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REVIEW

From Research to Practice: An Integrative Framework for the Development of Interventions for Children with Fetal Alcohol Spectrum Disorders

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Abstract Since fetal alcohol syndrome was first described over 35 years ago, considerable progress has been made in the delineation of the neurocognitive profile in children with prenatal alcohol exposure. Preclinical investigators have made impressive strides in elucidating the mechanisms of alcohol teratogenesis and in testing the effectiveness of pharmacological agents and dietary supplementation in the amelioration of alcohol-induced deficits. Despite these advances, only limited progress has been made in the development of evidence-based comprehensive interventions for functional impairment in alcohol-exposed children. Having performed a search in PubMed and PsycINFO using key words, interventions, treatment, fetal alcohol syndrome, prenatal alcohol exposure, and fetal alcohol spectrum disorders, we found only 12 papers on empirically-based interventions. Only two of these interventions had been replicated and none met the criteria of "well-established," as defined by Chambless and Hollon (Journal of Consulting and Clinical Psychology 66(1):7–18, 1998). There has been only limited cross-fertilization of ideas between preclinical and clinical research with regard to the development of interventions. Therefore, we propose a framework that allows integrating data from preclinical and clinical investigations to develop comprehensive intervention programs for children with fetal alcohol spectrum disorders. This framework underscores the importance of multi-level evaluations and interventions.

Keywords Empirically-based interventions · Evidence-based interventions · Fetal alcohol spectrum disorders · Fetal alcohol syndrome · Pharmacological interventions

Acronyms

ABT-239	histamine H3 receptor antagonist
ADHD	Attention Deficit/Hyperactivity Disorder
AMPAR	alpha-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid receptors
CCT	Cognitive Control Therapy
CFT	Childhood Friendship Training
CNS	Central Nervous System
FMF	Families Moving Forward
5-HT	serotonin
5-HT1A	agonists such as buspirone and ipsapirone
HPA axis	Hypothalamic-pituitary- adrenal axis
LLT	Literacy or language training
LTP	long-term potentiation
MILE	Math Learning Experience
NAC	N-acetylcysteine
NAP	peptide derived from naturally occurring glial proteins
PCIT	Parent Child Interaction Therapy
PSM	Parenting Support and Management
RCT	Randomized clinical trial
ROS	Reactive oxygen species
SAL	peptide derived from naturally occurring glial proteins

Introduction

Since fetal alcohol syndrome was first described in the medical literature over 35 years ago (Jones and Smith 1973;

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Lemoine et al. 1968), researchers have invested considerable efforts to delineate morphological and neurocognitive outcomes of prenatal alcohol exposure (See reviews by Lebel et al. 2011; Wozniak and Muetzel 2011; O'Leary-Moore et al. 2011; and Crocker et al. 2011 in the current issue for details). It is now known that children exposed to moderate to heavy amounts of alcohol in utero display a wide range of morphological and neurocognitive outcomes (O'Leary-Moore et al. 2011), which are collectively referred to as fetal alcohol spectrum disorders (FASDs). While clinically discernable morphological differences are observed only in a minority of children with FASDs, neurocognitive deficits and behavioral-emotional disturbances are ubiquitous in this clinical group. An extensive body of literature on FASDs has documented a wide range of cognitive deficits and behavioral-emotional disturbances in children and adults with FASDs (Crocker et al. 2011). Children with FASDs, compared to their typically developing peers, have been found to have deficits in intellectual abilities (Mattson et al. 1997), attention and cognitive control (Kodituwakku et al. 2001; Rasmussen and Bisanz 2008), information processing (Burden et al. 2005; Coles et al. 1997), language (Becker et al. 1990), visual processing (Mattson et al. 1996), learning and memory (Uecker and Nadel 1996), number processing (Kopera-Frye et al. 1996), social cognition (Greenbaum et al. 2009; McGee et al. 2008) motor skills (Connor et al. 2006; Conry 1990). Researchers have found that the interactive effects of life stressors and the cognitive difficulties lead to a wide range of secondary disabilities, including trouble with the law, confinement, inappropriate sexual behaviors and alcohol/drug problems (Streissguth et al. 2004). Children with FASDs have also been found to display deficient adaptive behavior (Thomas et al. 1998), particularly deficient social skills (Carmichael Olson et al. 1998; Whaley et al. 2001). Furthermore, researchers have observed higher rates of psychiatric problems in individuals with FASDs, which have been attributed to the interactive effects of adverse life experiences and alcohol's teratogenic effects on the neurotransmitter systems (O'Connor et al. 2002). Recent developments in neuroimaging have allowed researchers to delineate patterns of neuroanatomical anomalies associated with these cognitive and behavioral problems (Lebel et al. 2011; Wozniak and Muetzel 2011)

The above disabilities place a heavy burden on families and the society in general, with the lifetime cost for care of one individual with FAS being estimated at $2 million (Lupton et al. 2004). Therefore, FASD constitutes a serious health problem in the United States and worldwide. Notwithstanding the seriousness of the problem, there is a scarcity of *empirically supported* interventions for FASDs (Kalberg and Buckley 2007; Paley and O'Connor 2009).

The label *empirically supported* has been used to refer to those interventions that have been found to be efficacious by established scientific standards (Kazdin 2002). An intervention is judged efficacious when its benefits have been demonstrated to be due to the effects of treatment rather than due to chance or confounding factors jeopardizing internal validity of the research design, such as the effects of repeated testing, maturation etc. (Campbell and Stanley 1963). According to Chambless and Hollon (1998), efficacy of an intervention is best be demonstrated in randomized clinical trials (RCTs), in which clients are randomly assigned to the treatment or one or more comparison groups. Considered the gold standard of outcome studies, RCTs also incorporate procedures such as blind assessments, diagnosis made with objective criteria, adequate sample sizes, treatment manuals, treatment fidelity measures, and reliable and valid outcome measures (Chambless and Hollon 1998; Nathan and Gorman 2002). Nathan and Gorman (2002) classify treatment outcome studies into a number of categories, which they label Type 1 studies, Type 2 studies and so on. Type 1 studies represent the most rigorous randomized prospective clinical trials, whereas Type 2 studies include those that lack some aspects of the Type 1 methodological requirements (e.g. failure to maintain double-blind). However, critics have pointed out that the findings from RCTs that administer manualized procedures to well-diagnosed volunteers over a fixed number of trials may lack external validity because therapists in the real world use therapies in a flexible manner to address complex problems of their clients (Seligman 1995). Some have countered this criticism by saying that the RCT methodology can be used to systematically assess the clinical utility of a therapy after establishing its efficacy (Jacobson and Christensen 1996).

Premji et al. (2007) and Peadon et al. (2009) found respectively only 10 and 12 published studies of intervention for FASDs that met the search criteria (e.g. randomized control, quasi control etc.). We also searched PubMed and PsycINFO using keywords such as prenatal alcohol exposure, treatment, intervention, and fetal alcohol spectrum disorders and found no new studies published since 2009. The last three decades have also witnessed the development of a number of animal models of experience-based interventions aimed at the amelioration of behavioral deficits resulting from prenatal alcohol exposure (Hannigan et al. 2007; Klintsova et al. 1997, 2000). The focus of another line of research has been on testing the efficacy of nutrition supplements (Thomas et al. 2000, 2004) and specific pharmacological agents in mitigating alcohol exposed damage (Savage et al. 2010).

Despite the evidence from animal and human studies showing that alcohol-induced learning and behavioral deficits are amenable to interventions, only limited cross-

fertilization of ideas from these two areas of research has occurred, mainly because of fundamental differences in the focus of study. While human studies have focused on higher-order cognitive functions such as literacy and self-regulation, animal models have used simpler forms of learning and motor functions as targets of interventions. In the current review, we will first examine human intervention studies that have been published in peer-reviewed journals. In the next section, we will present animal models of interventions, including those designed to test pharmacological agents. In the third section, we will elaborate on a previously described theoretical framework (Kodituwakku 2009; Kodituwakku et al. 2011) that sought to integrate the findings from animal and human studies. In the fourth and final section, we will discuss the relevance of this integrative framework for the development of future research on interventions for children and adults with FASDs.

Human Studies

Most of the human intervention studies have aimed to improve specific cognitive or adaptive skills in children with FASDs (Paley and O'Connor 2009). The targeted cognitive skills have included language, math, working memory, and self-regulation. Some studies have targeted adaptive behaviors such as safety skills and social skills. While a number of these studies have incorporated some form of parent training because parent involvement is important for achieving desirable therapeutic outcomes, one study has investigated the effects of the parent–child interaction therapy on the child's behavior and parents' stress level. In the following pages, we will examine each of these human intervention studies in some detail. Table 1 presents a summary of these studies.

Literacy Training

Having observed that children with FASD from an impoverished community in South Africa were markedly deficient in language skills, Adnams et al. (2007) piloted a literacy training program with alcohol- affected children in this community. Participants were 40, 9-year old children with FASDs and 25 aged-matched children without FASDs. The children with FASDs, diagnosed by an international team of dysmorpholists, were randomly assigned either to a literacy or language training (LLT) group or to a control group (FASD-C). The non-FASD children (NONEXP-C) served as an additional control group. All participants then received a test battery that comprised scholastic tests, teacher and parent questionnaires, and specific literacy and language tests. The LLT group was administered 19 h of language therapy and 19 h of literacy and phonological awareness training by an experienced therapist over a period of nine school-term months. Because of significant performance variability in the LLT group, training materials were adjusted to the ability level of the learners.

Results showed that the LLT group had gained more than the FASD-C group in a few categories of language and literacy, including syllable manipulation, letter sound knowledge, written letters, word reading and non-word reading, and spelling. There were no parallel improvements, however, in general scholastic skills, suggesting the specificity of training-induced effects. Furthermore, the two FASD groups remained significantly weaker in scholastic skills at posttest.

Considering the level of intensity of the intervention (36 weeks), the aforementioned therapeutic gains can be considered minimal. Limited gains in literacy despite the intervention raise the question of whether adverse conditions in alcoholic homes interfered with learning in the FASD group. Some variables that could have moderated the effects of training such as life stressors and the amount of language heard at home (language input) were not assessed in this study. Although the study involved a randomized, prospectively designed clinical trial, the authors do not provide sufficient information on inclusion/exclusion criteria, assessment procedures (e.g. blind assessment), and treatment fidelity measures. Inclusion of a non-exposed group was useful, since it allowed investigators to assess the relative magnitude of the effect produced by language training. Because of the aforementioned limitations and lack of other published reports on literacy training in this clinical group, LLT can be considered *possibly efficacious* by the Chambless et al. criteria.

Math Skills

Given that children with FASDs have been found to show greater difficulty with math than with other academic subjects (Meintjes et al. 2010; Streissguth et al. 1994), Kable et al. (2007) designed a program, the Math Learning Experience (MILE), to examine an intervention aimed to treat numerical skill deficits in alcohol affected children. The program was evaluated in a study involving a randomized control design, in which 61 children with FASDs, aged 3 to 10 years, participated. The participants were diagnosed by a clinical team including a pediatric geneticist and had a diagnosis of fetal alcohol syndrome, or partial fetal alcohol syndrome, or substantial prenatal alcohol exposure with some dysmorphia. After families completed two introductory workshops, they were randomly assigned to either the math intervention group or the standard psychoeducational group. The psychoeducational group

Table 1 Human studies examining efficacy and effectiveness of behavioral interventions

Intervention	Sample and study design	Outcome measures	Treatment procedures	Findings
Literacy (LLT) Adnams et al. (2007)	40 children with FASD and 25 controls; The FASD group was assigned either to a LLT or a control group (FASD-C); *LLT:* M age 9.52 years.; boys 50%; Verbal ability M %ile 9.62; *FASD-C*: M age 9.63 years; boys 55.6%; verbal ability 9.62%ile; *NONEXP-C*: M age 9.42 years boys 48.8%; verbal ability M %ile 26.09; Participants were of South African mixed ancestry; Design: prospective design with random assignment;	UCT (University of Cape Town) Reading Test, UCT Spelling Test, Ballard 1-Min Addition and Subtraction; Phonological Awareness and Early Literacy	The LLT group received 38 h of therapy over a 9-month period; language therapy (19 h) alternating with literacy training (19 h)	The LLT group did not show significant gains over control groups in scholastic achievement, but showed greater improvement in selected language related tasks; No follow up data
Math interactive Kable et al. (2007)	61 children with FASD, ages 3–10 years; 56 completed*; Math group*: boys 51.7%; M age 6.5 years; cognitive ability M 81.1; African American 34.5% *Psycho educational group*: boys 65.4; age M 6.2 years; cognitive ability M 83.1 African American 42.3% Design; Prospective design with random assignment	Parent satisfaction scale Parent Knowledge scale Child Behavior Checklist, Test of Early Mathematical Ability-2, Key Math R/NU, Pre math concepts from the Bayley Scales	Two parent workshops (behavior and math) Math intervention: 6-week tutoring (Curriculum based on the High Scope Series); Psycho educational group received assistance with placement	Parents benefited from workshops. The math group showed significant gains in math knowledge (>1 S.D. on math scores). These gains were maintained at 6-month follow-up (Coles et al. 2009)
Rehersal training Loomes et al. (2008)	33 children with FASD; Divided into two groups. Experimental; N 17, M age 7:5, 8 boys; Control: N 16, M age 7:6, 11 boys;	Digit span	The experimental group received instruction on rehearsal; Digit span was tested immediately and several days after (M 10.6 days)	The experimental group showed improved performance following rehearsal instructions
Neurocognitive habilitation Chasnoff et al. (in Bertrand 2009)	78 children with prenatal exposure; ages 6–11 years and 11 months; randomly assigned to either Treatment or control group	Behavior Rating Scale of Executive Function (BRIEF); Robert Apperception Test for Children (RATC)	12 weekly 75-min group therapy sessions based on the Alert Program; Control group referred to regular services	Positive behavior changes on both the BRIEF and RATC; No follow-up data
Cognitive control Adnams et al. (in Riley et al. 2003)	Ten children with FAS; Two of 13 schools in the community were randomly selected; Treatment and Control groups were matched on some variables; All participants from impoverished backgrounds	Personal behavior checklist; Teacher ratings of academic progress	Cognitive control therapy for 1 h each week for ten school months; used the procedures described by Santostefano (1978)	Positive effects on behavior but not on cognitive functions
CFT O'Connor et al. (2006)	100 children with FASD; 51 in CFT group (M age 8.32 years; 56.8% White; 43.2% other ethnic groups, i.e. Hispanic, Black, Asian, mixed; M IQ 95.53) 49 in Delayed tx (M age 8.66 years; 44.9% boys; 51.1% White; M IQ 99.02	Test of Social Skills Knowledge (TSSK); Social Skills Rating System (SSRS)	The CTF group received 12 each 90 min long, over 12 weeks	The CFT group showed improved social skills fewer problem behaviors. Gains were maintained at 3 month follow up
Safety Skills Coles et al. (2007)	32 children aged 4–10 years, with FASD; randomly assigned to one of two experimental conditions: Fire Safety or Street Safety. Fire Safety: M age 6.98 years; ability score 83.13, adaptive behavior 73.13, boys 87.5%, Caucasian 68.75%; Street Safety: M age 6.8, ability score 77.53, adaptive behavior 73.07, boys 43.8%, Caucasian 50%	Verbal knowledge of four safety elements for both street and fire safety conditions	Fire safety: played a virtual game involving fire safety to mastery Street safety: played virtual game involving street safety to mastery Knowledge questions were administered pre and post practice and at 1 week follow-up	Children showed significantly better knowledge of the game to which they were exposed, immediately and a week later. Children succeeded in demonstrating knowledge behaviorally

Parent–Child Interaction (PCIT) Gurwitch et al. (in Bertrand 2009)	58 children, 3–7 years of age, with FASD; Children were assigned to two groups: PCIT and comparison groups using a block randomization procedure to ensure equal distribution of parent type (adopted vs. biological) and gender	Parenting stress index-3rd edition Eyberg child behavior inventory Child behavior checklist Dyadic parent–child interaction coding system-II	14 weekly sessions, each 90 min. PCIT: training in parent–child interaction through in-vivo-coaching Comparison: received information on parenting (e.g. behavioral contracts, star charts etc.)	Only 46% of the families completed. Problem behaviors diminished over the 14-week period. There was no significant group difference in improvement rates.
Behavioral consultation Carmichael Olson et al. (in Bertrand 2009). Behavioral Consultation (Continued)	52 children, 5–11 years of age, with FASD. Their families were divided in to two groups: Families Moving Forward (FMF) and Standard Care. A stratified randomized block design approach was used in group assignment.	Parenting Sense of Efficacy Scale; Parenting Stress Index, Eyberg Child Behavior Inventory, and parent ratings of changes in parental self-care, provider skills, the extent to which needs met	At least 16 every-other-week session, each lasting 90 min; A manualized curriculum used; MFM services were provided in families' homes	96% completed ; Caregivers in the FMF group showed improved sense of parenting self-efficacy and increased engagement of self-care behaviors; No difference in child-related parenting stress. The FMF group also reported higher levels of satisfaction and having their needs met more often.
Methylphenidate Oesterheld et al. 1998	Four children, aged 5–12 years, with FAS or partial FAS; randomized double-blind cross-over design	Conners parent and teacher rating scales	Methylphenidate and two placebos were administered. Each treatment lasted for 5 days	A significant effect of Methylphenidate on hyperactivity, but not on daydreaming/inattention
Methylphenidate Doig et al. 2008	27 children with FASD, ages 5 through 14 years; boys 70.4%	Teacher MTA-SNAP-IV ratings	Data were obtained from the medical charts of children who participated in a medication trial in which dosages and medications were changed	ADHD medications are less likely to reduce inattentive symptoms in children with FASD

received a comprehensive neurodevelopment assessment and assistance with development of individualized educational plans. The math training group received these services plus 6-weeks of interactive math tutoring services. The curriculum incorporated exercises aimed at addressing specific cognitive deficits contributing to math difficulties in children with FASDs such as slow information processing and difficulty with visual spatial materials.

Children and caregivers were evaluated prior to participating in the workshops and within 4 weeks of completing the math training program. The results showed that while both groups had gained in math knowledge, those in the training group showed higher gains as assessed by standardized math tests. Furthermore, caregivers rated high levels of satisfaction with the workshops and fewer problems in the child's behavior. At 6-month follow-up, the participants were found to maintain the therapeutic gains in math knowledge and behavior (Coles et al. 2009).

The merits of the MLE study include incorporating measures to control for potential threats to internal validity (randomization, blind assessment of outcome measures), instituting measures to increase motivation for participation (parent training), and incorporating a 6-month follow-up. However, given the control group did not receive some form of tutoring, the effect of face to face contact with a tutor is not addressed in the design. It should also be noted that the targeted group in this research included only young children aged 3 to 6 years. There is evidence that children with FASDs are able to carry out simple mathematical operations, but have difficulty with relatively complex computational tasks such as cognitive estimation (Kopera-Frye et al. 1996). Therefore, the question of whether children with FASDs can be trained to perform complex computational tasks can be raised. Since the investigators reported the therapeutic gains maintained at 6 months, this study can probably be efficacious in teaching simple math concepts to younger children.

Working Memory

Children with FASD have been found to exhibit marked deficits in working memory, particularly in spatial working memory (Green et al. 2009; Mattson et al. 2010). Therefore, Loomes et al. (2008) investigated whether verbal working memory in children with FASD could be improved through rehearsal, a strategy for keeping information in memory by repeating it over and over. In this study, 33 children with FASD, aged 4 to 11 years, were divided into two groups, experimental and controls, so that the groups were matched on some demographic variables (age and gender). All participants had previously been diagnosed as having an FASD using the 4-Digit Diagnostic system (Astley 2004). Prior to rehearsal training, the participants were required to repeat aurally presented digit sequences of increasing length (2–7) in a 10-s delay recall condition. Then, the experimental group received instructions in rehearsal of digits whereas the control group did not receive any instructions on strategy. The two groups completed posttests twice, one on the same day and the other on average 10 days after pretest. Results showed that the experimental group performed better in digit recall than the control group, particularly at posttest 2.

While these results are interesting, a number of questions can be raised about the findings. The results indicate that the provision of brief instructions was sufficient to effect a performance improvement on the Digit Span test. It is unknown what cognitive processes facilitated maintenance rehearsal in the experimental group. Since the authors do not provide sufficient information on group characteristics (Verbal IQ, gender), it is difficult to determine possible contributions from such background variables to the performance of the Digit Span. Given that the inability to retain information (e.g. forgetful) is a core characteristic of this clinical group (Streissguth et al. 1998), detailed information on background cognitive characteristics of the participants would have been helpful for the reader. Since children in the experimental group were reminded of using rehearsal at Posttest-2, it is unknown if they had used the strategy spontaneously. Therefore, the clinical significance of such strategy training is unknown. Furthermore, since the reported findings have not been replicated in children with FASDs, the study can be categorized only as possibly efficacious.

Neurocognitive Habilitation

On behalf of the Interventions for Children with FASD Research Consortium, Bertrand (2009) recently reported the findings from a number of novel interventions, including neurocognitive habilitation, parent–child interaction therapy and behavioral consultation. Because children with FASDs have been reported to show deficits in executive functioning (Kodituwakku et al. 1995; Mattson et al. 1999), Chasnoff, Wells and Bailey (Children's Research Circle, Chicago, Illinois) evaluated the efficacy of a self-regulation training program in the remediation of behavioral problems in children with FASDs. A total of 78 foster and adopted children with confirmed prenatal alcohol exposure, 6 to 11 years of age, were randomly assigned to either the intervention group or the control group. The brief account of the study presented by Bertrand (2009) does not describe what procedures were used to ascertain maternal drinking history and to diagnose the participants. The intervention group received a 12-week, 75-min neurocognitive group

therapy, which consisted of exercises adapted from a self-regulation training program, the Alert (Williams and Shellenberger 1996). This program utilizes the metaphor of a car engine to teach children to monitor and regulate their levels of arousal and activity. The parents/caregivers of these children concurrently participated in a parent education group. The control group received standard services through community agencies and school-based programs.

The results showed that, according to parent reports, the intervention group had made greater improvements in executive functioning and social perception than the control group. The results of this study have been interpreted as indicating that self-regulation led to improvement in executive functioning. It should be noted, however, that executive functioning was assessed by means of a questionnaire rather than using cognitive tasks. The fact that only the cognitive habilitation group had the parent education component might have posed a threat to the internal validity of this study. It is possible that parent education created positive impressions toward neurocognitive habilitation, biasing parent responses to the items on the executive functioning questionnaire. It is also difficult to determine whether parent education or neurocognitive habilitation or both contributed to the therapeutic outcomes of the study. Furthermore, the participants ranged in age from 6–11 years. It is unknown if interventions were adjusted to the child's developmental level.

Cognitive Control Therapy

Adnams et al. (Riley et al. 2003) conducted a pilot study to evaluate the effectiveness of cognitive control therapy (CCT) in the remediation of learning and behavioral issues in children with FASDs. Based on a 'biodevelopmental framework" rooted in developmental and psychodynamic theories, CCT involves training children in a graded series of activities, ranging from conceptualization of the body's motility in space to categorization of information (Santostefano 1978, 1985). Given that CCT facilitates development of cognitive processes from a sensory-motor level to a higher-order control level, it conceptually parallels with self-regulation training.

Adnams and colleagues selected two schools for the study from a South African community with high prevalence rates of fetal alcohol syndrome. Five children with a previous diagnosis of FAS were selected from the same grade in each school. All children in this study were diagnosed by an international team of dysmorphologists. They were matched with respect to age, SES, first language, and other demographic characteristics. The students in one school received CCT while those in the other school served as controls. Two trained therapists administered CCT to the intervention group 1 hour per week over a period of ten school term months. The control group received regular classroom lessons. The two groups underwent a comprehensive test battery including measures of cognitive functioning, academic skills and behavior before and after the intervention. The results showed that the intervention group showed greater improvement in behavior compared to the control group, but not in cognitive or academic skills.

These outcomes can indeed be considered of limited clinical significance, given that the CCT group received interventions for 10 months. Furthermore, considering the small sample size and the use of nonequivalent groups, one cannot draw firm conclusions from the results. The results merely suggest that CCT might be helpful in the treatment of children with FASDs, particularly their behavioral issues.

Social Skills

In view of convergent evidence from animal and human studies of FASD showing a link between prenatal alcohol exposure and social difficulties in offspring, O'Connor et al. (2006) have evaluated the effects of a child friendship training program on social behavior in alcohol-exposed children. Using a longitudinal design, these investigators assigned 100 children with FASDs, aged 6–12 Yrs., into two groups: treatment and delayed treatment control. Detailed information on maternal drinking was obtained by means of the UCLA Women Questionnaire and an FASD diagnosis was assigned using the 4-Digit Code system. Participants were recruited in consecutive cohorts, each including 14 to 16 eligible children. After completion of pretests, the children in a cohort were assigned, in alternative sequence, to one of the two study conditions. The treatment group received a child friendship training (CFT) program in 12 sessions, each of 90 min in duration, administered over the course of 12 weeks. The CFT is an empirically tested program (Frankel 2005), which is designed to teach friendship skills, for example, through the instruction of simple rules of social behavior, modeling, and homework assignments etc. Results showed that at the end of the program, the CFT group had improved social knowledge of appropriate social behavior and fewer problem behaviors than the control group. Furthermore, the treatment group showed lower rates of hostile attribution as indexed by performance of a cartoon story task (Keil et al. 2010). Results also showed that these gains were maintained at 3 month follow-up.

Except for randomization, the study design of the CFT program has the features of a rigorous randomized trial, including careful selection of participants, use of trained therapists, assessment of treatment integrity, utilization of a

manualized treatment protocol, relatively large sample size, and use of validated outcome measures. Because the findings have been replicated by the same group of investigators, the CFT can be considered probably efficacious by the Chambless et al. Criteria.

Safety Skills

Given that children with disabilities are at higher risk for sustaining injuries than typically developing children, Coles et al. (2007) explored the utility of using computer games to children with FASDs fire and street safety. Participants were 32 children, ages 4–10 years, who were diagnosed with FAS or partial FAS. Based on standardized scores of intellectual and adaptive behavior tests, the level of functioning of these children was placed in the borderline range. After completion of pretests, the children were randomly assigned to either fire or street safety training conditions. Using 3D game engine software and Java programming two learning environments were created, in which an animated dog named Buddy conducted safety training in incremental steps providing appropriate feedback. The fire safety virtual environment comprised a home with six rooms and a meeting place in the backyard. The street safety virtual environment included a standard crosswalk approached on a sidewalk. The child learned the correct sequences of action in these virtual environments through repeated practice. Following the mastery of the games, the children were able to verbally respond to the questions on safety procedures and the majority (72%) of them were successful in generalizing the newly acquired safety knowledge to more "real life" situations.

One interesting line of research on self-regulation has shown that one's regulatory capacity is resource-limited and that it can be depleted under stressful conditions such as highly emotional situations (Muraven and Baumeister 2000). The limited strength model predicts that children with FASDs may have difficulty with applying the newly acquired knowledge in emotionally stressful situations such as a house fire. This is, however, an empirical question that can be tested by creating different levels of stress. Pending the findings from such future studies, the use of virtual games to teach adaptive skills can be classified as probably efficacious for improving safety knowledge.

Parent–Child Interaction Therapy

Parent–Child Interaction Therapy (PCIT) is a widely used behavioral family therapy approach to the psychological treatment of preschool children and their parents, which is based on a conceptual framework derived from operant conditioning and play therapy (Eyberg and Matarazzo 1980; Eyeberg and Boggs 1998). Gurwitch and colleagues (reported in Bertrand 2009) evaluated the efficacy of PCIT in reducing behavioral problems in children with FASDs and parenting stress in their caregivers. In this study, a total of 58 children with FASDs, 3 to 7 years of age, and their caregivers were randomly assigned to either treatment [parent–child interaction therapy (PCIT)] or comparison [parenting support and management (PSM)] groups. A clinical geneticist made FASD diagnoses using a modified set of the Institute of Medicine criteria. Children participating in the study were required to have cognitive functioning at ≥30 months and parents to have IQ of ≥65. The treatment group received 14 weeks of PCIT (Eyeberg and Boggs 1998), which involved caregivers practicing with their child specific parenting skills while receiving in-vivo coaching from therapists through a communication device placed in the parent's ear. The PSM group also received an intervention administered in a parent-only format, which consisted of psycho-education about development and instructions about general behavioral management methods. The results showed that both interventions produced reductions in child behavioral problems and parenting stress among caregivers. Group comparisons revealed, however, that the PCIT group did not fare markedly better than the PSM group, suggesting the possibility that PCIT may not be as effective with behavioral problems arising from CNS dysfunction as with those related to dysfunctional parent–child interaction patterns.

A major problem with the study was high attrition rate, with only about 46% of the participants completing the intervention program. The investigators found that the high attrition rate was due to life circumstances rather than to treatment procedures. This underscores the fact that interventions that require a time commitment and effort from families that are under significant life stressors may prove to be ineffective. The finding that the PSM group benefited from interventions as much as the PCIT group did indicates the importance of developing brief parenting programs for families raising children with FASDs.

Behavioral Consultation

Carmichael Olson et al. (see Bertrand 2009) have developed and tested a behavioral consultation program, called the Families Moving Forward (FMF), to address clinically concerning behavioral problems in children with FASDs. The chief aim of this program was to reduce behavioral problems in alcohol-affected children by means of changing parenting attitudes and behaviors through positive support. The FMF program incorporated empirically tested parent training techniques and the clinical wisdom of what works

with alcohol-affected children. A total of 52 children (7.7% FAS), 5 to 11 years of age, and their parents participated in this study. 26 of these children and families were randomly assigned to the FMF program and the remainder to a community standard of care group. The FMF group received supportive behavioral consultation in 90-min long, every-other- week sessions over a period of 9 to 11 months. Of the 26 families enrolled in the FMF program, 96% completed this intervention program suggesting overall parent satisfaction with it. Results showed that compared to the control group, the FMF group had achieved desirable outcomes in a number of areas, including reduction of problem behaviors in children and improved sense of self-efficacy in parents. Particularly, a higher percentage of parents in the FMF group reported that they engaged in more self-care behaviors than the parents in the comparison group. The two groups did not however differ with respect to parental stress level.

The main virtue of the FMF program is taking a family systems approach to addressing behavioral problems in children with FASDs. The benefits of training parents as therapists have long been recognized (Patterson et al. 1967). The strengths of the study design include using a reasonable approach to assigning the participants into the two groups, manualization of the sessions, and utilization of a wide range of outcome measures. Given that the results were published in a summary form by Bertrand (2009), it is unclear if teacher reports of child behavior changes were obtained. It is also unknown if caregivers maintained their therapeutic gains, given that the intervention did not reduce parenting stress. Despite these limitations, family-oriented interventions developed through FMF may prove to be an essential component of a multi-level intervention program for children with FASDs.

Pharmacological Interventions

Children with FASDs have been observed to show high rates of comorbid mental health problems, with over 80% of children meeting criteria for a psychiatric disorder in clinic-referred samples (O'Connor et al. 2002). Attention deficit hyperactivity disorder is the most commonly diagnosed comorbid condition in this population (Burd et al. 2003). A number of investigators have examined the effectiveness of psychostimulants in the management of behavioral problems in alcohol-affected children (Doig et al. 2008; O'Malley and Nanson 2002; Oesterheld et al. 1998; Snyder et al. 1997). Administering a fixed dose of methylphenidate and two placebos to four Native American children with FAS or partial FAS in a randomized double-blind cross-over design, Oesterheld et al. (1998) found that the stimulant had a significant effect on hyperactivity, but not on daydreaming. Snyder et al. (1997) compared the effects of three psychostimulants, namely methylphenidate, dextroamphetamine, and pemoline, on sustained attention and behavior in 11 children with FASD. The results showed significant beneficial effects of the stimulants on behavior as rated by parents, but not on sustained attention. A retrospective case series study conducted by O'Malley et al. (2000) indicated that children with FASD responded more positively to dextroamphetamine than to methylphenidate. Doig et al. (2008) found that hyperactive and impulsive symptoms in alcohol-exposed children with ADHD were more responsive to medication than their inattentive symptoms. Frankel et al. (2006) found however, that children with FASD treated with neuroleptics performed better in a social skills training program than did those treated with psychostimulants.

Accordingly, children with FASDs show considerable variability in their response to medication, particularly to psychostimulants. Given that alcohol-exposed children are a heterogeneous group, such variability in response to medication is not surprising. Although the study by Osterheld et al. employed a randomized double-blind cross-over design, it included only four participants. The studies reported by O'Malley et al. (2000) and Doig et al. (2008) were retrospective studies that involved chart reviews. Despite these methodological limitations, converging evidence seems to suggest that hyperactive symptoms, but not inattentive symptoms, in children with FASDs respond to psychostimulant medications. Those children with specific psychiatric issues appear to respond better to neurolepetics than to stimulants.

Comments on Human Studies

Summarizing the findings from the Interventions for Children with FASDs Research Consortium, Bertrand (2009) identified two factors contributing to positive therapeutic outcomes: inclusion of a parent training component and the provision of direct instructions to the child. Parent involvement in an intervention is critically important not only for assuring the child's attendance in therapy sessions, but also for creating a family/social environment that supports the implementation of treatment procedures (e.g., homework). The provision of direct interventions tailored to the child's cognitive profile allows skill building in specific areas, which eventually leads to positive outcomes in other areas. Interventions that focused on positive support for parents or parent–child interactions either did not substantially reduce parent stress level or did not produce therapeutic effects exceeding those resulting from standard interventions. Therefore, the provision of direct interventions for the child in combination with parent

education/support seems to produce better outcomes than either intervention alone.

Another key finding from a number of studies is that the mastery of skills in a given domain may not produce the effects that generalize to other domains. Children who received language and literacy training for nine school-term months, for example, demonstrated marked gains in language-related skills, but not in other scholastic skills (Adnams et al. 2007). Despite its labor-intensiveness, cognitive control therapy produced positive outcomes only in behavior (Riley et al. 2003). These findings are not surprising given that academic skills are closely associated with general intellectual ability.

Preclinical Studies

Using in vivo experimental animal models and a range of in vitro approaches, preclinical investigators have made considerable strides in uncovering the mechanisms of alcohol's teratogenecity (Goodlett and Horn 2001; Goodlett et al. 2005; Guerri 2002). These investigations have led to testing potential pharmacological agents and nutritional supplements as means of mitigating the teratogenic effects of alcohol (Guerri et al. 2005). For example, in view of the finding that prenatal alcohol exposure disrupts the development of the sertonergic system (Zhou et al. 2005, 2001), investigators have administered 5-HT1A agonists to reverse this effect in rat and mouse models (Druse et al. 2004; Lee et al. 2009). The evidence supporting the hypothesis that the teratogenic effects of alcohol are mediated by alteration in cell adhesion molecules has led to testing the efficacy of ethanol antagonists in reversing alcohol-induced birth defects. Given oxidative stress has been found to be another mechanism underlying alcohol teratogenesis, antioxidants have been used as a potential treatment for alcohol-induced effects. Some investigators have obtained evidence that prenatal and postnatal choline supplementation is effective in the treatment of alcohol's tertogenic effects. The focus of another line of preclinical research has been on evaluating the efficacy of experience-based interventions or cognition-enhancing agents in the remediation of cognitive and behavioral deficits in the alcohol-exposed offspring.

Since animal models allow systematically manipulating experimental conditions and assaying outcome variables at multiple levels (e.g. neurochemical, neuroanatomical and behavioral), preclinical investigators are able to draw valid conclusions from small samples of subjects. Therefore, the primary issue concerning animal models of interventions is not about their validity but about their utility. In other terms, the main question concerns whether the findings from animal research lead to the development of efficacious and practical interventions for children with prenatal alcohol exposure. In the following section, we will briefly review preclinical studies of interventions for FASDs under two headings: Interventions for mothers and interventions for offspring.

Interventions for Mothers

5-HT_{1A} Agonists

Using animal models, preclinical studies have established that prenatal alcohol exposure impairs the development of most neurotransmitter systems (Druse 1996). The effects of prenatal alcohol exposure on the serotonergic system have received considerable attention partly because serotonin (5-HT) plays a critical role in brain development (Whitaker-Azmitia et al. 1996). A defective serotonergic system can also lead to various psychiatric problems such as anxiety and obsessive-compulsive disorders and to sleep problems such as insomnia. The 5-HT neurons germinate in the midline region of the brainstem (raphe nuclei) and send axonal projections to different regions in the brain. Researchers have obtained evidence that exposure to alcohol in utero would cause incomplete fusion of the midline tissue in the brainstem, affecting the development of the 5-HT system (Sari et al. 2001; Zhou et al. 2001). Reduced concentrations of 5-HT and its metabolite, 5-HIAA, have been observed throughout the brain in alcohol-exposed animals (Druse et al. 1991). In a series of studies, Druse and colleagues have demonstrated that maternal treatment with 5-HT_{1A} agonists, buspirone and ipsapirone, mitigated the ethanol-induced damage to the 5-HT system (Eriksen and Druse 2001; Tajuddin and Druse 1999).

Neuroprotective Peptides

NAP and SAL (or ADNF-9), two peptides derived from naturally occurring glial proteins, have been shown to be neuroprotective in rodent models. For example, treatment of Down syndrome cortical neurons with NAP and SAL has been found to produce a reduction of degenerative processes (Busciglio et al. 2007). A number of investigators have documented that combinatorial treatment with NAP and SAL prevented the deleterious effects of alcohol on the developing fetus (Parnell et al. 2007; Spong et al. 2001; Vink et al. 2005; Zhou et al. 2004). Spong et al. (2001) found that the prenatal administration of NAP+SAL to alcohol-treated pregnant mice significantly increased the survival rates of fetuses. Prenatal administration of NAP +SAL has also been found to prevent alcohol-induced spatial learning difficulties (Vink et al. 2005) and reduce birth defects such as ocular anomalies (Parnell et al. 2007).

The mechanisms through which NAP and SAL prevent alcohol-induced damage have not been fully explained. One

potential mechanism is that these peptides prevent the ethanol inhibition of LI-mediated cell adhesion (Wilkemeyer et al. 2004). NAP and SAL also have been found to counteract alcohol-induced oxidative stress (Parnell et al. 2007). Zhou et al. (2008) have obtained evidence that NAP and SAL protect against alcohol-induced neural tube defects and serotonin neuron loss.

Antioxidants

Oxidative stress, the imbalance between the production and degradation of reactive oxygen species (ROS), is considered a primary mechanism of ethanol teratogenesis (Cohen-Kerem and Koren 2003; Goodlett, et al. 2005). It appears that alcohol induces oxidative stress by increasing free radicals such as hydroxyl and superoxide and by reducing intracellular antioxidant capacity (Cohen-Kerem and Koren 2003). It has been reported that early exposure to ethanol, but not to red wine at the same alcohol concentration, induced behavioral and brain neurotrophin alternations in a mouse model (Fiore et al. 2009). This differential effect has been attributed to antioxidants in red wine. As mentioned above, NAP and SAL are also believed to mitigate the teratogenecity of alcohol partly through reducing oxidative stress (Spong, et al. 2001). Parnell et al. (2010) recently reported that dietary administration of N-acetylcysteine (NAC), which is known to reduce oxidative stress, mitigated alcohol's teratogenecity. Similarly, vitamin E and beta-carotene supplementation have been found to reduce alcohol-induced damage (Mitchell et al. 1999). Some researchers, however, have failed to find beneficial effects of vitamin E supplementation on ethanol-induced cerebellar damage (Tran et al. 2005).

Choline Supplementation

Choline is an essential nutrient that plays a critical role during fetal development by influencing stem cell proliferation and apoptosis. It is needed for normal cholinergic neurotransmission, muscle function and lipid transport from liver (Zeisel 2006). In a series of studies, Thomas and colleagues have found that prenatal and postnatal choline supplementation mitigates adverse effects of prenatal alcohol exposure (Ryan et al. 2008; Thomas et al. 2000, 2004, 2007, 2009, 2010). These investigators found that choline supplementation attenuated alcohol-induced effects on birth and brain weight (Thomas et al. 2009). Beneficial effects of choline supplementation have also been found on various measures of cognition and behavior. Particularly, choline-treated animals with prenatal alcohol exposure demonstrated better performances than untreated controls on measures of spatial learning (Thomas et al. 2007), and discrimination learning (Thomas et al. 2000). Choline supplementation has also been found to reduce overactivity (Thomas et al. 2004) and improve trace fear conditioning (Wagner and Hunt 2006) in alcohol-exposed animals. Perinatal choline supplementation, however, did not attenuate alcohol-induced motor deficits, which indicates that the beneficial effects of choline are task specific (Thomas et al. 2004).

The results of the above studies show that specific pharmacological agents and dietary supplements mitigate the deleterious effects of alcohol on the developing fetus. However, the utility of these agents in preventing alcohol-induced birth defects in humans is questionable because women who are at risk for drinking during pregnancy are not easily accessible for interventions (Hans 1999). It is known that women who abuse alcohol and drugs avoid contact with health professionals for fear that their children might be removed from home or they might be incarcerated (Stratton et al. 1996). Therefore, some investigators have focused on the development of interventions that can eventually be used with alcohol-affected children. These include experience-based interventions and cognition-enhancing drugs.

Interventions for Alcohol-Exposed Offspring

Experience-Based Interventions

It has long been recognized that experience plays a critical role in brain development (Hebb 1947). Convergent evidence from rehabilitation neuroscience and preclinical research has also shown that damaged-brains can be rehabilitated (Lippert-Gruener et al. 2007; Robertson 2002). Therefore, investigators have explored the effects of experience-based interventions on alcohol-exposed animals using a number of established paradigms, namely neonatal handling, environmental enrichment, and rehabilitative training.

Neonatal Handling

Neonatal handling is a well-established procedure that involves daily removal of animals from their home cage for a brief period during the first weeks of life. This simple procedure has been shown to have an effect on avoidance learning (Levine 1956), responsiveness to stress (Meaney et al. 1996), and memory (Meaney et al. 1988). In view of these finding, a number of investigators have explored the utility of neonatal handling in the amelioration of learning and behavioral deficits induced by prenatal alcohol exposure.

These investigations, however, have produced equivocal results. Weinberg et al. (1995) found that neonatal handling attenuated increased hypothermia observed in male rats.

Early handing also eliminated a deficit in preweaning weight gain observed in alcohol-exposed animals. Lee and Rabe (1999) investigated the effects of neonatal handling on reversal learning in alcohol-exposed animals. These investigators trained alcohol-exposed and control animals in a T-maze to learn a position response and then to reverse the learned response. As expected, alcohol-exposed animals were impaired at reversal learning. Neonatal handling during the first 3 weeks, which involved daily separation from home cages and tactile stimulation, was effective in eliminating this learning deficit. Researchers have failed, however, to eliminate spatial memory deficits in alcohol-exposed animals through neonatal handling (Gabriel et al. 2002). Gabriel et al. (2000) have also reported that neonatal handling was ineffective at ameliorating hypothalamic-pituitary-adrenal hyperresponsiveness to stress and at normalizing hypothalamic corticotropin-releasing factor levels in alcohol-exposed animals.

Environmental Enrichment

Environmental enrichment includes a set of experimental procedures including systematic alteration of physical environment (e.g. large cages, toys, running wheels for voluntary physical activity, etc.) and social environment (e.g. larger group with increased opportunity for social interaction). There exists a large body of literature documenting that enriched environments enhance learning and memory (Greenough 1976), increase the number of neurons in some regions of the brain (e.g. hippocampus), and facilitate synaptogenesis (Renner and Rosenzweig 1987). Gage and colleagues have obtained evidence for neurogenesis in adult hippocampus (Deng et al. 2010; Gage 2000; Gage and Verma 2003) probably as a function of an animal's experiences such as hippocampal dependent learning and voluntary running.

A number of investigators have evaluated the effectiveness of postnatal enriched experiences at mitigating alcohol-induced behavioral and learning deficits in rodent models (Choi et al. 2005; Hannigan et al. 1993; Mothes et al. 1996; Wainwright, et al. 1993). Hannigan et al. (1993) found that placement of alcohol-exposed rats in socially and physically enriched environments reduced alcohol-induced motor and learning deficits. Wainwright et al. (1993) reported that alcohol-exposed animals in an enriched environmental condition performed better on the Morris Water Maze task than those placed in an isolated environmental condition. In contrast, Choi et al. (2005) found an interaction between environmental condition and exposure history in a mouse model. That is, while control mice placed in the enriched environment showed a two-fold increase in hippocampal neurogenesis, alcohol-exposed mice placed in the enriched environment did not demonstrate such a neurogenic response. Berman et al. (1996) also failed to find the effects of environmental enrichment on hippocampal dendritic spine density.

Motor Training

Klintsova and colleagues have investigated the effectiveness of a rehabilitative training program designed to mitigate motor deficits in alcohol-exposed animals (Klintsova et al. 1997, 2000, 2002, 2004). In one study, these investigators (Klintsova et al. 1997) assigned alcohol-exposed and control animals to either Inactive (IC) or Rehabilitative (RC) conditions. RC rats received five trials of training per day for 10 days on an elevated obstacle course, which included narrow rods, ropes, rope ladders etc. Animals were urged to perform these rehabilitative exercises by gently squeezing the hindquarters. Results showed that at the end of the training period the alcohol-exposed and control groups all performed the tasks at a comparable level. Furthermore, the RC rats from the alcohol-exposed group showed significantly more parallel fiber synapses per Purkinje neuron than did animals from the same group in an inactive home cage condition. Subsequent studies by these investigators have provided further evidence for experience-induced plasticity in the cerebellum in alcohol-exposed rats (Klintsova et al. 2000, 2002).

Cognition-Enhancing Drugs

In view of recent successes in the treatment of neurological illnesses with nootropic compounds, some investigators have examined the effectiveness of such pharmacological agents in the amelioration of cognitive deficits in alcohol-exposed animals. Since synaptic transmission mediated by alpha-amino-3 hydroxy-5-methyl-4- isoxazolepropionic acid receptors (AMPARs) is impaired in alcohol-exposed animals, investigators have used Aniracetam to treat alcohol-induced memory and learning deficits (Vaglenova et al. 2008; Vaglenova and Vesselinov Petkov 2001; Wijayawardhane et al. 2008). These investigators have reported that animals treated with Aniracetam performed significantly better than controls on behavioral and electrophysiological measures of learning. In view of the finding that histamine H_3 receptor antagonists facilitate acetylcholine, dopamine, and glutamate release, Savage and colleagues (Savage et al. 2010; Varaschin et al. 2010) have evaluated the effectiveness of ABT-239 as a cognition-enhancing agent in a rat model of FASD. These investigators have found that ABT-239 was effective in reversing alcohol-induced long-term potentiation deficits in alcohol-exposed animals. ABT-239 did not, however, enhance LTP in control animals. The data from another group of investigators show that Vinpocetine facilitated plasticity of the sensory

system in alcohol-affected animals (Krahe et al. 2009; Medina and Krahe 2008; Medina et al. 2006).

Comments on Preclinical Research

Thus, preclinical research has made progress in the development of treatments to counteract the basic biological mechanisms underlying alcohol-induced central nervous system damage. Elucidation of the mechanisms of alcohol teratogenesis such as damage to sertonergic system and oxidative stress has allowed investigators to select appropriate pharmacological agents to reverse alcohol's teratogenic effects. Consistent with human studies, animal models have provided evidence of training-induced plasticity. Furthermore, choline supplementation and cognition-enhancing drugs also have produced promising results. A pilot study currently being conducted at the University of Minnesota is exploring the effectiveness of choline supplementation in alcohol-affected children. However, other compounds tested in animal models have not been used with prenatally alcohol-exposed children.

Animal models of experience-based training are inherently limited since these models can be used only for relatively simple functions such as sensory-motor. Most difficulties in alcohol-exposed children result from deficits in complex skills such as executive control functions and social cognition. Researchers have begun to extend the findings from some experience-based training trials to humans. In an attempt to extend Klintsova et al.'s (2002) work to humans, we recently trained alcohol-exposed children and controls in a series of motor sequences for two months. The preliminary results show evidence of training-induced plasticity of the motor system.

A theoretical assumption underlying preclinical research is that changes at a molecular biological level will lead to improvement in cognition and behavior. However, there is a growing body of literature showing this reductionist assumption of upward causation is inadequate for explaining biological phenomena (Kohl et al. 2010) Systems biologists have presented evidence that biological systems comprise multi-levels that interact (Noble 2008). In this view, upper level activities such as social experiences can modify lower level processes (e.g. structural connectivity in the brain). In the next section, we present an integrative theoretical framework for the development of interventions for children with FASDs based on the ideas from systems biology and developmental sciences. As Kazdin (1999) remarked, "A theoretical framework "that is intended to account for, explain, understand relations among variables, how they operate, and the processes involved" (P. 533) is critically important for the development of effective therapies.

Integrative Framework

A main stumbling block to the development of an integrative framework that allows optimally combining the results of preclinical and clinical research is the theoretical premise that behavior can be adequately explained using variables at a given level. Behaviorally oriented clinicians often use behavioral methods to address cognitive-behavioral problems in alcohol-affected children. Similarly, preclinical researchers have not heeded the developments in clinical sciences. The ultimate goal of preclinical research has been to uncover the mechanisms of alcohol teratogenesis at a molecular level with a view to developing pharmacological agents to reverse the deleterious effects of ethanol. The expectation is that by understanding the roots of cognitive behavioral problems at a molecular level, these problems can be eliminated.

As mentioned above, we take the position that neurocognitive functioning and behavior in children with FASDs are the products of dynamic interactions between multiple levels and systems. The importance of considering dynamic interactions between systems or levels to understand functions of an individual has been underscored by developmental psychologists (Karmiloff-Smith 2009; Thelen and Esther 1994), cognitive scientists (Westermann et al. 2007), and systems biologists (Noble 2008). As we outlined in a recent publication (Kodituwakku 2010), this dynamic interactive model is consistent with a theoretical framework in developmental psychology labeled neuroconstructivism (Sirois et al. 2008; Westermann et al. 2007). The central premise of neuroconstructivism is that experience alters the 'brain hardware', which in turn leads to new experiences and to further alterations of the neural systems.

In their formulation of neuroconstructivism, Westermann et al. (2007) delineated a number of levels, including genes, cells, brain, body, and social. Noble (2008) has defined biological functionality as involving multiple levels from genes to higher-level organism. Both of these theoretical formulations underscore the notion that changes at upper levels influence those at lower levels and vice versa. Therefore, interventions targeting molecular biological levels (e.g. pharmacological agents) and those targeting neural connectivity (e.g. transcranial magnetic stimulation) can be assumed to change cognitive functioning and behavior at higher levels. Similarly, behavioral interventions have been found to effect changes at the neuronal and biochemical levels. Such bi-directional causation in biological systems provides a theoretical basis for the development of multimodal or systems approaches to interventions for children with neurodevelopmental disorders. The findings from the Multimodal Treatment Study of ADHD (The MTA Cooperative Group) underscore the importance of optimally combining interventions at multiple levels (Molina et al.

2009; The MTA Cooperative Group 1999). The results of this 14-month randomized clinical trial initially showed that a combination of medication and behavioral interventions or medication management alone yielded significantly better outcomes than routine community care in reducing ADHD symptoms in children aged 7 to 9.9 years. However, at 8-year follow-up the MTA group was found to fare worse than the normal control group (Molina et al. 2009), partly due to discontinuation of medication. The authors (Molina et al. 2009) emphasize the importance of involving parents and teachers in intervention programs to address motivational factors.

Implications for the Development of Interventions

When conceptualized within the dynamic interactive framework, a successful behavioral intervention can be characterized as planned and guided experiences that give rise to a chain of reciprocal interactions between neural activities and structures, ultimately resulting in improved performance. With regard to guided experiences, a range of questions related 'what', 'how', 'how much or how long' and 'when' can be raised. Findings from the aforementioned clinical and preclinical studies and a growing body of literature on neural plasticity point to specific variables relevant for answering these questions. We briefly summarize these variables under 3 headings: social, biological, and matching interventions to neurocognitive profile.

Social The term social encompasses the child's family, school, and community. Since social relations are critically important for development, a number of investigations reviewed above specifically targeted social functioning in children with FASDs (e.g., social skills training, Families Moving Forward, and Mother-Child Interaction). Streissguth et al. (2004) observed that children with FASDs who were placed in stable and loving homes fared better than those who were not placed in such homes. O'Connor and colleagues (O'Connor and Paley 2006; O'Connor et al. 1987) demonstrated that mother's with a history of alcohol abuse demonstrated disorganized mother-infant interaction patterns. These investigators reported that alcohol-exposed children displayed more negative affect than controls and that mothers of children with negative affect were less connected to their children. Evidence from developmental neuroscience has revealed that the quality of mother-child interaction and the psychological state of the mother influence the child's stress responses as indexed by glucocorticoid levels (Albers et al. 2008; Lupien et al. 2009). Particularly, children of clinically depressed mothers have been observed to show heightened activity of the hypothalamic-pituitary-adrenal (HPA) axis (Lupien et al. 2009). Data from developmental sciences show that the heightened activity of the HPA axis leads to deficits in self-regulation (Blair and Diamond 2008) and, thus, to behavioral problems. It has been hypothesized that increased emotionality depletes self-regulatory resources (Muraven and Baumeister 2000). Therefore, stable social relationships, particularly mother-child relationship, constitute a critical component of a multimodal therapeutic program for young children with FASDs.

Early interventions developed within the framework of a developmental systems model (Carmichael Olson et al. 2009; Guralnick 1998) have focused on maximizing positive interactions and reducing parenting stress through provision of psychological and physical resources needed for raising children with disabilities. As the results of the family consultation program developed by Carmichael Olson et al. (Bertrand 2009) show such interventions yield positive effects on changing the outlook of parents raising children with FASDs.

Parents and teachers also play a critical role in structuring the learning environment for children with FASDs (Kalberg and Buckley 2007). Structured teaching has the potential of improving encoding and retention of new information.

Biology The above example of the effects of stress on cognitive functioning highlights the need for understanding the mediating and moderating effects of biological processes in the development of interventions. Moderating effects of genetic factors on treatment outcomes have received considerable attention in recent years. There is a growing body of literature showing that at least four genes (DRD4, DAT, COMT, and MAOA) are involved in attention networks in the brain (Fossella et al. 2008). Rueda et al. (2005) found that the long form of the dopamine transporter gene was associated with stronger effortful control in an attention training study. Therefore, assessment of genetic variation among children with FASDs may help personalizing treatment programs.

Evidence from animal models shows that prenatal alcohol exposure disrupts nearly all neurotransmitter systems in the brain (Hannigan and Randall 1996). Since children with FASDs also experience significant life stressors, it is reasonable to hypothesize that interaction between increased stress and disrupted neurotransmitter systems lead to high prevalence rates of psychiatric problems in this population, particularly during adolescence. As mentioned above, O'Connor et al. (2002) found that nearly 87% of a clinic-referred sample of children with FASDs showed psychiatric problems. Therefore, pharmacological interventions aimed at reducing emotional difficulties may constitute an important component of interventions for alcohol-affected children.

Matching Interventions to Cognitive Profile

Despite of a wealth of information on neurocognitive functioning of children with FASDs, the question whether alcohol-affected children have a unique profile of cognitive skills remains unanswered. Recently, we proposed the hypothesis that children with FASDs have a generalized deficit in the processing and integration of multiple elements or relations (Kodituwakku et al. 2011). Associated with slow information processing, this deficit manifests itself as impaired performance on relatively complex tasks involving executive control (Kodituwakku 2007, 2009). Children with prenatal alcohol exposure have also been observed to show significant behavioral problems (Greenbaum et al. 2009; Streissguth et al. 1998).

The hypothesis on the neurocognitive profile of FASDs has implications for teaching children alcohol-affected children. In view of the difficulty managing multiple elements or relations in working memory and slow processing, the presentation of information at a slower rate, use of concrete examples, and repetition of information (Kodituwakku 2010) may proved to be effective teaching strategies. Furthermore, breaking down a problem into parts and teaching them to systematically integrate them may also be helpful.

Some investigators have suggested the merits of teaching preschoolers self-regulatory skills rather than academic skills. While some have effectively used computer-based training in executive functioning with preschool age children (Rueda et al. 2005), the most effective and natural methods of teaching cognitive control to this age have predominantly included social interaction and play (Bodrova and Leong 2007; Diamond et al. 2007). There is increasing evidence that early training in cognitive control and self-regulation has far-reaching effects, since such training prepares the child to interact with peers more effectively and to gain more from academic experiences. Blair and Razza (2007) found that measures of cognitive control including response inhibition and attentional set shifting in preschool age children were associated with their emerging literacy and math skills. While one study has explored the effectiveness of self-regulation training in older children with FASDs (Bertrand 2009), no study of self-regulation training in preschool age children has been published.

Vygotsky's (1962) profound insights into the development of self-regulation and academic skills in children have significant implications for the development of training programs for children with FASDs. Particularly, *the concept of the child's zone of proximal development* is useful in the selection of appropriate tasks and strategies for training. Given that children with FASD demonstrate difficulty with integration of multiple elements and multiple relations, one must consider using the tasks with graded difficulty for training where complexity is defined in terms of the number of elements and relations. We have begun to employ this approach to teaching motor and attentional skills to children with FASDs. Furthermore, given that life stressors and poverty are common among children with FASDs (Coles et al. 2009) social- level interventions and nutrition supplementation may constitute an important part of a program designed within the dynamic interactive framework.

Accordingly, the framework outlined here involves multi-level assessments and multi-level interventions. The provision of early interventions is critically important because the foundation for the development of self-regulatory skills is laid during the first 4 years of life. Life stressors resulting from insecure attachments, abuse, exposure to violence, and other adverse conditions lead to increased activation of the HPA axis, which may eventually disrupt self-regulation. Given that ethanol is known to produce disruptions in the HPA axis (Marcri et al. 2007), children with FASDs are at higher risk for showing increased fear responses and difficulties in emotional regulation. These findings have implications for providing support for families and making policies regarding placement of children in foster care. As noted above, individual differences in temperament and genetic variation among alcohol-exposed children are poorly understood. Understanding individual differences is critically important for evaluation of treatment effects. Therefore, we propose that combining parent support and direct interventions with children constitutes the core of an intervention program developed for this group. Addition of a pharmacological agent for controlling mood disturbances or behavioral problems may be necessary in most cases. Dietary supplements and cognition-enhancing agents may also prove to be useful elements in future intervention programs. This integrative framework is consistent with the recommendations by the Committee on Integrating the Science of Early Childhood Development which underscored the multi-level influences from *Neurons to Neighborhoods* (Shonkoff and Phillips 2000).

Conclusions

In this paper, we reviewed a wide range of preclinical and clinical interventions that have been reported in the literature. Clinical interventions included social skills training, literacy training, math skills training, neurocognitive habilitation, cognitive control therapy, working memory training, safety skills training, parent–child interaction

therapy, behavioral consultation, and medication. Preclinical investigators have evaluated the effectiveness of a number of pharmacological agents, nutrition supplementation and rehabilitative training in the amelioration of alcohol-induced deficits in animal models. A limited cross-fertilization of ideas between preclinical and clinical disciplines has occurred with regard to the development of interventions for fetal alcohol spectrum disorders, mainly because of fundamental differences in focus in these disciplines. Therefore, we proposed a dynamic interactive model that allows integrating pharmacological interventions, nutrition supplementation, and behavioral and social interventions for designing programs for children with FASDs. The development of a rational approach to optimally combining these elements is an important task to be undertaken by future interdisciplinary studies of interventions for children with FASDs.

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