Fetal Alcohol Syndrome

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Abstract

Maternal alcohol consumption during pregnancy is known to produce a spectrum of morphological and neurocognitive outcomes in the offspring. The most severely affected on the spectrum exhibit a cluster of birth defects called fetal alcohol syndrome, which is characterized by a unique pattern of anomalies on the

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face, prenatal and/or postnatal growth deficiency, and evidence of central nervous system (CNS) dysfunction (Jones et al, Lancet 1:1267–1271, 1973). The characteristic pattern of malformations on the face includes a smooth philtrum, thin upper lip, and short palpebral fissures (see Fig. 1). Children with FASD are usually small in stature, with their height and weight falling below the 10th percentile. The deleterious effects of alcohol on the central nervous system are evidenced by microcephaly and cognitive and behavioral deficits. Children with prenatal alcohol exposure have also been observed to exhibit birth defects involving other systems such as cardiac (e.g., atrial and ventricular septal defects), skeletal (e.g., clinodactyly and camptodactyly), ocular (e.g., strabismus), and auditory (e.g., conductive hearing loss). However, the majority of children on the spectrum display only some or none of the above physical features but exhibit evidence of CNS dysfunction. The term, "alcohol-related neurodevelopmental disorder" (ARND), is used to label neurodevelopmental difficulties in those alcohol-exposed children without clinically discernable physical anomalies (Stratton et al (eds) Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment. National Academy Press, Washington, DC, 1996). Although not a diagnostic label, the term "fetal alcohol spectrum disorders" (FASDs) has been introduced to denote the full spectrum of morphological and neurocognitive outcomes resulting from prenatal alcohol exposure. While estimated prevalence rates of FAS range from .5 to 2 cases per 1,000 live births, the rate of FASD is estimated at 1 per 100 (Sampson et al, Teratology 56:317–326, 1997).

Keywords

Antisaccades · Attention and executive functions · Attention-deficit/hyperactivity disorder (ADHD) · Blood oxygen level-dependent (BOLD) response patterns · Cambridge neuropsychological test automated battery (CANTAB) · Diffusion tensor imaging (DTI) · Digit span test · Eyeblink conditioning · Fetal alcohol syndrome · Intellectual function · Neuropsychological model · Prosaccades · Social cognition · Wisconsin card sorting test

Introduction

Maternal alcohol consumption during pregnancy is known to produce a spectrum of morphological and neurocognitive outcomes in the offspring. The most severely affected on the spectrum exhibit a cluster of birth defects called fetal alcohol syndrome, which is characterized by a unique pattern of anomalies on the face, prenatal and/or postnatal growth deficiency, and evidence of central nervous system (CNS) dysfunction (Jones et al. 1973). The characteristic pattern of malformations on the face includes a smooth philtrum, thin upper lip, and short palpebral fissures (see Fig. 1). Children with FASD are usually small in stature, with their height and weight falling below the 10th percentile. The deleterious effects of alcohol on the central nervous system are evidenced by microcephaly

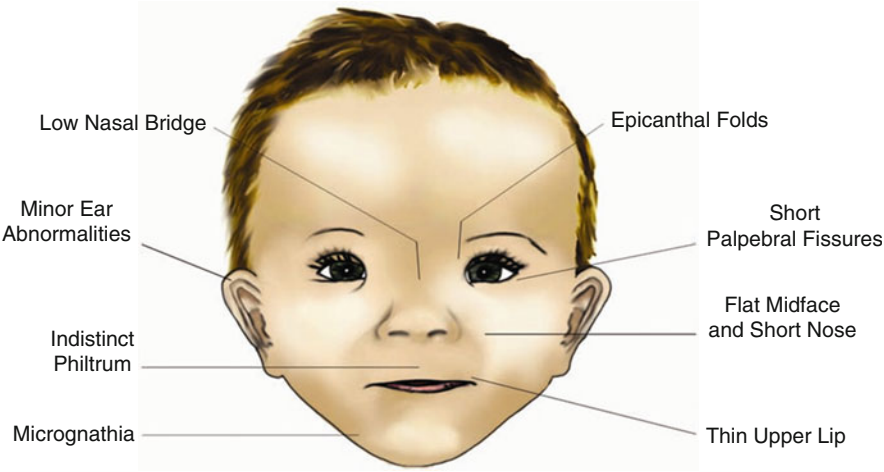

Fig. 1 Facial anomalies commonly observed in children with heavy prenatal alcohol exposure (Reprinted with permission from Warren, K.R.; Hewitt, B.G.; Thomas, J.D. "Fetal alcohol spectrum disorders: Research challenges and opportunities," Alcohol Research & Health, Vol 34(1):4–14, 2011)

and cognitive and behavioral deficits. Children with prenatal alcohol exposure have also been observed to exhibit birth defects involving other systems such as cardiac (e.g., atrial and ventricular septal defects), skeletal (e.g., clinodactyly and camptodactyly), ocular (e.g., strabismus), and auditory (e.g., conductive hearing loss). However, the majority of children on the spectrum display only some or none of the above physical features but exhibit evidence of CNS dysfunction. The term, "alcohol-related neurodevelopmental disorder" (ARND), is used to label neurodevelopmental difficulties in those alcohol-exposed children without clinically discernable physical anomalies (Stratton et al. 1996). Although not a diagnostic label, the term "fetal alcohol spectrum disorders" (FASDs) has been introduced to denote the full spectrum of morphological and neurocognitive outcomes resulting from prenatal alcohol exposure. While estimated prevalence rates of FAS range from .5 to 2 cases per 1,000 live births, the rate of FASD is estimated at 1 per 100 (Sampson et al. 1997).

In the absence of clinically observable malformations, identification of children with ARND remains a daunting task. Particularly, clinicians find it difficult to distinguish children with ARND from other clinical groups such as attention-deficit/hyperactivity disorder, conduct disorder, and learning disability. Therefore, the question of whether alcohol-exposed children display a syndrome-specific neurobehavioral phenotype has attracted considerable attention over the last 35 years because identification of a pattern of behavior uniquely associated with prenatal alcohol exposure will aid in diagnosing ARND. Defining a behavioral phenotype in FASD will also inform the development of intervention programs for alcohol-affected children.

Neurobehavioral studies of FASD have now yielded sufficient data for formulating a reasonable hypothesis on the neurobehavioral phenotype of FASD. Particularly, the studies that employed probes to investigate elementary functions such as orienting responses, eyeblink conditioning, and backward masking have shed light on the cognitive mechanisms underlying the cognitive-behavioral profile of alcohol-affected children. In parallel with the advances in understanding the neurobehavioral phenotype, basic science research has made impressive strides in elucidating the neurobiological mechanisms underlying alcohol's teratogenic effects and in evaluating potential pharmacological agents to counteract those effects. Furthermore, recent developments in neuroimaging have allowed investigators to probe the sources of neurocognitive difficulties at a neuronal level in alcohol-exposed individuals.

To organize the topics covered in this chapter, we use a causal modeling framework, which has proven useful in understanding biological and environmental factors contributing to neurodevelopmental disorders such as autism and dyslexia (Morton 2004; Morton and Frith 1995). As Fig. 2 shows, the interactive effects of prenatal alcohol exposure, genetic/epigenetic factors, and environmental conditions, including nutrition, lead to atypical brain development in children with FASD. Dynamic interactions between postnatal experiences and defective brain hardware contribute to anomalous developmental trajectories of cognitive functions, both at elementary and complex levels. These cognitive difficulties and nonoptimal environmental conditions lead to the development of a range of disabilities at the behavioral level such as academic failures and poor social skills.

In the first two sections of this chapter, we will review animal studies and neuroimaging studies of FASD to highlight the fact that specific brain regions such as the cerebellum, hippocampus, and caudate are more sensitive to the teratogenic effects of alcohol than the other regions of the brain. Investigators have turned to the study of elementary cognitive functions subserved by these regions because such elementary functions may serve as "biomarkers" of alcohol-induced brain damage.

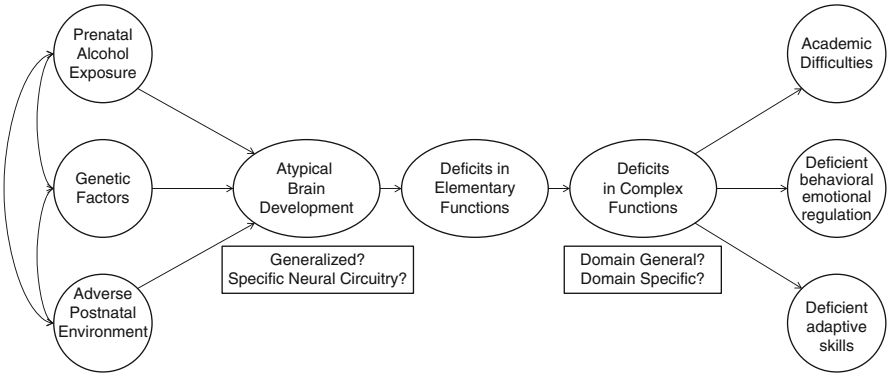

Fig. 2 A neuropsychological model of cognitive and behavioral outcomes of prenatal alcohol exposure (Reprinted from *Neuroscience and Biobehavioral Reviews*, 31[2], Kodituwakku, P.W. Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: A review [p. 194]. Copyright 2007, with permission from Elsevier)

In section "Elementary Functions," we will review the literature on a number of elementary functions that have been investigated in children with FASD (e.g., orienting responses, associative learning, and saccades). In the next section, we will focus on the data generated by the studies of complex cognitive skills such as executive function and language. In section "Elementary Functions," we will examine the findings from the studies that have utilized parent- and teacher-rated questionnaires to assess behavioral and emotional functioning in alcohol-affected children. In section "An Integrative Framework," we will present an integrative framework to summarize the data from different levels of analysis. In the final section, we will discuss the implications of this framework for the development of interventions for children with FASD.

Animal Studies

Researchers have been successful at reproducing one or several morphological or behavioral characteristics of FASD in a number of animal models including nonhuman primates, rodents (e.g., rats, mice), large animals (e.g., sheep), and simple organisms (e.g., fish) (Cudd 2005; Wilson and Cudd 2011). Because animal models allow investigators to systematically manipulate exposure (e.g., quantity, timing, and frequency), genetic, and environmental variables, these models have been employed to demonstrate the specificity of alcohol's teratogenesis (Sulik et al. 1981) to probe the mechanisms underlying the teratogenic effects (Goodlett and Horn 2001) and to test the efficacy of behavioral and pharmacological interventions to ameliorate these effects (Hannigan et al. 2007; Kelly et al. 2009).

In the early 1980s, Sulik and colleagues (Sulik and Johnston 1983; Sulik et al. 1981) demonstrated that acute exposure to alcohol during gastrulation stages of embryonic development led to a range of malformation including microcephaly, short palpebral fissures, and deficiencies in the philtral region. Sulik (2005) also observed alcohol-induced deficiencies in the forebrain including the corpus callosum, basal ganglia, hippocampus, and anterior cingulate. Using the imaging procedures, such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), these investigators have confirmed and extended the aforementioned neuroanatomical findings. Godin et al. (2010) found that acute heavy-dose exposure on gestational day 7 (GD7) resulted in median facial and forebrain deficiencies. Alcohol-induced birth defects, including growth restrictions, facial anomalies, and defects in the central nervous system, have also been demonstrated in nonhuman primate models of FASD (Astley et al. 1999; Clarren et al. 1988). Exposure during epithelial cell proliferation and migration, which occur from gestation day 12–21 in the rat and 7–21 weeks of gestation in the human, has been shown to disrupt the development of cerebral cortex as evidenced by decreased brain size (Guerri et al. 2009) and the formation of specific structures (e.g., corpus callosum). Animal studies modeling alcohol exposure during the third trimester of human gestation have shown evidence of neuronal loss in multiple structures including the hippocampus and cerebellum (Hunt et al. 2009; West et al.

1990). In nonhuman primates, researchers have demonstrated the alcohol-induced deficits in higher-level skills such as object permanence (Clarren et al. 1992). Animal models of FASD have also revealed that prenatal alcohol exposure disrupts neurotransmitter systems (e.g., amino acid and biogenic amine systems) (Valenzuela et al. 2011).

Thus, animal studies of fetal alcohol spectrum disorders have demonstrated that specific regions of the brain are more vulnerable to the deleterious effects of alcohol. Researchers have also developed and validated sensitive measures to assay the behavioral outcomes of alcohol-induced brain damage. For example, associative learning paradigms, such as eyeblink conditioning, have been used to assess alcohol's teratogenic effects on the cerebellum. Brown et al. (2008) found that the rate at which conditioned eyeblink responses were acquired diminished proportionate to cerebellar Purkinje cell loss due to alcohol. Similarly, the Morris Water Maze has been found to be a sensitive measure of learning deficits resulting from alcohol-induced hippocampal damage (Sutherland et al. 2000). As will be shown in section "Elementary Functions," these functional measures have been successfully used with humans. Animal models of FASD have also considerably advanced our knowledge of the mechanisms underlying alcohol-induced damage in the developing brain. It is now known that a number of mechanisms (e.g., disruption of glial development, oxidative stress, and interruptions of neurotransmitters) contribute to alcohol-induced brain anomalies (Goodlett and Horn 2001).

As we have discussed in detail elsewhere (Kodituwakku and Kodituwakku 2011), animal research has contributed considerably to our knowledge of potential behavioral strategies and pharmacological agents that can be used to ameliorate alcohol-induced deficits (Hannigan et al. 2007). There is evidence that procedures such as neonatal handling (Lee and Rabe 1999; Weinberg et al. 1995), environmental enrichment (Hannigan et al. 1993), and rehabilitative training (Klintsova et al. 1998, 2002) produce behavioral changes in alcohol-exposed rodents. The neonatal handling procedure usually involves separating pups from the dam for a brief period and stimulating them tactilely. Although this procedure appears to eliminate deficits in response inhibition (Gallo and Weinberg 1982) and reversal learning (Lee and Rabe 1999), it has been shown to be ineffective in the amelioration of spatial navigation deficits (Gabriel et al. 2002) or in the attenuation of hypothalamic-pituitary-adrenal hyperresponsiveness associated with prenatal alcohol exposure (Gabriel et al. 2000). Environmental enrichment procedures, such as the provision of increased opportunities for social interactions with conspecifics, enhancement of sensory experiences through increasing the variety and complexity of sensory input, and creation of an environment that promotes greater locomotor activity, have been found to reduce alcohol-induced behavioral deficits (Hannigan et al. 2007).

Neuroimaging

Consistent with the aforementioned findings from the animal models, neuroimaging studies have revealed structural brain anomalies in alcohol-exposed children. Using voxel-based morphometry, Sowell et al. (2001) found that, compared to controls,

those with FASD showed relative increases in the gray matter and decreases in the white matter in the perisylvian cortices of the temporal and parietal lobes. O'Hare et al. (2005) observed significant structural changes in the cerebellum associated with prenatal alcohol exposure, particularly reductions in the midline sagittal areas of the anterior vermis and posterior-inferior vermis.

A number of studies have reported abnormalities of the corpus callosum, ranging from microstructural anomalies in the posterior tracts (Wozniak et al. 2009) to partial or complete agenesis (Riley et al. 1995). Bookstein et al. (2002) reported that adults with prenatal alcohol exposure differed from controls on morphometric indices of the corpus callosum (e.g., midline shape). Diffusion tensor imaging (DTI) studies have provided evidence for altered microstructure integrity in specific regions of the corpus callosum in individuals with FASD such as isthmus (Wozniak et al. 2006) and the lateral aspect of the splenium (Sowell et al. 2008). Some investigators have observed differences in both the genu and splenium of the corpus callosum (Lebel et al. 2008; Ma et al. 2005). Others have observed anomalies in the white matter innervating a number of areas, including the bilateral medial and occipital lobes (Fryer et al. 2009), lateral temporal lobes (Sowell et al. 2008), basal ganglia, and thalamus (Lebel et al. 2008).

A number of investigators have observed structural and neurochemical differences associated with prenatal alcohol exposure in the caudate (Archibald et al. 2001; Cortese et al. 2006). Cortese et al. (2006) observed volumetric reductions as well as elevated metabolite ratio of *N*-acetyl-asparate to creatine (NAA/cr), which is an index of neural function, in the caudate nucleus of alcohol-exposed children. However, Fagerlund et al. (2006) found that metabolite ratios, NAA/cr and NAA/cho (*N*-acetyl-asparate to choline), were lower in alcohol-exposed children compared to controls in a number of regions, including the parietal and frontal cortices, corpus callosum, and thalamus (Fagerlund et al. 2006).

Researchers have recently utilized functional imaging methodologies such as magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to investigate neural activation patterns in children with FASD during performances of working memory, response inhibition, and verbal learning tasks (Fryer et al. 2007; Malisza et al. 2005; Sowell et al. 2007; Stephen et al. 2011). The fMRI studies have consistently shown that alcohol-exposed children exhibit blood oxygen level-dependent (BOLD) response patterns different from controls during task performance. For example, Malisza et al. (2005) found an overall increase in inferior-medial frontal activity in children with FASD during performance of a working memory task. Typically developing control children, on other hand, displayed increased BOLD responses in superior frontal and parietal regions. Such findings have been interpreted as indicative of inefficiency of neural circuitries or use of compensatory strategies in alcohol-exposed participants. Similarly, MEG studies have provided evidence of inefficient processing of sensory information by children with FASD (Stephen et al. 2011).

Thus, convergent evidence from animal models and brain imaging studies indicates that specific brain regions or specific neural circuitries are selectively affected in children and adults with FASD. In view of these findings, we can ask the question: Do individuals with FASD exhibit selective impairments in elementary or higher-order functions?

Elementary Functions

In a recent paper, we used the term "elementary" to refer to those simple functions that emerge early in development such as associative learning (e.g., eyeblink conditioning) and reflexive responses (e.g., prosaccades) (Kodituwakku et al. 2011). The delineation of brain function at an elementary level is comparable to the characterization of intermediate phenotypes or endophenotypes of neurogenetic disorders. As we pointed out, the study of alcohol's teratogenic effects on elementary functions allows generalizing animal research to humans since both animals and human share numerous elementary processes (e.g., eyeblink conditioning, fear conditioning, etc.). In this chapter, we briefly examine the effects of prenatal alcohol exposure on three elementary functions: eyeblink conditioning, prosaccades, and orienting responses. Since these functions are subserved by neural circuitries that mature early (Cheng et al. 2008; Herbert et al. 2003), they have been employed in the study of early markers of prenatal alcohol exposure in children.

Eyeblink Conditioning (EBC)

EBC is a widely used paradigm of associative learning in which the eyeblink reflex is conditioned to a neutral stimulus (e.g., tone) that predicts an unconditioned stimulus (e.g., puff of air). It has been established that EBC engages a neural circuitry involving the cerebellum and the hippocampus (Cheng et al. 2008), which is highly vulnerable to the effects of alcohol. Therefore, EBC has been used as a biomarker of alcohol's teratogenecity in animal models (Brown et al. 2008; Stanton and Goodlett 1998). These studies found that alcohol-exposed animals show impairments at the acquisition of EBC, as indexed by later-onset or later-peaked conditioned responses. Consistent with these results, human studies have shown that children with FASD are slow at the acquisition of EBC (Coffin et al. 2005; Jacobson et al. 2008).

Prosaccades

Saccades refer to rapid eye movements that shift the line of sight from one point of fixation to another in the visual field (Leigh and Kennard 2004). Like eyeblink conditioning, saccades are known to be subserved by a well-delineated neural circuitry that comprises early maturing (e.g., brainstem, cerebellum) as well as late maturing (e.g., dorsolateral prefrontal cortex) regions of the brain (Munoz and Everling 2004). In a typical saccade experiment, participants are instructed to look from a central fixation point toward a sudden-onset target on the periphery (prosaccades) or to look away from the peripheral target toward its mirror image location (antisaccades). It is now established that a sudden-onset stimulus captures our attention, generating a reflexive saccade toward it (Munoz and Everling 2004). In contrast, antisaccades require a deliberate effort to inhibit the prepotent ocular-motor response of looking at the sudden-onset stimulus. There is evidence that the saccade

network in the brainstem and cerebellum is involved in controlling accuracy and velocity of saccades and the higher-order cortical regions (frontal cortex), in programming them (Salman et al. 2006). Researchers have obtained evidence that the saccadic network is sensitive to the effects of prenatal alcohol exposure (Green et al. 2009; Green et al. 2007). Children with FASD have been found to show longer reaction times than controls during performance of prosaccades, suggesting a deficit in saccade initiation.

Orienting Responses

Since the vagus nerve responds rapidly to metabolic changes in the brain by regulating the heart's pacemaker (Porges 1998), investigators have used heart rate as a physiological index of information processing (Reed et al. 1999). Kable and Cole (2004) investigated encoding of auditory and visual stimuli in 6-month-old infants with prenatal alcohol exposure by assessing changes in heart rate (e.g., deceleration). These investigators reported that alcohol-exposed infants responded slower to stimuli (orienting responses) but showed higher levels of arousal compared to controls. The finding of slowness in orienting responses is consistent with the findings from a study reported by Jacobson (1998), who investigated information processing in infants exposed to three different teratogens: polychlorinated biphenyls (PCB), alcohol, and cocaine. The alcohol-exposed group was found to show slower rates of information processing compared to the other exposed group.

In summary, slowness of responding to novel stimuli, processing information, and acquiring responses emerges as the main finding from the above studies of elementary functions.

Complex Functions

Complex functions refer to those cognitive skills that require deliberate attention. These include intellectual functions, executive control, language, memory and learning, social cognition, and number processing.

Intellectual Functions

Studies of intellectual functioning in children with FASD have revealed that prenatal alcohol exposure is associated with diminished IQ scores, with average IQs of this population falling within the borderline to low average ranges (Mattson and Riley 1998). Given that tests of intellectual functioning, such as the Wechsler Intelligence Scale for Children (WISC), comprise subtests assessing a wide range of intellectual abilities, IQ test results provide a general picture of a child's cognitive profile. If prenatal alcohol exposure leads to selective damage to some functions, then one can expect an uneven profile of subtest scores, particularly a discrepancy between verbal

comprehension and perceptual organization. In a review of literature covering both single case and group studies of intellectual functioning in FASD, Mattson and Riley (1998) concluded that both verbal and nonverbal abilities in alcohol-exposed children were equally diminished. Consistent with this pattern, Adnams et al. (2001) found that children with FASD showed greater difficulty with intellectually more demanding subtests of the Griffith Scales of Mental Development such as verbal and visual reasoning than with less demanding ones such as gross motor behavior.

Attention and Executive Functions

Attention and executive functions in children with FASD have been the focus of numerous studies because prenatal alcohol exposure has been found to be associated with deficits in these areas (Lee et al. 2004; Nanson and Hiscock 1990). Researchers have documented that children with FASD display deficient performances on different components of attention, such as vigilance and sustained attention (Lee et al. 2004). Coles et al. (1997) compared to children with FASD and attention-deficit/hyperactivity disorder (ADHD) on a battery of tests assessing four components of attention: Focus, Sustain, Encode, and Shift. These investigators found that the FASD group exhibited greater difficulty in Encode (i.e., temporarily holding information in memory while performing a mental operation upon it) and Shift (e.g., shifting attention from one stimulus dimension to another in response to feedback) components than in Focus (i.e., the ability to concentrate on a particular stimulus or a task) and Sustain (i.e., the ability to stay on a task) components. The ADHD group displayed a distinct profile, which was notable for greater difficulty with Focus and Sustain than with the other components.

An examination of the tests utilized to assess the Encode and the Shift components, the Digit Span test and the Wisconsin Card Sorting test, respectively, reveals that they both demand higher-level cognitive control or executive functions. For example, on the digit span backward condition, the examinee is required to listen to strings of digits of increasing length and to recite them in the reverse order. To succeed on this task, one has to hold and manipulate digits in working memory while inhibiting prepotent responses (the habit of repeating digits forward as when memorizing a telephone number). Similarly, on the Wisconsin Card Sorting test, the participant is required to sort cards by a specific stimulus dimension and then shift attention to sort them by a different stimulus dimension using the examiner's feedback. This type of set shifting, referred to as extra-dimensional set shifting, involves both working memory and response inhibition.

Researchers have demonstrated that children with FASD display impaired performance on a number of other tasks that involve working memory and response inhibition. For example, children with FASD are deficient in cognitive planning, as assessed by look-ahead puzzles such as the Progressive Planning test (Kodituwakku et al. 1995; Aragon et al. 2008), the California Tower Task (Mattson et al. 1999), and the Stockings of Cambridge (Green et al. 2009). These puzzles require participants to move a number of balls or disks from an initial position to a goal position under

the constraints of specific rules. Because the moves are constrained by rules, the examinee must plan ahead before making a response. Children with FASD have also been found to be deficient in nonverbal and verbal fluency (Kodituwakku et al. 2006b; Schonfeld et al. 2001) and multiple measures of concept formation (McGee et al. 2008).

Recently, a number of studies have directly examined working memory and response inhibition in children with FASD using test batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB). Green et al. (2009) reported that children with FASD were markedly impaired at the Visual Working Memory Test of the CANTAB. On this task, the FASD group made significantly more errors than did the control group. Noland et al. (2003) reported that children exposed to alcohol performed less well than controls on a tapping inhibition task. There is also evidence that alcohol-exposed children are deficient in inhibiting reflexive eye movements (antisaccades), a function that involves executive control (Green et al. 2007).

In summary, deficits in attention and executive skills have been consistently observed in children with prenatal alcohol exposure. There is also evidence that children with FASD display greater difficulty with more complex tasks of executive functioning than with less complex ones. Aragon et al. (2008) reported that alcohol-exposed children succeeded in solving simple planning problems that could be solved using perceptual strategies but demonstrated marked difficulty in solving those complex problems that involved holding and manipulating information in working memory. Kodituwakku et al. (2006b) found that the FASD group had greater difficulty with letter fluency than with category fluency. The letter fluency task involves the examinee generating words beginning with specific letters under certain constraints and hence is more demanding than the category fluency task, in which the examinee generates exemplars form a semantic category. Green et al. (2009) also have observed that children with FASD performed worse than the control group on a number of tests assessing executive functions, with group differences becoming pronounced with increased task complexity.

Learning and Memory

Several investigators have sought to delineate the patterns of learning and memory in children with FASDs using standardized tests (Kaemingk and Halverson 2000; Kaemingk et al. 2003; Willford et al. 2004) such as the Wide Range Assessment of Memory and Learning and the Children's Memory Scale. Kaemingk et al. (2003) found that the FASD group showed deficient performance on both verbal and visual learning tasks but was able to retain the limited information that they acquired. Willford et al. (2004) found learning deficits in a large cohort of adolescents with prenatal alcohol exposure who did not have significant morphological anomalies. Consistent with Kaemingk et al.'s finding, these investigators observed specific difficulty with encoding information in alcohol-affected children. Mattson and Roebuck (2002) also found deficits in verbal and nonverbal learning in children

with prenatal alcohol exposure, particularly in initial learning. It should be noted that the efficiency of initial learning is dependent on multiple variables such as attention, motivation, and strategy application.

In view of the evidence that the hippocampus is vulnerable to the effects of prenatal alcohol exposure, some investigators have investigated memory and learning in children with FASD using experimental tasks sensitive to hippocampal functioning. Hamilton et al. (2003) demonstrated that children with FASD were impaired at spatial learning and memory using a computerized (virtual) version of the Water Maze. Uecker and Nadel (1996) reported a study in which the Memory for Objects task, a test sensitive to hippocampal functioning, was administered to children with FASD. The results showed that the FASD group showed performance deficits at the delayed but not at the immediate, recall trial. These investigators also observed that the FASD group was impaired at non-hippocampal visual tasks, indicating a generalized pattern of visual spatial difficulties.

Accordingly, children with FASD seem to display deficits in the acquisition of both verbal and visual information, a finding commensurate with deficient verbal and performance IQ deficits in these children.

Language

Early studies of children with moderate levels of prenatal alcohol exposure failed to find significant deficits in language (Fried et al. 1992; Greene et al. 1990). In contrast, researchers have documented a wide range of language deficits in clinic-referred samples of children with higher levels of prenatal alcohol exposure. These include deficits in naming, grammatical and semantic abilities, phonological awareness, pragmatics, and expressive language. Children with FASD identified through population-based studies in South Africa and Italy have been found to show impairments of grammar comprehension (Adnams et al. 2001; Kodituwakku et al. 2006b).

Given that children with FASD often grow up in disruptive environments with limited language input and that their parents may have language-based learning disabilities, the extent to which environmental and genetic factors contribute to the above language deficits in this population of children is unknown. However, studies of older children who have received several years of schooling show greater difficulty with complex language tasks such as social communication and narrative discourse (Coggins et al. 2007) than with simple tasks such as reading.

Visual Perception and Visual Construction

Despite reports that children with FASD have visual impairments and ocular abnormalities, relatively little is known about object recognition and motion perception in alcohol-affected children. Uecker and Nadel (1996) found that children with FASD were relatively unimpaired at facial recognition but were markedly impaired at tests

assessing visual motor integration such as the Beery Visual Motor Integration and Clock Drawing tests. Mattson et al. (1996) reported that children with FASDs had greater difficulty than controls in copying and recalling local features of hierarchical stimuli, such as a large letter *D* (global) made up of small letters *y* (local features). In a recent study of early stages of visual processing in children with FASD, Verney (July 2011, personal communication) found that alcohol-affected children were slower than controls in letter recognition in a backward masking paradigm, a finding consistent with the reports of slow information processing in this population.

In summary, children with FASD appear to be unimpaired at simple perceptual tasks but are impaired at tasks that require visual motor integration. The FASD group may also be slower than controls in object recognition. The basis for the differential performance on global and local features is unknown.

Social Cognition

In view of the reports of poor social skills in children with FASD, the question of whether impaired social cognition contributes to these deficits has attracted the attention of numerous investigators. Bishop et al. (2007) contrasted performances of children with autism and FASD on the Autism Diagnostic Observation Schedule and found that the two groups exhibited distinctive patterns of impairments in social interaction and communication. While children with FASD did not have difficulty initiating social interactions and using nonverbal communication, they exhibited socially inappropriate behaviors and difficulty with peers. In other words, social deficits in children with FASD appear to be associated with poor self-regulation rather than with an impairment of social sense. Schonfeld et al. (2006, 2009) have obtained evidence that deficient executive functions in children with FASD are associated with reported deficits in social skills, which is consistent with the findings reported by Bishop et al. (2007). Rasmussen et al. (2009) found that children with FASD showed performance deficits on tests assessing theory of mind, which is a building block of social skills, and that these deficits were associated with impaired executive functioning.

McGee et al. (2009) found that children with FASD were deficient in social information processing. In this study, participants were required to view video vignettes depicting different social situations and then to respond to specific questions designed to tap social information processing. The results showed that children with FASDs had maladaptive processing patterns in both the generation and evaluation of responses in social situations. Greenbaum et al. (2009) compared children with FASD and ADHD on a battery of tests assessing social cognition and emotional processing with a view to delineating unique profiles associated with the two disorders. Results showed that the FASD group demonstrated weaker social cognition and facial affect identification than the ADHD and typically developing groups.

Thus, numerous investigators have documented that children with FASD have deficits in social cognition and that these deficits contribute to their social problems. A number of researchers have found that deficient social cognition in children with

FASD is linked to impairments of higher-level processes, particularly executive control skills and intellectual disabilities.

In summary, children with FASD have diminished intellectual functioning, with both verbal and visual abilities being equally affected. The studies that have investigated attention and executive functioning show that alcohol-exposed children exhibit pronounced performance deficits on tasks that demand higher levels of cognitive control. The studies of specific cognitive skills, such as memory, language, and social cognition, have demonstrated performance decrements with increased task complexity.

Parent- and Teacher-Rated Behaviors

A number of investigators have examined behavioral data on children with FASD, which were acquired through rating scales or interviews with caregivers, to determine if there is a syndrome-specific profile. Streissguth et al. (1998) administered a behavioral checklist to parents and caregivers of 472 individuals with prenatal alcohol exposure. The results of this study helped the investigators identify 36 items from the checklist that were considered to be associated with the behavioral phenotype of FASD. These included the items designed to measure behaviors such as overreacting to situations, being unaware of consequences of their actions, talking a lot, but saying a little, interrupting others, and having difficulty completing tasks. It should be noted that these behaviors index poor self-regulation, which is seen in a number of neurodevelopmental disorders including attention-deficit/hyperactivity disorder (ADHD). As mentioned, Schonfeld et al. (2006, 2009) found that deficient social skills in children with FASD were related to executive control dysfunction.

Nash et al. (2006) compared children with FASD and ADHD on the Child Behavior Checklist and found that a number of items discriminated between the two groups: acting young, cruelty, absence of guilt, lying or cheating, stealing from home, and stealing outside the home. Thus, predominantly delinquent behaviors seem to characterize the behavioral phenotype associated with FASD. After eliminating the items referring to conduct problems from the above list, one item stood out as unique to FASD, namely, acting young. The behavior, acting young, can be considered to be consistent with diminished intellectual functioning and deficient executive control.

A methodological issue related to defining a behavioral phenotype based on reports by adult informants concerns the fact that environmental factors heavily influence the behavior of a child. Having experienced multiple life stressors, children with FASD seen in clinic settings often show numerous behavioral problems (Lynch et al. 2003). Therefore, the question of whether non-referred children with FASD who are living in stable home environments display a unique profile of behaviors has been raised. To answer this question, a questionnaire tapping disruptive behaviors was administered to a group of children with FASD identified through a population-based epidemiological study conducted in Italy (Kodituwakku et al. 2006a). Results showed that teachers rated children with FASD as having more inattentive behaviors

than controls and that these inattentive behaviors were associated with academic problems in these children. Increased incidence of inattentive behaviors in the classroom can be interpreted in terms of slow information processing and diminished intellectual functioning.

A number of studies have documented that children with FASD are deficient in adaptive skills that are essential for independent living, such as communication and socialization. Researchers have consistently found that children with FASD score lower than typically developing controls across different domains of functioning (Kalberg et al. 2006; Olson et al. 1998). A number of investigators, however, have reported that children with FASD show relatively greater deficits in socialization than in other domains, with social deficits becoming more pronounced when they reach adolescence (Thomas et al. 1998; Whaley et al. 2001). It is reasonable to hypothesize that social demands during adolescence dramatically increase since social interactions during this period of development involve the ability to coordinate a range of complex skills such as reading nonverbal cues and understanding metaphorical language and humor. As mentioned above, researchers have found that social skills in children with FASD are associated with executive control skills.

In summary, children with FASD have been rated by parents as showing behavioral problems such as overreaction to situations, failure to anticipate consequences, and impulsivity. These behaviors are related to executive control dysfunction. Children with FASD have been rated by teachers as being inattentive and acting young for their age. These observations are consistent with slow information processing and intellectual disabilities.

An Integrative Framework

As we suggested (Kodituwakku et al. 2011) recently, using a causal modeling approach to the study of developmental disorders such as fetal alcohol syndrome allows integrating information from different levels of analysis. In the above sections, we summarized the findings from basic science and neuroimaging studies of FASD, investigations targeting elementary and complex cognitive functions, and parent-rated questionnaires. Evidence converging from animal models and neuroimaging studies shows that some regions of the brain are more vulnerable to the teratogenic effects of alcohol. However, the studies of elementary and complex cognitive functions in children with FASD have revealed evidence of slow information processing and difficulty with simultaneously handing multiple pieces of information. It is reasonable to hypothesize that slow processing and difficulty with integrating multiple pieces of information are closely related. Slow processing of information at the neuronal level perhaps disrupts the formation of neural circuitries that support complex functions. Furthermore, rapid processing of information is essential for successful performance of complex tasks. It also appears that deficits in cognitive functioning lead to a range of behavioral problems, particularly acting young for age and poor regulatory behaviors. A question can be raised regarding why damage to specific regions of the brain lead to a generalized pattern of cognitive

and behavioral deficits. We have suggested that the answer to this question lies in a developmental neuroscience perspective, according to which damage to specific regions lead to generalized deficits through the processes of plasticity (Kodituwakku 2007).

Outlook

The characterization of the cognitive-behavioral phenotype of FASD as a generalized deficit in the processing and integration of information has specific implications for the development of behavioral interventions for alcohol-affected children. A number of strategies can be used in classroom settings to address diminished intellectual functioning and slow information processing. These include the use of concrete examples and the presentation of information at a slower rate. In particular, the provision of hands-on-experiences to children with FASD may prove to be a useful method. The finding that children with FASD are impaired at complex language tasks that involve pragmatics (Abkarian 1992) has implications for the planning speech therapy programs aimed at improving communication skills. Since executive control deficits contribute to difficulties in social communication, such a program may include strategies aimed at addressing executive control problems such as impulsivity and poor perspective taking. Clinical psychologists working with alcohol-affected children have also recognized the importance of addressing executive control difficulties as a part of social skills training programs. Investigators have also explored the utility of parent-child interaction therapy and neurocognitive rehabilitation in addressing behavioral and cognitive difficulties associated with executive dysfunction in children with FASD (Bertrand 2009).

The target of a burgeoning area of research has been to develop cognitive enhancing drugs using animal models of FASD (see Kodituwakku and Kodituwakku 2011). Researchers have obtained evidence that aniracetam, a cognitive enhancer, improved learning and memory in alcohol-exposed rodents (Vaglenova et al. 2008). Some investigators have explored the utility of ABT-239, a histamine H3 receptor, in the treatment of learning and memory deficits in alcohol-exposed animals (Savage et al. 2010). Thomas et al. (2004) have found that both prenatal and postnatal choline supplementation is effective in the reduction of alcohol-induced cognitive deficits. Therefore, it is reasonable to expect that future clinicians will be able to optimally combine cognition-enhancing drugs and experiential therapies in the treatment of cognitive and behavioral deficits in children with FASD.

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