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A neurodevelopmental framework for the development of interventions for children with fetal alcohol spectrum disorders

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Abstract

Despite considerable data published on cognitive and behavioral disabilities in children with FASD, relatively little information is available on behavioral or pharmacological interventions for alcohol affected children. The main goals of this paper, therefore, are to summarize published intervention studies of FASD and to present a neurodevelopmental framework, based on recent findings from a number of disciplines, for designing new therapies for alcohol affected children. This framework assumes a neuroconstructionist view, which posits that reciprocal interactions between neural activity and the brain's hardware lead to the progressive formation of intra and inter-regional neural connections. In this view, behavioral interventions can be conceptualized as a series of guided experiences that are designed to produce neural activation. Based on evidence from cognitive neuroscience, it is hypothesized that specific interventions targeting executive attention and self-regulation may produce greater generalizable results than those aimed at domain specific skills in children with FASD. In view of reciprocal interactions between environmental effects and neural structures, the proposed framework suggests that the maximum effects of interventions can eventually be achieved by optimally combining behavioral methods and cognition enhancing drugs.

Keywords

fetal alcohol spectrum disorders; behavioral interventions; neuroconstructivism; neurodevelopmental framework; pharmacotherapy

Introduction

It is now known that heavy exposure to alcohol in utero produces a wide spectrum of morphological and behavioral outcomes in offspring, commonly referred to as fetal alcohol spectrum disorders (FASD). Terms such as fetal alcohol syndrome [FAS], partial fetal alcohol syndrome (PFAS), alcohol related birth defects (ARBD), and alcohol related neurodevelopmental disorder (ARND) have been used to label different clusters of anomalies along the spectrum. Although not a formal diagnosis, the term fetal alcohol spectrum disorders will be used in this paper to denote the broad range of morphological and behavioral anomalies observed in children with prenatal alcohol exposure. Common to all

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children on the spectrum are cognitive and behavioral problems that result from central nervous system damage.

There exists a large body of literature documenting cognitive deficits and behavioral-emotional difficulties in children with FASD (Kodituwakku, 2007; Riley and McGee, 2005). Compared to typically developing age-matched peers, children with FASD display deficits in intellectual abilities (Mattson et al., 1997), executive functioning (Kodituwakku et al., 2001a; Rasmussen and Bisanz, 2008), attention and information processing (Burden et al., 2005b; 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), and social cognition (McGee et al., 2008; Schonfeld et al., 2005). Researchers have found that individuals with FASD often experience a range of adverse life outcomes, called secondary disabilities, which include disrupted school experience, trouble with the law, confinement, inappropriate sexual behaviors on repeated occasions, and alcohol/drug problems (Streissguth et al., 2004). A number of researchers have documented that children with FASD display deficient adaptive behavior (Thomas et al., 1998), with social deficits becoming pronounced as they grow older (Carmichael Olson et al., 1998; Whaley et al., 2001).

The lifetime cost for care of one individual with FAS has been estimated at $2 million (Lupton et al., 2004), whereas the emotional impact of life stressors caused by FASD on caregivers and the individual is immeasurable. Accordingly, FASD continues to be a grave public health problem in North America and in countries around the world. Despite the seriousness of the problem, surprisingly little published information on evidence-based interventions for FASD is available. Although four decades have elapsed since fetal alcohol syndrome was first described in the medical literature (Jones and Smith, 1973; Lemoine et al., 1968), only a few studies using an experimental approach to evaluating the efficacy of interventions (e.g. random assignment of subjects) for alcohol-affected children had been published between 1973-2006 (O'Connor et al., 2006; Oesterheld et al., 1998; Premji et al., 2007; Riley et al., 2003). Less than a dozen of intervention studies have been published since Premji et al. reported their survey (Adnams et al., 2007; Bertrand, 2009; Coles et al., 2007; Kable et al., 2007; Paley and O'Connor, 2009). The limited progress in the development of evidence -based interventions for alcohol-affected children is puzzling, given that successful animal models of interventions for FASD have been developed (Hannigan et al., 2007; Klintsova et al., 2000; Klintsova et al., 1997), and that the past 4 decades have witnessed remarkable advances in the treatment of other neurodevelopmental disorders such as autism and attention-deficit/ hyperactivity disorder.

One possible reason for the limited progress in the development of intervention methods concerns the failure of neurobehavioral research on FASD to inform practice. Despite significant advances in the delineation of cognitive functions in children with prenatal alcohol exposure, there is no consensus among researchers regarding what constitute the core deficits in these children. Therefore, teachers and clinicians have employed interventions based on their experience in working with alcohol-affected children rather than research data. Furthermore, the cross-fertilization of ideas generated in human and animal research on FASD has not been optimal, partly because of fundamental differences in methodologies and therefore, successes in animal models have not been readily translated into the development of interventions for humans. Another possible reason for hampering the progress in the development of interventions is the prevalence view that FASD is not a global health problem. Citing the results of a comparative risk analysis conducted by the World Health Organization, Room (2005) has argued that fetal alcohol syndrome does not loom large as a global health problem. Accordingly, fewer resources have been allocated to

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the study of FASD compared with those devoted to the study of disorders such as ADHD and autism.

Although drinking during pregnancy may not be a universal problem because women in some countries do not consume alcohol because of religious or cultural reasons, FASD remains a leading preventable cause of mental retardation in the Western World. Sampson et al. (1997) have estimated the combined prevalence rates for FAS and ARND at 1 per 100 live births. Some communities in South Africa have experienced a devastating effect of fetal alcohol syndrome, with the prevalence rates estimated at 68.0-89.2 per 1000 live births (May et al., 2007). Accordingly, the development and testing of evidence-based interventions for children with FASD is long overdue. Evidence converging from animal research and a limited number of human studies has shown that those with prenatal alcohol exposure do indeed respond to interventions. Despite the lack of agreement among researchers as to a set of core deficits in FASD, there is a consensus that a range of cognitive skills are deficient in children with FASD. A review of the literature has revealed an emerging pattern of cognitive performance in these children, namely a generalized deficit in processing and integration of information (Kodituwakku, 2007, 2009; Kodituwakku, in press).

The main goals of this paper are to summarize published intervention studies of FASD and to present a neurodevelopmental framework for the development of behavioral interventions for children with FASD, based on the evidence from clinical neuroscience, developmental psychology, and neuropsychology.

Interventions for FASD

As noted above, animal models of FASD have provided evidence for experience-induced plasticity in rodents (Hannigan et al., 2007; Klintsova et al., 2000). These models have systematically investigated the effects of neonatal handling, enriched environment and specific training programs (e.g. motor training) on neural plasticity in alcohol-exposed rodents. As mentioned above, there also exist a number of human intervention studies of FASD that have sought to test the efficacy of specific training programs such as social skills training, and literacy training (Paley and O'Connor, 2009).

Animal Models

It has long been known that early experiences induce alterations in neuronal functions and behavior in adulthood. Using experimental procedures such as neonatal handling (Levine, 1956; Levine et al., 1957), selective deprivation of sensory input (Hubel and Wiesel, 1963; Wiesel and Hubel, 1963), environmental enrichment (Rosenzweig, 1966) and training (Rosenzweig et al., 1962), researchers have obtained evidence for experience-induced plasticity of the brain. A number of investigators have employed these procedures to investigate neural plasticity in alcohol-exposed animals (Hannigan et al., 2007).

Neonatal handling (NH)

Since early (neonatal) handling was demonstrated to have an effect on avoidance learning in rats (Levine, 1956; Levine et al., 1957), this procedure has been widely used in the study of responses in animals to challenging or stressful situations. There is now substantial evidence that the effects of NH on adaptive responses to stress can be attributed to an enduring reduction of fearfulness (Fernandez-Teruel et al., 2002). For example, rats handled during the neonatal period have been found to show increased exploratory and novelty seeking behaviors. There is a growing a body of literature showing that the effects of NH are mainly mediated by altered responses of the hypothalamic pituitary-adrenal axis (HPA) to stressful

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events (Levine, 2005; Weinberg et al., 2008). Researchers have also found that neonatal handling may enhance cognitive function in adulthood (Pondiki et al., 2006).

Weinberg et al. (1995) found that neonatal handling attenuated adverse effects of prenatal alcohol exposure, particularly increased hypothermia observed in male rats. Weinberg and colleagues later investigated the effects of prenatal alcohol exposure on the responsiveness of the HPA axis to stress and the ability of postnatal handling to mitigate these effects (Gabriel et al., 2005). Results of these studies showed that prenatal alcohol exposure was associated with increased responsiveness of the HPA axis to stress, but postnatal handling was ineffective in normalizing the elevated physiological responses. Lee and Rabe (1999) investigated the effects of neonatal handling on performance of ethanol-exposed animals in a T-maze learning task. In this study, Lee and Rabe trained offspring of rats chronically exposed to alcohol throughout pregnancy and controls in a T-maze to learn a position response and then to reverse the learned response. As expected, alcohol-exposed animals were deficient in reversal learning. Neonatal handling during the first 3 weeks, which involved daily separation from home cages and tactile stimulation, was found to eliminate this learning deficit. Researchers have failed, however, to eliminate spatial memory deficits on the Morris Water Maze task through neonatal handling (Gabriel et al., 2002). Thus, efforts at mitigating alcohol-induced deficits in animals by early handling have produced inconsistent results.

Enriched environment

Since Hebb (1947) introduced ‘environmental enrichment’ as an experimental concept, researchers have devoted considerable attention to the study of the effects of environmental manipulation on neural plasticity (Greenough, 1976; van Praag et al., 2000). Environmental enrichment procedures typically include systematically changing 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). Enriched environments have been shown to enhance learning and memory, increase the number of neurons in some regions of the brain (e.g. dentate gyrus of the hippocampus), and enhance synaptogenesis (Renner and Rosenzweig, 1987). Researchers have obtained evidence that animals with bilateral cerebral lesions showed improved performance on learning tasks following enriched experiences (Will et al., 1977).

A number of investigators have demonstrated that postnatal enriched experiences mitigate the effects of prenatal alcohol exposure on behavior and learning in rats (Hannigan et al., 1993; Mothes et al., 1996). Hannigan et al. (1993) found that rats exposed to alcohol and reared in isolation exhibited ataxic gait and impairments of spatial learning. These investigators succeeded in eliminating these motor and learning deficits by placing the animals in socially and physically enriched environments.

As shown above, there exist some data showing that behavioral gains resulting from environmental enrichment are associated with changes in specific neural processes (e.g. enhanced synaptogenesis). Researchers have failed, however, to observe such changes in the structures that play a critical role in learning such as the hippocampus in alcohol-exposed animals placed in enriched environments (Berman et al., 1996). Thus, the neural mechanisms underlying the observed behavioral improvements associated with environmental enrichment are yet to be delineated.

Domain-specific training

A third approach to the study of the effects of behavioral interventions in alcohol-exposed animals involves the provision of training targeted at a specific area of function. For

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example, Klintsova and colleagues have investigated the effects of a complex motor training program, in which alcohol-exposed and control animals were urged to perform a series of tasks (Klintsova et al., 2004; Klintsova et al., 2000; Klintsova et al., 1997; Klintsova et al., 2002). In one of their initial studies, these investigators (Klintsova et al., 1997) assigned alcohol-exposed and control groups (gastrostomy controls that received maltose/dextrin and suckle controls) to one of two conditions: Inactive (IC) or Rehabilitative (RC). RC rats received 5 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 the motor task 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; Klintsova et al., 2002).

Human studies

As mentioned above, a few outcome studies of behavioral interventions for children with FASD have been published (Bertrand, 2009; Paley and O'Connor, 2009). While there are no human studies that are direct parallels of animal models of environmental enrichment, it has been documented that children with FASD placed in good stable environments had better life outcomes than those placed in unstable environments (Streissguth et al., 2004). Whereas most FASD intervention studies have involved the provision of training targeted at improving skills within a specific domain, e.g. social skills, math skills, safety skills, literacy etc. some have focused on training general processes such as working memory and cognitive control.

Social skills

In view of the reports that children with FASD show decreased social competence (Carmichael Olson et al., 1998) and difficulty in social communication and that their deficient social skills become more pronounced as they grow older (Whaley et al., 2001), O'Connor et al. (2006) evaluated the efficacy of social skills training for children with prenatal alcohol exposure. Using a longitudinal design, these investigators assigned 100 children with FASD, aged 6-12, into two groups: treatment and delayed treatment control. The treatment group received a child friendship training (CFT) program over 12 sessions of 90 minutes in duration. The CFT is an empirically tested program (Frankel, 2005), which is designed to teach critical friendship skills through the instruction of simple rules of social behavior, modeling, 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. Results also showed that these gains were maintained at 3 month follow-up. Improvements in social skills did not however generalize to improved academic performance in children with FASD.

Math skills

Numerous studies have documented that children with FASD have greater difficulty with math than other with other academic subjects. Therefore, Kable et al. (2007) developed and tested a program aimed at teaching math skills to children with FASD. The authors randomly assigned 61 children with FASD, ages 3 to 12, to either the math intervention or standard psychoeducational care groups. The math intervention group received instruction through a specially designed program that incorporated compensatory strategies for cognitive deficits in children with FASD (e.g. use of tangible objects and tools to

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compensate for visual spatial deficits; and the presentation of materials at a slow pace to accommodate for information processing deficits). Additionally, given that life stressors and behavioral problems often interfere with academic functioning in children with FASD, supports for learning readiness were provided through case management services, psychiatric consultations etc. All parents received instructions on topics such as FAS, behavior regulation, and advocacy through workshops. After 5 months, while both groups of children demonstrated gains in math knowledge, the math instruction group had gained significantly more than the control group, suggesting the efficacy of direct math training.

Literacy skills

Adnams et al.(2001) found that children with FASD from an impoverished community in South Africa were notably more deficient in language skills than their peers without FASD. Therefore, the efficacy of a literacy training program was piloted as a part of a larger behavioral intervention study of FASD in South Africa. Forty children with FASD, 9 years of age, were randomly assigned to either the literacy or language training (LLT) or control groups. Twenty non-FASD children were also recruited to serve as an additional control group. After completion of pretests, the LLT group received 19 hours of language therapy alternating with 19 hours of literacy and phonological awareness training over a period of 9 school-term months. Results showed that the LLT group had gained more than the FASD control group in specific categories of language and literacy. The LLT group did not show however notable gains compared to the FASD control group in general scholastic skills, suggesting that the benefits of the intervention was domain specific.

Safety skills

Coles et al. (2007) have reported a study designed to test the effectiveness of using computer games to teach children with FASD fire and street safety. Participants were 32 children, ages 6-12 years, who were diagnosed with FAS or partial FAS. These children were randomly assigned to either fire or street safety training conditions. Using 3D game engine software and Java programming the two learning environments were created, in which an animated dog named Buddy conducted safety training in incremental steps providing appropriate feedback. Following the mastery of this game, children were able to verbally respond to the questions on safety procedures and the majority (72%) of them was successful in generalizing the newly acquired safety knowledge to more "real life" situations.

Working Memory

Loomes et al. (2008) evaluated the effect of rehearsal training on working memory in children with FASD. In this study, the investigators administered a digit memory task, in which children were required to repeat aurally presented digit sequences of increasing length (2-7) under a 10-second delay recall condition. After completion of pretests, 32 children with FASD were randomly assigned either to experimental or control groups. 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 on posttest 2.

Behavioral Consultation

In view of the fact that an overwhelming number of children with FASD display behavioral problems, Carmichael Olson et al. (see Bertrand, 2009) have developed and tested a behavioral consultation program, called Families Moving Forward (FMF). The chief aim of this program was to reduce clinically concerning behavioral problems (e.g. disruptive behaviors) in children through changing specific parenting attitudes and behaviors. In a recently completed randomized trial that utilized this positive support approach, 52 children (7.7% FAS), ages 5 through 11, and their parents participated. Twenty six of these children and families were assigned to the FMF program and the remainder to a community standard of care group. The FMF group received supportive behavioral consultation in 90-minute long, every-other- week sessions over a period of 9 to 11 months. 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.

Neurocognitive Habilitation

On behalf of the Interventions for Children with Fetal Alcohol Spectrum Disorders Research Consortium, Bertrand (2009) recently summarized the findings from a number of novel interventions, including neurocognitive habilitation and parent-child interaction therapy. The main objective of the neurocognitive habilitation program (Chasnoff, Wells & Bailey at Children's Research Circle, Chicago, Illinois) was to address behavioral issues in children with FASDs through the provision of training in self-regulation skills. A total of 78 children, 6 to 11 years of age, were randomly assigned to either the intervention or the control group. The intervention group received a 12-week, 75-min neurocognitive group therapy sessions based on a self-regulation program called the Alert Program (Williams and Shellenberger, 1996). The control group received standard interventions such as speech therapy and occupational therapy. The results showed the intervention group showed greater improvements in executive functioning than the control group.

Parent-Child Interaction Therapy

The primary focus of parent-child interaction therapy (Gurwitch, Mulvhill, Chaffin, & Grim, University of Oklahoma Health Sciences Center, Oklahoma City) was to explore the effects of improved parent-child interactions on child behavior and parenting stress among caregivers. In this study, a total of 58 children 3-7 years of age with FASD and their caregivers were randomly assigned to either treatment (parent-child interaction therapy) or comparison (parenting support and management) groups. The treatment group received 14 weeks of parent-child interaction therapy (Eyeberg and Boggs, 1998), which involved caregivers practicing with their child specific parenting skills while receiving in-vivo coaching from therapists through a device placed in the parent's ear. The comparison group also received an intervention administered in a parent-only format, which included psychoeducation 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.

Cognitive Control Therapy

In a pilot study conducted in South Africa, Adnams et al. (Riley et al., 2003) found that ‘cognitive control therapy’ (CCT) produced improvements in behavior as assessed by the Personal Behavior Checklist-36 (Streissguth et al., 1998), but not in academic skills, in children with fetal alcohol syndrome. 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 (Kalberg and Buckley, 2007).

Summary

Accordingly, the foregoing studies provide evidence that behavioral interventions are effective in ameliorating selected areas of cognitive functioning and behavior in animals and

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humans exposed to alcohol prenatally. Some animal studies have documented that training-induced behavioral gains are associated with discernable morphological and neurochemical changes in the brain. The above findings also indicate that training-induced changes in a specific domain of functioning may not generalize to other areas of functioning. Furthermore, the evidence converging from animal and human studies suggests that only some interventions are effective in the amelioration of cognitive and behavioral deficits resulting from prenatal alcohol exposure. This necessitates the formulation of a theoretical framework that guides the choice and administration of interventions that produce optimal results.

A neurodevelopmental framework

Rationale

Most of the foregoing human intervention studies of FASD have employed strategies that have proven to be successful with other neurodevelopmental disorders such as autism, ADHD, or language delay. While a specific strategy can be used across multiple developmental disorders, the full benefits of an intervention can not be reaped unless it is tailored to the profile of strengths and weaknesses of a given disorder. Although children with ADHD and FASD are often characterized as having a primary deficit in attention, these two groups have distinct cognitive profiles (Coles et al., 1997) and hence, may respond differently to a given intervention targeting attention problems. Similarly, a visual strategy developed for children with autism may not be as effective with children with FASD since the latter group does not display visual strengths (Kable et al., 2007). Therefore, the development of intervention strategies directly addressing the cognitive-behavioral phenotype in FASD is critically important. Another key element of a successful therapeutic program is a theory “that is intended to account for, explain, understand relations among variables, how they operate, and the processes involved” P. 533 (Kazdin, 1999).

The main thrust of this paper is that recent advances in developmental neuroscience offer a theoretical framework for the development of interventions for children with FASD. The past two decades have witnessed considerable progress in our understanding of the neural basis of developmental disorders and plasticity of the brain. Since the advent of sophisticated neuroimaging methods, researchers have been able to better understand how neural networks function, how they are assembled during development, and how they are altered through interventions (Lyon and Rumsey, 1996). Advances in human genetics, particularly the mapping of the human genome, have opened avenues to understand the physical basis of individual differences in cognitive functioning (Venter et al., 2001). Parallel achievements in cognitive and developmental sciences have provided greater understanding of the architecture of various cognitive functions and their development. A theoretical framework grounded in the above advances will allow the integrating animal and human data and generation of novel intervention strategies to address cognitive and behavioral issues in children with FASD.

Theoretical foundation

A tacit assumption of much of the neurobehavioral research on FASD is that neuroanatomical anomalies and cognitive impairments are directly associated. In view of the finding that the hippocampus is particularly vulnerable to the effects of alcohol, researchers have designed human studies using tests sensitive to hippocampal functions (Hamilton et al., 2003; Uecker and Nadel, 1996); the finding that the corpus callosum is often damaged in children with FASD has led to investigations aimed at testing the interhemispheric transfer of information (Dodge et al., 2009; Roebuck et al., 2002); similarly, orbitofrontal dysfunction in FASD has been considered a putative cause of deficient reversal learning

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(Kodituwakku et al., 2001b). This assumption of a direct brain-behavior relationship in neurodevelopmental disorders is rooted in a modular view of the mind, according to which cognitive functions comprise relatively independent modules that develop under considerable genetic influence (Baron-Cohen, 1995; Pinker, 1994). An implication of this theoretical perspective is that some modules in the developing brain can be damaged in the presence of intact domains, resulting in an uneven profile of cognitive functioning. In this view, therefore, the development of intervention programs involves focusing on damaged modules. If children with FASD, for example, have 'specific' impairments of number processing, a researcher may focus on the development of strategies to improve number sense.

In light of recent developments in epigenetics and developmental science, the assumptions of the modular view of the brain have been challenged (Elman et al., 1999). Evidence from several lines of research shows that development is a product of mutually induced changes between the neural and cognitive processes and hence, is context dependent (Sirois et al., 2008). This dynamic interactive model of development has been formalized into theoretical framework labeled neuroconstructivism (Sirois et al., 2008; Westermann et al., 2007), which posits that experience alters the 'brain hardware', which in turn leads to new experiences and to further alterations of the neural systems (Westermann et al., 2007). This paper proposes that the notion of dynamic reciprocal interactions between experiences and neural system offers a practical framework for understanding the neurocognitive profile in children with FASD and developing appropriate interventions for these children.

Westermann et al. (2007) have delineated constraints on development at different levels, which include genes, encellment, embrainment, embodiment, and ensocialment. Neuroconstructivists take a probabilistic epigenetics view of development (Gottlieb, 2007), which underscores the reciprocity of influences within and between different levels, ranging from genetic to social. Westermann et al. (2007) use the term encellment to describe developmental constraints at a neuronal level. It has been well documented that neural activity is critical for the formation of neural networks (Quartz and Sejnowski, 1997). The term embrainment underscores the contributions from interregional interactions of the brain to development. Recent neuroimaging studies have provided evidence that functional properties of a given region of the brain are shaped by its interactions with other regions (Friston and Price, 2001). Developmental constraints resulting from the brain being a part of the body have been labeled embodiment. For example, the integrity of sensory organs is critically important for the development of perceptual functions. The body is also instrumental in manipulating the physical environment, and thereby generating novel sensory inputs that influence brain development. The fact that the body is also embodied in a social environment places additional constraints on the development, which are referred to as ensocialment. It has been well documented that disruptions of attachment in early development have devastating effects on the development of specific neural networks of the brain, as observed in children raised in orphanages (Chugani et al., 2001; Eluvathingal et al., 2006). The neuroconstructionist view also posits that interactions between the above constraints contribute to the formation of within-region networks as well as between-region pathways (Mareschal et al., 2007). For example, social inputs influence not only the formation of neural networks underpinning social interaction, but also the expression of specific genes (Eisenberg, 1995).

The neuroconstructivist hypothesis that brain development results from reciprocal interactions between neural activity and neural structures has profound implications for the development of intervention methods for children with FASD. According to neuroconstructivism, an efficacious intervention produces neural activity leading to plasticity of neural structures, which in turn results in substantial changes in experiences.

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These changes are considered to reciprocally affect brain structures, resulting in a progressive formation of a neural circuitry supporting a specific skill. The studies of motor training (Klintsova et al., 2000) outlined above demonstrate the effects of planned and guided motor experiences on plasticity of specific neural structures in alcohol-exposed rats. As mentioned, behavioral changes resulting from specific guided experiences such as social skills training have been documented, but no data on experience-induced plasticity in specific brain regions of alcohol-affected children have been published.

Guidelines

A successful intervention can be characterized as a series of planned and guided experiences that give rise to a chain of reciprocal interactions between neural activities and structures, ultimately resulting in improved performance. A range of parameters related to experiences and structures can determine the effectiveness of producing such interactions. In particular, type of experiences, intensity and frequency of practice and suitability can all contribute to therapeutic outcomes. Similarly, the level of structural integrity is an important determinant of the responsiveness to specific experiences. We submit that recent findings in cognitive neuroscience, neuropsychology of FASD can be utilized to develop guidelines to maximize the outcomes of interventions designed for alcohol-affected children.

a). Pay heed to the child's overall cognitive-behavioral profile when designing an intervention program for him or her

As noted above, despite an extensive body of literature documenting cognitive dysfunction in children with FASD, the question of whether alcohol-exposed children display a unique pattern of dysfunction remains unanswered. Recently, we proposed that a generalized deficit in the processing and integration of information characterizes the essence of the cognitive-behavioral phenotype in children with FASD (Kodituwakku, 2007, 2009; Kodituwakku, in press). Numerous studies have consistently documented that children with FASD show lower intellectual abilities than their age peers, with perceptual and verbal skills both being diminished (Mattson and Riley, 1998). Researchers have also consistently found children with FASD are slower in processing information than typically developing controls (Burden et al., 2005a; Jacobson, 1998). Furthermore, children with FASD perform worse than typically developing peers on relatively complex tasks selected from different domains of cognitive functioning, whereas the two groups do not show differences in performance on relatively simple tasks. For example, children with FASD show greater difficulty than controls on letter fluency, but not on category fluency (Kodituwakku et al., 2006a). Similarly, children with FASD perform worse than controls on complex, but not on simple, tests of cognitive planning (Aragon et al., 2008).

In view of the above findings, a therapist designing an intervention program for FASD must incorporate strategies to address deficits in processing and integration of information. These may include presentation of information at a slower rate than normal, using multi-modalities and repetition of presented information. Clinical experience suggests that hands-on experiences facilitate encoding information in children with FASD. Related to the use of hands-on experiences is the utilization of computer games to teach materials, as demonstrated by Coles et al. (2007).

b). Utilize strategies appropriate for the child's Zone of Proximal Development

Consistent with neuroconstructivism, Vygotsky's developmental theory (Vygotsky, 1978) underscored the importance of contributions from social-cultural environment to cognitive development. Vygotsky made a distinction between the child's actual developmental level, as indexed by independent problem solving, and the child's potential developmental level, as

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determined by problem solving under adult guidance or in collaboration with more capable peers. The gap between these two levels was called the Zone of Proximal Development (ZPD), as it reflected what the child is ready to achieve in the future or the child's emerging skills. Therefore, the task of educators and adults is to assist the child attain his or her potential by means of the provision of hints, strategies, and guidance. The emphasis is placed on providing the child activities that are just beyond his or her independent level of performance, but within what the child can do with assistance.

As noted above, alcohol-induced brain damage may interfere with the child's progression from the independent (current) to assisted (potential) levels of performance. A common stumbling block to the attainment of the assisted level performance in a child with FASD is difficulty with retention of information. This issue can be addressed through teaching executive control skills, as described below.

c). Provide training in attention and self-regulation early

The provision of training in executive attention and self-regulation to children with FASD is critically important because of a number of reasons. First, the effects of attention and self-regulation training are more far-reaching than those resulting from domain-specific training (Posner and Rothbart, 2005, 2007). It has long been known in psychology and education that skills acquired in one domain do not readily transfer to a different domain (Ericsson and Chase, 1982). However, recent neuroimaging studies have revealed that attentional networks influence with other neural networks in the brain, suggesting that attention training may produce effects that are generalizable across domains (Posner and Rothbart, 2005). Second, the emergence of specific self-regulatory skills during preschool years predicts long-term developmental outcomes. In a landmark study of the development self-regulation, Mischel and colleagues (1989) have demonstrated that the ability to delay gratification in a group of children at age 4 predicted their academic achievement and response inhibition during adolescence. Researchers have also obtained evidence that specific self-regulatory skills in preschool children are strongly associated with academic outcomes independent of general intellectual ability ((Blair and Razza, 2007). In particular, inhibitory control was positively associated with early math and reading abilities. McClelland et al. (2000) found that work-related skills, which are associated with self-regulation, in preschool children uniquely predicted academic outcomes at school entry. These findings are not surprising because attentional skills allow the child to encode information efficiently because of his or her ability to sustain attention in the presence of interference and the ability to hold more information in working memory (Posner and Rothbart, 2005, 2007).

There is evidence that children with FASD respond to early interventions (Streissguth et al., 2004). There is growing evidence that early interventions targeting self-regulation and executive attention may produce more far-reaching effects than domain-specific interventions such as literacy training or math training. Researchers have successfully used specific teaching strategies such as those in the Tools of the Mind Curriculum (Bodrova and Leong, 2007; Diamond et al., 2007) and computer-based training programs (Rueda et al., 2005) to teach young children self-regulation and executive attention. These strategies may prove useful in teaching self-regulatory skills to children with FASD.

d). Provide enriched input in a guided fashion

There exists a vast literature showing that enriched environmental input enhances cognitive functioning in humans and animals (Huttenlocher, 1998; Huttenlocher et al., 1998; Rosenzweig, 1966). As noted above, Huttenlocher (1998) has documented that the child's language development is directly related to the speech they hear at home and at school. It was also mentioned that researchers have obtained evidence that postnatal enriched experiences mitigate the effects of prenatal alcohol exposure on behavior and learning in rats (Hannigan et al., 1993; Mothes et al., 1996). We found that a group of children, particularly girls, with FASD from a community in South Africa displayed some improvement in language after entering school (Kodituwakku et al., 2006b). The effects of enriched input can however be enhanced by providing experiences in a guided and controlled fashion. For example, by using words and grammar just beyond what the child is able to produce may help develop vocabulary and grammar. Similarly, the child can be systematically challenged with visual and block building tasks of increasing difficulty.

The above guidelines are presumed to assist in planning guided experiences so that their impact on neural structures (epigenesis) is enhanced. Recent advances in molecular genetics and neuroimaging have allowed researchers to probe and manipulate neural structures directly. These advances have profound implications for the development of novel intervention methods for children with children with FASD. For example, researchers have obtained evidence for genetic variation in executive attention (Fan et al., 2003; Fossella et al., 2008). In particular, there is evidence that alleles in a number of dopamine genes (e.g. DAT1) are associated with performance of tests assessing executive attention. These developments have implications for the development of drugs that directly target specific neural structures.

e). Combine evidence-based behavioral and pharmacological intervention, unless clinically contra-indicated

As mentioned above, using animal models, researchers have made considerable progress in the development of molecular interventions that ameliorate cognitive and behavioral deficits resulting from prenatal alcohol exposure. The focus of one line research has been on experimental therapeutics that can be administered during pregnancy to counteract the deleterious effects of alcohol. A number of investigators have obtained evidence that peptides derived from activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP) protect against the effects of alcohol (Sari and Gozes, 2006; Wilkemeyer et al., 2004; Zhou et al., 2008). In particular, a nine-amino acid peptide derived from ADNF labeled SAL and an eight- amino acid peptide derived from ADNP labeled NAP have been found to be efficacious in attenuating the teratogenic effects of alcohol (Wilkemeyer et al., 2004). The finding that prenatal alcohol exposure causes damage to the development of 5-HT system has led some researchers to examine the utility of maternal treatment with 5-HT agonists such as busipirone and ipsapirone (Eriksen and Druse, 2001). Druse et al. (2004) have found that maternal treatment with busipirone or ipsapirone reduced the adverse effects of ethanol on the 5-HT system in the offspring. Furthermore, using a rat model of prenatal alcohol exposure, Thomas and colleagues have demonstrated that both prenatal and postnatal choline supplementation is effective in reducing the severity of alcohol effects, as indexed by improved performance on various learning paradigms such as spatial reversal learning, trace eyeblink conditioning, and spatial learning (Thomas et al., 2004; Thomas et al., 2000).

Given that alcoholic mothers are notoriously non-compliant with prenatal care, some investigators have utilized animal models to test therapeutic agents that can eventually be used with alcohol-affected children during their neonatal period or late childhood. Since children with FASDs display a range of cognitive deficits, researchers have investigated the effects of a class of therapeutic agents called cognitive enhancers in animal models of prenatal alcohol exposure. Medina et al. (2006) have reported that Vinpocetine, a phosphodiesterace inhibitor, restored ocular dominance plasticity in the ferret model of fetal alcohol exposure. Vaglenova et al (2008) found that Aniracetam, a cognitive enhancer, reversed learning and memory deficits in alcohol-exposed rodents. The histamine H_3 receptor as a target for the treatment of cognitive disorders has been the focus of research in

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some laboratories because it regulates the release of other neurotransmitters (Esbenshade et al., 2008). Savage et al. (2009) have reported that ABT-239, a histamine H_3 receptor antagonist, ameliorated a number of learning and memory deficits in prenatally ethanol exposed rat offspring.

The above molecular interventions are considered to directly influence the neural processes that subserve cognitive functioning. Pharmacotherapy may also prove to be an integral part in the treatment of co-morbid conditions that are associated with FASD. Numerous studies have documented that children with FASD exhibit a range of psychiatric problems including attention deficit hyperactivity disorder, depressive disorders, and specific phobias (Fryer et al., 2007; Streissguth and O'Malley, 2000). These disorders can be hypothesized to interfere with the effects of behavioral interventions. Therefore, the combined use of pharmacotherapy and behavioral interventions may be necessary to gain the full benefits of interventions. Frankel et al. (2006) found that neuroleptics, but not stimulants, enhanced the effects of a 12- week social skills training program administered to children with FASD. It is possible that neuroleptics mitigated the negative effects of emotions on attention, thus allowing children to benefit from social skills training sessions. There is evidence that social cognition and attention are subserved by closely linked regions in the medial frontal cortex (Amodio and Frith, 2006).

Conclusions and future directions

Thus, the neurodevelopmental framework presented in this paper provides conceptual tools to integrate data from multiple sources (e.g. neuropsychology, cognitive neuroscience, genetics, and neuropharmacology) and to generate interventions for children with FASD. Recent findings in cognitive neuroscience suggest that training in executive attention and self-regulation will produce greater generalizable effects than interventions targeting specific cognitive domains. In line with the neuroconstructivist view, it is hypothesized that reciprocal interactions between neural activity and the brain's hardware lead to progressive modification of neural systems. The proposed framework also proposes that children with FASD may gain optimal results by a combined use of carefully designed behavioral interventions and cognition-enhancing drugs. Novel functional neuroimaging methods such as functional magnetic resonance imaging (fMRI) and magnetoencephalograpy (MEG) may offer opportunities for mapping the experience or drug-induced alterations in neural networks that accompany behavioral outcomes. It is hoped that the convergence of evidence from neural and behavioral sciences will lay the foundation for a new interdisciplinary approach to the development of interventions for children with FASD.

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References

Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. Alcohol Clin Exp Res 2001;25:557–562. [PubMed: 11329496]

Adnams CM, Sorour P, Kalberg WO, Kodituwakku P, Perold MD, Kotze A, September S, Castle B, Gossage J, May PA. Language and literacy outcomes from a pilot intervention study for children with fetal alcohol spectrum disorders in South Africa. Alcohol 2007;41:403–414. [PubMed: 17936509]

Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 2006;7:268–277. [PubMed: 16552413]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Aragon AS, Kalberg WO, Buckley D, Barela-Scott LM, Tabachnick BG, May PA. Neuropsychological Study of FASD in a Sample of American Indian Children: Processing Simple Versus Complex Information. Alcohol Clin Exp Res. 2008

Baron-Cohen, S. Mindblindness. Cambridge, Massachusettes: The MIT Press; 1995.

Becker M, Warr-Leeper GA, Leeper HA Jr. Fetal alcohol syndrome: a description of oral motor, articulatory, short-term memory, grammatical, and semantic abilities. J Commun Disord 1990;23:97–124. [PubMed: 2341602]

Berman RF, Hannigan JH, Sperry MA, Zajac CS. Prenatal alcohol exposure and the effects of environmental enrichment on hippocampal dendritic spine density. Alcohol 1996;13:209–216. [PubMed: 8814658]

Bertrand J. Interventions for children with fetal alcohol spectrum disorders (FASDs): overview of findings for five innovative research projects. Res Dev Disabil 2009;30:986–1006. [PubMed: 19327965]

Blair C, Razza RP. Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. Child Dev 2007;78:647–663. [PubMed: 17381795]

Bodrova, E.; Leong, DJ. Tools of the mind: The Vygotskian approach to early childhood education. 2nd. Upper Saddle River, New Jersey: Pearson/Merrill Prentice Hall; 2007.

Burden MJ, Jacobson SW, Jacobson JL. Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. Alcoholism: Clinical and Experimental Research 2005a; 29:1473–1483.

Burden MJ, Jacobson SW, Jacobson JL. Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. Alcohol Clin Exp Res 2005b;29:1473–1483. [PubMed: 16131856]

Carmichael Olson H, Feldman JJ, Streissguth AP, Sampson PD, Bookstein FL. Neuropsychological deficits in adolescents with fetal alcohol syndrome: clinical findings. Alcohol Clin Exp Res 1998;22:1998–2012. [PubMed: 9884144]

Chugani HT, Behen ME, Muzik O, Juhasz C, Nagy F, Chugani DC. Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. Neuroimage 2001;14:1290–1301. [PubMed: 11707085]

Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res 1997;21:150–161. [PubMed: 9046388]

Coles CD, Strickland DC, Padgett L, Bellmoff L. Games that “work”: using computer games to teach alcohol-affected children about fire and street safety. Res Dev Disabil 2007;28:518–530. [PubMed: 16965894]

Diamond A, Barnett WS, Thomas J, Munro S. Preschool program improves cognitive control. Science 2007;318:1387–1388. [PubMed: 18048670]

Dodge NC, Jacobson JL, Molteno CD, Meintjes EM, Bangalore S, Diwadkar V, Hoyme EH, Robinson LK, Khaole N, Avison MJ, et al. Prenatal alcohol exposure and interhemispheric transfer of tactile information: Detroit and Cape Town findings. Alcohol Clin Exp Res 2009;33:1628–1637. [PubMed: 19519722]

Druse MJ, Tajuddin NF, Gillespie RA, Dickson E, Atieh M, Pietrzak CA, Le PT. The serotonin-1A agonist ipsapirone prevents ethanol-associated death of total rhombencephalic neurons and prevents the reduction of fetal serotonin neurons. Brain Res Dev Brain Res 2004;150:79–88.

Eisenberg L. The social construction of the human brain. Am J Psychiatry 1995;152:1563–1575. [PubMed: 7485618]

Elman, JL.; Bates, EA.; Johnson, MH.; Karmiloff-Smith, A.; Parisi, D.; Plunkett, K. Rethinking innateness. Cambridge, Massachusettes: The MIT Press; 1999.

Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 2006;117:2093–2100. [PubMed: 16740852]

Ericsson KA, Chase WG. Exceptional memory. Am Sci 1982;70:607–615. [PubMed: 7181217]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Eriksen JL, Druse MJ. Astrocyte-mediated trophic support of developing serotonin neurons: effects of ethanol, buspirone, and S100B. Brain Res Dev Brain Res 2001;131:9–15.

Esbenshade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD. The histamine H3 receptor: an attractive target for the treatment of cognitive disorders. Br J Pharmacol 2008;154:1166–1181. [PubMed: 18469850]

Eyeberg, SM.; Boggs, SR. parent-child interaction therapy for oppositional preschoolers. In: Shaefer, CE.; Briesmeister, JM., editors. Handbook of parent training: parents as co-therapists chidlren's behavior problems. New York, Wiley: 1998. p. 61-97.

Fan J, Fossella J, Sommer T, Wu Y, Posner MI. Mapping the genetic variation of executive attention onto brain activity. Proc Natl Acad Sci U S A 2003;100:7406–7411. [PubMed: 12773616]

Fernandez-Teruel A, Gimenez-Llort L, Escorihuela RM, Gil L, Aguilar R, Steimer T, Tobena A. Early-life handling stimulation and environmental enrichment: are some of their effects mediated by similar neural mechanisms? Pharmacol Biochem Behav 2002;73:233–245. [PubMed: 12076742]

Fossella J, Fan J, Liu X, Guise K, Brocki K, Hof PR, Kittappa R, McKay R, Posner M. Provisional hypotheses for the molecular genetics of cognitive development: imaging genetic pathways in the anterior cingulate cortex. Biol Psychol 2008;79:23–29. [PubMed: 18261834]

Frankel, F. Parent-assisted children's friendship training. In: Hibbs, ED.; Jensen, PS., editors. Psychosocial treatments for child and adolescent disorders: Empirically based approaches. Washington, DC: American Psychological Association; 2005. p. 693-715.

Frankel F, Paley B, Marquardt R, O'Connor M. Stimulants, neuroleptics, and children's friendship training for children with fetal alcohol spectrum disorders. J Child Adolesc Psychopharmacol 2006;16:777–789. [PubMed: 17201621]

Friston KJ, Price CJ. Dynamic representations and generative models of brain function. Brain Res Bull 2001;54:275–285. [PubMed: 11287132]

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 2007;119:e733–741. [PubMed: 17332190]

Gabriel KI, Glavas MM, Ellis L, Weinberg J. Postnatal handling does not normalize hypothalamic corticotropin-releasing factor mRNA levels in animals prenatally exposed to ethanol. Brain Res Dev Brain Res 2005;157:74–82.

Gabriel KI, Johnston S, Weinberg J. Prenatal ethanol exposure and spatial navigation: effects of postnatal handling and aging. Dev Psychobiol 2002;40:345–357. [PubMed: 12115293]

Gottlieb G. Probabilistic epigenesis. Dev Sci 2007;10:1–11. [PubMed: 17181692]

Greenough, WT. Enduring brain effects of differential experience and training. In: Rosenzweig, MR.; Bennett, EL., editors. Neural mechanisms of learning and memory. Cambridge, Mass.: MIT Press; 1976. p. 255-278.

Hamilton DA, Kodituwakku P, Sutherland RJ, Savage DD. Children with Fetal Alcohol Syndrome are impaired at place learning but not cued-navigation in a virtual Morris water task. Behav Brain Res 2003;143:85–94. [PubMed: 12842299]

Hannigan JH, Berman RF, Zajac CS. Environmental enrichment and the behavioral effects of prenatal exposure to alcohol in rats. Neurotoxicol Teratol 1993;15:261–266. [PubMed: 8413080]

Hannigan JH, O'Leary-Moore SK, Berman RF. Postnatal environmental or experimental amelioration of neurobehavioral effects of perinatal alcohol exposure in rats. Neurosci Biobehav Rev 2007;31:202–211. [PubMed: 16911827]

Hebb DO. The effects of early experience on problem solving in maturity. Am Psychol 1947;2:306–307.

Hubel DH, Wiesel TN. Receptive Fields of Cells in Striate Cortex of Very Young, Visually Inexperienced Kittens. J Neurophysiol 1963;26:994–1002. [PubMed: 14084171]

Huttenlocher J. Language input and language growth. Prev Med 1998;27:195–199. [PubMed: 9578994]

Huttenlocher J, Levine S, Vevea J. Environmental Input and Cognitive Growth: A Study Using Time-Period Comparisons. Child Dev 1998;69:1012–1029. [PubMed: 9768484]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Jacobson SW. Specificity of neurobehavioral outcomes associated with prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research 1998;22:313–320.

Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973;2:999–1001. [PubMed: 4127281]

Kable JA, Coles CD, Taddeo E. Socio-cognitive habilitation using the math interactive learning experience program for alcohol-affected children. Alcohol Clin Exp Res 2007;31:1425–1434. [PubMed: 17550365]

Kalberg WO, Buckley D. FASD: What types of intervention and rehabilitation are useful? Neurosci Biobehav Rev 2007;31:278–285. [PubMed: 16919732]

Kazdin AE. Current (lack of) status of theory in child and adolescent psychotherapy research. J Clin Child Psychol 1999;28:533–543. [PubMed: 10587904]

Klintsova AY, Dickson E, Yoshida R, Greenough WT. Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise. Brain Res 2004;1028:92–104. [PubMed: 15518646]

Klintsova AY, Goodlett CR, Greenough WT. Therapeutic motor training ameliorates cerebellar effects of postnatal binge alcohol. Neurotoxicol Teratol 2000;22:125–132. [PubMed: 10642121]

Klintsova AY, Matthews JT, Goodlett CR, Napper RM, Greenough WT. Therapeutic motor training increases parallel fiber synapse number per Purkinje neuron in cerebellar cortex of rats given postnatal binge alcohol exposure: preliminary report. Alcohol Clin Exp Res 1997;21:1257–1263. [PubMed: 9347087]

Klintsova AY, Scamra C, Hoffman M, Napper RM, Goodlett CR, Greenough WT. Therapeutic effects of complex motor training on motor performance deficits induced by neonatal binge-like alcohol exposure in rats: II. A quantitative stereological study of synaptic plasticity in female rat cerebellum. Brain Res 2002;937:83–93. [PubMed: 12020866]

Kodituwakku PW. Defining the behavioral phenotype i children with fetal alcohol spectrum disorders: A review. Neurosci Biobehav Rev 2007;31:192–201. [PubMed: 16930704]

Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. Dev Disabil Res Rev 2009;15:218–224. [PubMed: 19731385]

Kodituwakku, PW. Is there a behavioral phenotype in children with fetal alcohol spectrum disorders?. In: Shapiro, BK.; Accardo, PJ., editors. Neurobehavioral disorders: science and practice. Baltimore: Maryland: Brookes Publishing Co.; in press

Kodituwakku PW, Adnams CM, Hay A, Kitching AE, Burger E, Kalberg WO, Viljoen DL, May PA. Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. J Stud Alcohol 2006a;67:502–509. [PubMed: 16736069]

Kodituwakku PW, Adnams CM, Hay A, Kitching AE, Burger E, Kalberg WO, Viljoen DL, May PAb. Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. J Stud Alcohol 2006b;67:502–509. [PubMed: 16736069]

Kodituwakku PW, Kalberg W, May PA. The effects of prenatal alcohol exposure on executive functioning. Alcohol Res Health 2001a;25:192–198. [PubMed: 11810957]

Kodituwakku PW, May PA, Clericuzio CL, Weers D. Emotion-related learning in individuals prenatally exposed to alcohol: an investigation of the relation between set shifting, extinction of responses, and behavior. Neuropsychologia 2001b;39:699–708. [PubMed: 11311300]

Kopera-Frye K, Dehaene S, Streissguth AP. Impairments of number processing induced by prenatal alcohol exposure. Neuropsychologia 1996;34:1187–1196. [PubMed: 8951830]

Lee MH, Rabe A. Infantile handling eliminates reversal learning deficit in rats prenatally exposed to alcohol. Alcohol 1999;18:49–53. [PubMed: 10386665]

Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Les enfants de parents alcooliques: anomailes observees a propos de 127 cas. Ouest Med 1968;25:476–487.

Levine S. A further study of infantile handling and adult avoidance learning. J Pers 1956;25:70–80. [PubMed: 13368033]

Levine S. Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology 2005;30:939–946. [PubMed: 15958281]

Levine S, Alpert M, Lewis GW. Infantile experience and the maturation of the pituitary adrenal axis. Science 1957;126:1347. [PubMed: 13495470]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Loomes C, Rasmussen C, Pei J, Manji S, Andrew G. The effect of rehearsal training on working memory span of children with fetal alcohol spectrum disorder. Res Dev Disabil 2008;29:113–124. [PubMed: 17317098]

Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. Am J Med Genet C Semin Med Genet 2004;127C:42–50. [PubMed: 15095471]

Lyon, GR.; Rumsey, JM. Neuroimaging: A window to the neurological foundations of learning and behavior in children. Baltimore: Paul H. Brookes Publishing Co.; 1996.

Mareschal, D.; Johnson, MH.; Sirois, S.; Spratling, MW.; Thomas, MS.; Westermann, G. Neuroconstructivism: How the brain constructs cognition. Oxford; Oxford University Press; 2007.

Mattson SN, Gramling L, Delis DC, Jones KL, Riley EP. Global-local processing in children prenatally exposed to alcohol. Child Neuropsychol 1996;2:165–175.

Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res 1998;22:279–294. [PubMed: 9581631]

Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. J Pediatr 1997;131:718–721. [PubMed: 9403652]

May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL, Robinson LK, Khaole NC, Snell C, Kalberg WO, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007;88:259–271. [PubMed: 17127017]

McClelland MM, Morrison FJ, Holmes DL. Children at risk for early academic problems: The role of learning-related social skills. Early Child Res Q 2000;15:307–329.

McGee CL, Fryer SL, Bjorkquist OA, Mattson SN, Riley EP. Deficits in social problem solving in adolescents with prenatal exposure to alcohol. Am J Drug Alcohol Abuse 2008;34:423–431. [PubMed: 18584572]

Medina AE, Krahe TE, Ramoa AS. Restoration of neuronal plasticity by a phosphodiesterase type 1 inhibitor in a model of fetal alcohol exposure. J Neurosci 2006;26:1057–1060. [PubMed: 16421325]

Mischel W, Shoda Y, Rodriguez MI. Delay of gratification in children. Science 1989;244:933–938. [PubMed: 2658056]

Mothes HK, Opitz B, Werner R, Clausing P. Effects of prenatal ethanol exposure and early experience on home-cage and open-field activity in mice. Neurotoxicol Teratol 1996;18:59–65. [PubMed: 8700044]

O'Connor MJ, Frankel F, Paley B, Schonfeld AM, Carpenter E, Laugeson EA, Marquardt R. A controlled social skills training for children with fetal alcohol spectrum disorders. J Consult Clin Psychol 2006;74:639–648. [PubMed: 16881771]

Oesterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H. Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and attention deficit/hyperactivity disorder: a controlled pilot study. J Child Adolesc Psychopharmacol 1998;8:39–48. [PubMed: 9639078]

Paley B, O'Connor MJ. Intervention for individuals with fetal alcohol spectrum disorders: treatment approaches and case management. Dev Disabil Res Rev 2009;15:258–267. [PubMed: 19731383]

Pinker, S. The language instinct. New York: William Morrow and Company, Inc.; 1994.

Pondiki S, Stamatakis A, Fragkouli A, Philippidis H, Stylianopoulou F. Effects of neonatal handling on the basal forebrain cholinergic system of adult male and female rats. Neuroscience 2006;142:305–314. [PubMed: 16905266]

Posner MI, Rothbart MK. Influencing brain networks: implications for education. Trends Cogn Sci 2005;9:99–103. [PubMed: 15737817]

Posner, MI.; Rothbart, MK. Educating the human brain. Washington, D.C.: American Psychological Association; 2007.

Premji S, Benzies K, Serrett K, Hayden KA. Research-based interventions for children and youth with a Fetal Alcohol Spectrum Disorder: revealing the gap. Child Care Health Dev 2007;33:389–397. discussion 398-400. [PubMed: 17584393]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Quartz SR, Sejnowski TJ. The neural basis of cognitive development: a constructivist manifesto. Behav Brain Sci 1997;20:537–556. discussion 556-596. [PubMed: 10097006]

Rasmussen C, Bisanz J. Executive Functioning in Children with Fetal Alcohol Spectrum Disorders: Profiles and Age-Related Differences. Child Neuropsychol 2008;15:1–15.

Renner, MJ.; Rosenzweig, MR. Enriched and impoverished environments: Effects on brain and behavior. New York: Springer; 1987.

Riley EP, Mattson SN, Li TK, Jacobson SW, Coles CD, Kodituwakku PW, Adnams CM, Korkman MI. Neurobehavioral consequences of prenatal alcohol exposure: an international perspective. Alcohol Clin Exp Res 2003;27:362–373. [PubMed: 12605086]

Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. Exp Biol Med (Maywood) 2005;230:357–365. [PubMed: 15956765]

Roebuck TM, Mattson SN, Riley EP. Interhemispheric transfer in children with heavy prenatal alcohol exposure. Alcohol Clin Exp Res 2002;26:1863–1871. [PubMed: 12500111]

Room R. Fetal alcohol syndrome: a biography of a diagnosis. Lancet 2005;365:1999–2000.

Rosenzweig MR. Environmental complexity, cerebral change, and behavior. Am Psychol 1966;21:321–332. [PubMed: 5910063]

Rosenzweig MR, Krech D, Bennett EL, Diamond MC. Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. J Comp Physiol Psychol 1962;55:429–437. [PubMed: 14494091]

Rueda MR, Rothbart MK, McCandliss BD, Saccomanno L, Posner MI. Training, maturation, and genetic influences on the development of executive attention. Proc Natl Acad Sci USA 2005;102:14931–14936. [PubMed: 16192352]

Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, Hanson JW, Graham JM Jr. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology 1997;56:317–326. [PubMed: 9451756]

Sari Y, Gozes I. Brain deficits associated with fetal alcohol exposure may be protected, in part, by peptides derived from activity-dependent neurotrophic factor and activity-dependent neuroprotective protein. Brain Res Rev 2006;52:107–118. [PubMed: 16488478]

Savage, DD.; Chavez, J.; Aramijo, L.; Rosenzweig, MR. Prenatal ethanol exposure alters Histamine H_3 receptor mediated neurotransmission in adult offspring. Paper presented at: 32nd Scientific Conference of the Research Society on Alcoholism; San Diego, California. 2009.

Schonfeld AM, Mattson SN, Riley EP. Moral maturity and delinquency after prenatal alcohol exposure. J Stud Alcohol 2005;66:545–554. [PubMed: 16240562]

Sirois S, Spratling M, Thomas MS, Westermann G, Mareschal D, Johnson MH. Precis of neuroconstructivism: how the brain constructs cognition. Behav Brain Sci 2008;31:321–331. discussion 331-356. [PubMed: 18578929]

Streissguth AP, Bookstein FL, Barr HM, Press S, Sampson PD. A fetal alcohol behavior scale. Alcohol Clin Exp Res 1998;22:325–333. [PubMed: 9581636]

Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004;25:228–238. [PubMed: 15308923]

Streissguth AP, O'Malley K. Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. Semin Clin Neuropsychiatry 2000;5:177–190. [PubMed: 11291013]

Thomas JD, Garrison M, O'Neill TM. Perinatal choline supplementation attenuates behavioral alterations associated with neonatal alcohol exposure in rats. Neurotoxicol Teratol 2004;26:35–45. [PubMed: 15001212]

Thomas JD, La Fiette MH, Quinn VR, Riley EP. Neonatal choline supplementation ameliorates the effects of prenatal alcohol exposure on a discrimination learning task in rats. Neurotoxicol Teratol 2000;22:703–711. [PubMed: 11106863]

Thomas SE, Kelly SJ, Mattson SN, Riley EP. Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls. Alcohol Clin Exp Res 1998;22:528–533. [PubMed: 9581664]

Uecker A, Nadel L. Spatial locations gone awry: object and spatial memory deficits in children with fetal alcohol syndrome. Neuropsychologia 1996;34:209–223. [PubMed: 8868278]

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Vaglenova J, Pandiella N, Wijayawardhane N, Vaithianathan T, Birru S, Breese C, Suppiramaniam V, Randal C. Aniracetam reversed learning and memory deficits following prenatal ethanol exposure by modulating functions of synaptic AMPA receptors. Neuropsychopharmacology 2008;33:1071–1083. [PubMed: 17609677]

van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nat Rev Neurosci 2000;1:191–198. [PubMed: 11257907]

Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, et al. The sequence of the human genome. Science 2001;291:1304–1351. [PubMed: 11181995]

Vygotsky, LS. Mind in Society: The development of higher psychological processes. Cambridge, Mass: Harvard University Press; 1978.

Weinberg J, Kim CK, Yu W. Early handling can attenuate adverse effects of fetal ethanol exposure. Alcohol 1995;12:317–327. [PubMed: 7546327]

Weinberg J, Sliwowska JH, Lan N, Hellemans KG. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J Neuroendocrinol 2008;20:470–488. [PubMed: 18266938]

Westermann G, Mareschal D, Johnson MH, Sirois S, Spratling MW, Thomas MS. Neuroconstructivism. Dev Sci 2007;10:75–83. [PubMed: 17181703]

Whaley SE, O'Connor Mj, Gunderson B. Comparison of the adaptive functioning of children prenatally exposed to alcohol to a nonexposed clinical sample. Alcohol Clin Exp Res 2001;25:1018–1024. [PubMed: 11505027]

Wiesel TN, Hubel DH. Effects of Visual Deprivation on Morphology and Physiology of Cells in the Cats Lateral Geniculate Body. J Neurophysiol 1963;26:978–993. [PubMed: 14084170]

Wilkemeyer MF, Chen SY, Menkari CE, Sulik KK, Charness ME. Ethanol antagonist peptides: structural specificity without stereospecificity. J Pharmacol Exp Ther 2004;309:1183–1189. [PubMed: 14762101]

Will BE, Rosenzweig MR, Bennett EL, Hebert M, Morimoto H. Relatively brief environmental enrichment aids recovery of learning capacity and alters brain measures after postweaning brain lesions in rats. J Comp Physiol Psychol 1977;91:33–50. [PubMed: 838916]

Williams, MS.; Shellenberger, S. How does the engine run? A leader's guide to the alert program. Albuquerque, New Mexico: Therapyworks Inc.; 1996.

Zhou FC, Fang Y, Goodlett C. Peptidergic agonists of activity-dependent neurotrophic factor protect against prenatal alcohol-induced neural tube defects and serotonin neuron loss. Alcohol Clin Exp Res 2008;32:1361–1371. [PubMed: 18565153]