and children with FASDs. Cortisol levels were found to be higher in children with FASDs in the afternoon and evening compared to that of control children. No changes were associated with participation in the motor skills program. Overall, these studies suggest that early cognitive remediation for school-aged children shows promise in improving some specific areas of difficulty for children with PAE.

Social Skills. In light of the well-established difficulties faced by children with FASDs in understanding social cues and problems in peer relationships, research has addressed whether interventions with a specific focus on social skills result in improvements. Six studies were identified, all targeting children in the 3- to 12-year-age group. The earliest of these was a single case study showing improvements in social communication in the short term (Timler et al., 2005). Subsequently, 3 CCTs (Keil et al., 2010; O’Connor et al., 2006, 2012) evaluated an adaptation of the Child Friendship Training (CFT) program. Children were taught simple rules of social engagement, including modeling, which they rehearsed and practiced across settings while being coached by parents. In the first of these studies, O’Connor and colleagues (2006) found parents who received the intervention reported improvement in their children at postintervention, while parents in the wait list group did not. Importantly, an analysis of clinical significance indicated that children in the intervention group scored in the lower end of the normal range at follow-up. In a later study, Keil and colleagues (2010) found that the children in the

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<th>Table 3. Quality Assessment Results for Included Studies</th>
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<tr>
<td>Developmental outcomes in infants</td>
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<td>Kartin and colleagues (2002)</td>
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<td>Vernescu (2008)</td>
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<td>Adnams and colleagues (reported in Riley et al., 2003)</td>
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<tr>
<td>Denys and colleagues (2011)</td>
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<td>Grant and colleagues (2004)</td>
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Confounders were not assessed for 1-group studies; blinding was not assessed for 1-group studies, case-file analyses or studies that did not require interaction with participants when collecting outcome assessments; withdrawals/dropouts were not assessed for case studies or retrospective case-file analyses.
CFT group demonstrated improved social skills and lower rates of hostile attribution (as measured by a cartoon story task) compared to a delayed treatment group. Furthermore, these gains were maintained at a 3-month follow-up for the group receiving CFT first.

Last, O’Connor and colleagues (2012) found posttreatment gains in social skills and self-esteem for children who received CFT compared to a standard care condition in a community mental health setting. Notably, the intervention was equally effective for children with PAE compared to those without. Indicating that children with PAE can be treated effectively in community settings if interventions are suitably adapted and therapists are appropriately trained. Gains in parent-rated social skills were also seen in a small \((n = 11)\) trial of a community-based social skills group (Sparks-Keeney et al., 2011). Conversely, a case study \((n = 4)\) found that children with PAE were not able to imitate a block building task after viewing a videotape of a boy of a similar age completing the same task (Meyer, 1998). Taken together, these studies provide strong evidence for the utility of structured programs that include children and parents in helping to improve social skills.

**Efficacy of Interventions that Support Parents, Caregivers, and Others**

**Parenting Skills.** Three studies provided explicit instruction in parenting skills. Olson and colleagues (reported in Bertrand, 2009) found a significant improvement in parental self-efficacy, parent needs and parent self-care, and a reduction in child behavior problems in families receiving the families moving forward program. One study evaluating parent–child interaction therapy compared to a parent-only parenting support and management program found reductions in child behavioral problems and parenting stress. The observed changes for both programs were clinically significant with mean scores on child behavior problems moving from the clinical to the nonclinical range for both groups (Gurwitch et al., reported in Bertrand, 2009).

Kable and colleagues (2012) carried out a controlled trial comparing parent education delivered in 3 formats: an information packet (i.e., community standard care), group workshops, and Internet training. All 3 groups showed increases in knowledge of behavioral learning principles. Some indication of differential improvement in behavior occurred across groups, with the workshop and the community group showing improvement but the Internet group showing none. Overall examination of the pattern of behavioral change found that approximately a quarter of the sample demonstrated clinically significant behavioral gains. In summary, the parent-based intervention studies provide promising evidence that parents and caregivers benefit from support in managing their children’s behavior and that this improvement is accompanied by improvements in parent/caregiver well-being.

**Support, Education, and Advocacy.** Four studies have investigated the effectiveness of specially designed education, support, and advocacy services. Leenaars and colleagues (2012) conducted a retrospective case-file analysis of the coaching families (CF) program that provides support for families across childhood and adolescence. Significant decreases in needs (e.g., housing and transport) and caregiver stress, and increases in goals (e.g., improving parenting skills, self-care, and health) were found. The greater the duration of engagement with CF, the greater the goals attained and needs reduced.

In addition, promising practices, an intervention for children and youth suspected or diagnosed with FASDs in out-of-home-care (Pelech et al., 2013) found that specialized FASD training for workers and foster caregivers was associated with a significant decline in the number of placement changes compared to standard care. In a study of students with FASDs and their teachers, improvements were found in classroom behavior, although the finding was limited by a small sample size (Clark et al., 2014). Nonetheless, this adds to a body of literature that supports the role of training in advocacy and knowledge as a way of potentially improving outcomes for individuals with FASDs.

Hume and colleagues (2009) prepared a summative report for the British Columbia Ministry of Children and Family Development on the Key Worker and Parent Support Program. This program provided support, education, and liaison to existing intervention services for families with children or youth affected by FASDs. Qualitative findings provided evidence for improvements following the intervention (e.g., parents and caregivers reported that they had a better understanding of FASD, increased emotional and practical support). However, limited pre/post data were available on caregiver stress, parenting self-confidence, and child behavior, and no statistically significant changes were found, although trends toward improvements were noted.

**Supporting Parents with FASDs.** Two case management studies indicated a reduction in secondary disabilities in parents with FASDs. Step-by-step was a 3-year, goal-driven, mentoring program aimed at increasing parents’ access to resources and support that targets parents affected or suspected of FASDs (i.e., the parents did not have access to an assessment during their time in the program to confirm the diagnosis). A retrospective case-file analysis conducted by Denys and colleagues (2011) found that following the program, parents reported significant reductions in needs (e.g., housing) and increases in goals (e.g., improving parenting skills). A second case management program that assisted mothers to address environmental difficulties and connect with available support services was implemented by Grant and colleagues (2004). This pilot intervention of the parent–child assistance program was modified to accommodate clients with FASDs. The participants were 19 women diagnosed with or suspected of having FASDs (i.e., “had characteristics of prenatal alcohol damage in the presence of
prenatal alcohol exposure”; Grant et al., 2004, p. 502). Following the intervention, the participants decreased their alcohol/drug use, increased use of contraception and health services, and were more likely to have obtained stable housing. These studies suggest that longer term case management during the transition to parenthood reduces the likelihood of secondary disabilities in young women with PAE.

DISCUSSION

This systematic review extended previous literature reviews (Kodituwakku, 2010; Paley and O’Connor, 2011; Petrenko, 2015) and the most recent systematic review (Peardon et al., 2009) by adopting a broader set of search criteria to capture studies that extended across the life span. Thirty-two studies were identified, and methodological quality was assessed. The studies were grouped according to the primary focus of the intervention to enable comparisons across studies to be made and conclusions regarding effectiveness to be drawn.

Four key findings from the assessment of study quality were found. The first point relates to selection bias. None of the reviewed studies randomly selected cases from a target population, so selection bias was rated as “moderate” (participants recruited from a clinic) or “weak” (self-referred participants). Future research should aim to select participants from geographical regions known to have high rates of FASDs in the general population rather than only clients who have attended FASD diagnostic clinics. Second, no studies were rated “strongly” with respect to “blinding,” as none of the 2-group studies described blinding of both outcome assessors and study participants.

The third issue relates to the information required in order for a study to be classified as an RCT. While many of the studies classified as CCTs reported that randomization had taken place, many had not included information on how this had occurred. While this reduced the overall number of studies classified as RCTs, both RCTs and CCTs are rated as “strong,” meaning that nearly two-thirds of the included studies were given a “strong” rating on study design. Last, one of the strongest findings to emerge was the rigor concerning outcome measurement. Twenty-seven studies received a rating of “strong” because they used reliable and valid measures.

Turning to the results of the studies, despite some studies with small samples and limited follow-up, the body of literature reviewed showed that it is possible to make improvements across many domains of functioning. In early infancy, mixed evidence was found for the potential to improve the developmental outcomes (Kartin et al., 2002; Yazdani et al., 2009), highlighting the importance of further systematic, rigorous research. Importantly, researchers need to consider measuring intervention effects using other tools in addition to standard developmental measures for infants and toddlers. If the focus of the intervention is to improve self-regulatory capacity and developmental outcome physiological measures such as heart rate, heart rate variability, and salivary cortisol could be used, as there is evidence that infants with PAE show compromised autonomic nervous system development (Oberlander et al., 2010). In addition, measurement of the infant’s environment that includes the quality of the caregiving relationship needs to be considered, given the evidence that a supportive warm relationship aids the development of self-regulatory skills (Calkins et al., 2008).

The importance of providing an optimal environment to promote development provides the impetus for early intervention (Dalziel and Segal, 2012) and is of particular relevance for children with FASDs whose early environmental experience is often less than optimal. Thus, program developers need to attend to the particular needs of families and children with FASDs and ensure that programs are adapted to suit the needs of this population.

Despite the mixed evidence for effectiveness in early infancy, the studies that focused on improving self-regulation and attentional control in early to middle childhood provided strong evidence for gains, demonstrated by improvement using parent/caregiver report, neuropsychological testing, and magnetic resonance imaging scans (Kerns et al., 2010; Nash et al., 2015; Soh et al., 2015; Wells et al., 2012). However, as the studies did not include, or only had a limited follow-up, the extent to which such changes are enduring has not been established.

The evidence for changes in specific skills was more variable. Notably, only 1 study (Kable et al., 2007) had a follow-up period that extended beyond the posttreatment period. The greatest gains were found in the studies that evaluated the MILE program (Kable et al., 2007, 2015; Millians and Coles, 2014). Gains extended beyond math skills and included improvements in child behavior. The one study that investigated the stress response in children with FASDs found no changes in cortisol levels. The most plausible reason for this was that the level of exercise intensity (i.e., improving motor skills rather than fitness) was not sufficient to influence the stress response (Keiver et al., 2015). While the study did not achieve its aims, there are sound theoretical reasons for carrying out further research on the physiological underpinnings of PAE (Calkins et al., 2013). More research is needed to see whether interventions could lead to physiological changes, which importantly, may underlie some of the self-regulatory difficulties for individuals with FASDs.

The studies aimed at improving social skills showed consistently strong results. The controlled trials of the CFT program (Keil et al., 2010; O’Connor et al., 2006, 2012) were methodologically strong and importantly included a 3-month follow-up demonstrating some enduring benefit. Intervention at this developmental stage may help to prevent the development of further dysfunction, given that social skills deficits become more pronounced with age in young people with FASDs (Mattson et al., 1999; Whaley et al., 2001). Further research is required to evaluate the impact of...
programs such as CFT with adolescents and adults. In summary, there is much to be optimistic about regarding the potential for improving aspects of children's functioning. However, currently, the lack of long-term follow-up limits any conclusions on whether the observed changes would endure over time.

Studies that included a specific focus on parenting skills found that helping parents understand and manage the complex set of behaviors they see in their children helped them feel less stressed (Gurwitch et al., reported in Bertrand, 2009), and improve their well-being and perceived capacity to cope (Olson et al., reported in Bertrand, 2009). Notably, however, all studies targeted younger children and none had a follow-up beyond posttesting, so it is not possible yet to ascertain whether the programs provide the skills required to help parents revise their strategies in response to the changing needs of the developing child.

The evidence was mixed for studies that took a support, education, and advocacy focus or that targeted parents with FASDs. First, studies that employed a case management style approach found that supporting and educating families resulted in a reduction in needs (Leenaars et al., 2012) and reduced secondary disabilities in parents with FASDs (Denys et al., 2011; Grant et al., 2004). Second, an important emerging area of intervention research is targeting education and advocacy for people outside the family. For example, improving child welfare practices (Peled et al., 2013) and assisting teachers to understand the cognitive deficits and make appropriate accommodations FASDs (Clark et al., 2014) resulted in improved outcomes for those with FASDs. Overall, considering the support, education, and advocacy interventions and parenting support interventions together, while interventions focused on case management were effective in improving outcomes for parents with FASDs, it remains unclear whether such interventions can result in improvements for children and youth who are affected by FASDs.

Implications for Research and Policy

The interventions included in the current review highlight both the potential for improving many different aspects of functioning for individuals with FASDs as well as methodological shortcomings. The majority of interventions are currently focused on improving outcomes for school-aged children. Future research is suggested to explore early intervention for infants and young children, ensuring that programs are informed by the evidence for clinical- and cost-effectiveness in high-risk families. Supporting adolescents and adults also needs to be considered as there is evidence that problems compound as children become older (Mattson et al., 1999; Whaley et al., 2001). It is also clearly evident that the difficulties facing individuals with FASDs do not lie in single domains of functioning. Thus, it would seem that the way forward for intervention research is to consider the dynamic interplay between individual characteristics and the wider ecological context in which the individual lives. Consequently, the available evidence provides support for a proposed unified conceptual framework (Petenko, 2015). Such a framework brings together models proposed by Kodiituwakku (2010) and Paley and O'Connor (2011) and takes into account the lived experiences of individuals and families with FASDs to guide intervention development. Taken together with the current review, this provides strong support for future interventions to address multiple domains of functioning for individuals with FASDs.

CONCLUSIONS

A number of interventions have been implemented with individuals and their families affected by PAE. The studies identified in this review differed considerably in their focus of the deficit(s) addressed. Further, there was considerable variability in their methodological rigor and the timeline for follow-up. Nonetheless, such attempts are critically important in propelling the field toward more rigorous and systematic intervention trials. We propose that considering the extensive deficits and the complexity of the life circumstances of many individuals, a deficit- or domain-specific focus for intervention is of limited utility. Rather, an approach that takes an ecological stance and looks at the multiple factors that may be at play will lead to more effective and enduring benefits. Ultimately, this is an empirical question and can only be answered by systematic and rigorous research trials.

CONFLICT OF INTEREST

None of the authors have a conflict of interest to report.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article: Data S1. Supplementary material.