Alcohol and Alcoholism

Effects on Brain and Development

Edited by

John H. Hannigan

Linda P. Spear

Norman E. Spear

Charles R. Goodlett

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Introduction: How Research on Alcohol and Alcoholism Has Informed Research on Developing Brains

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In theory, basic research on questions in the biomedical or biobehavioral sciences, such as how cells grow, or how neurons communicate biochemically, or how infants learn, provides the knowledge with which "real-life" problems can be solved. The knowledge is applied to the problems. In theory, research directly on clinical problems, such as abnormal cell growth, or alcoholism, or mental retardation, spawns methods and models and information that each illuminate the foundations of biology, physiology, and psychology. Solving problems leads to knowledge. In practice, both efforts in science operate simultaneously. Ideally, the basic and the clinical complement, inform, and facilitate each other.

This volume is an example of how well that interaction between basic and clinical research works. The questions and problems concern brain development and early learning, fetal alcohol effects, the acquisition of responses to alcohol, and alcoholism treatment. Because these are all very complex questions and problems, the answers and research are complex as well. In general, the chapters form a well focused collection of both human-clinical (chapters 1, 9, & 11) and basic-animal research (chapters 2 through 8 & 10). The research is both multidisciplinary and interdisciplinary.

The chapters are organized along several dimensions including ontogenetic, biobehavioral, and mechanistic aspects of responses to alcohol. In overview, chapters 1 through 5 discuss fetal alcohol effects; chapters 6 through 10 discuss factors affecting responses to alcohol, especially in young organisms (chapters 9 & 10); and chapter 11 describes community interventions for treatment of alcoholism. An important recurring theme common to chapters 2 and 4 through 7 is analysis of genetic factors that influence the neural and behavioral responses to alcohol.

The first five chapters present new research that draws a sharp focus on several of the defining principles of the field of teratology, in general, and of neurobehavioral teratology, in particular. Using studies of the effects of prenatal exposure to alcohol in humans and animals (in vivo models) and in tissue culture (in vitro models), the topics of these chapters serve as excellent examples of Wilson's principles applied to neurobehavioral teratology as defined by Vorhees (1986), including the principles of teratogenic response, of genetic and environmental determination, of specific mechanisms, target access (or critical organ), critical periods, and dose-response relationships. Furthermore, chapters 2, 3 and 4 illustrate the functional interrelatedness of mechanism(s) and critical periods for particular target tissues—even specific brain regions—in defining risk for teratogenesis.

Chapter 1 (Roebuck, Mattson & Riley) describes the state-of-the-art in our understanding of the relationships among structural central nervous system (CNS) abnormalities and neuropsychological dysfunction in children with fetal alcohol syndrome (FAS). In addition to providing a cogent clinical description of FAS as background for chapters 2 through 5, this research presents evidence that some CNS areas in children appear more sensitive to the teratogenic impact of alcohol than others *(principle of target access and principle of teratogenic response)*. It is valuable to recognize in this chapter the role that basic-animal research played in defining the neurobiological and behavioral hypotheses assessed in the clinical research (cf. Hannigan, 1996). That continuing influence of basic research, by Riley and his colleagues and others, reflects a key feature of this volume as a whole: that of basic research informing clinical studies.

Chapter 2 (Chen & West) reports on risk factors associated with fetal alcohol effects. The authors review studies assessing the influence of co-drug use and other constitutional and behavioral factors that increase the risk for fetal alcohol effects in rodents *(principle of genetic and environmental determination)*. Chen and West review evidence that the patterns of maternal alcohol consumption (how much is drunk *and* when), as well as parental genetics (varying rodent strains) and poly-drug exposure (e.g., perinatal cocaine), increase the magnitude of neurobehavioral fetal alcohol effects. Recognizing such risk factors may give clues to the mechanisms of alcohol teratogenesis, as well as suggest potential treatments and means of prevention.

In chapter 3, Hannigan, Saunders, Treas, & Sperry examine studies assessing pharmacological and environmental treatments for fetal alcohol effects in rats. Diminished CNS responses to environmental enrichment suggest that prenatal alcohol exposure produced enduring alterations in neural plasticity in vivo. The authors propose a general hypothesis about the neural mechanism(s) contributing to diminished neural plasticity *(principle of specific mechanisms),* and use in vitro techniques to examine the roles of neural growth factors (e.g., retinoic acid and GAP43/B50) in fetal alcohol effects.

Chapter 4 (Goodlett & Johnson) can be viewed as a treatise on the *principle of critical periods*. Indeed, this research shows how susceptibility of specific areas within the CNS *(principle of target access),* depends on when during CNS maturation the alcohol exposure occurs. Goodlett and Johnson argue that *critical periods* can be defined systemically by understanding how the cellular mechanisms of teratogenesis change over time.

Allan and Savage (chapter 5) detail their research on one potentially critical aspect of dysfunctional neurobiology after prenatal alcohol exposure: the profound effects on $GABA_A$ receptors. Allan and Savage take advantage of the fact that genetic differences in the expression of $GABA_A$ receptor subtypes is well-defined, and that the pharmacology of these receptors is well-characterized, to assess the contribution of GABA stimulation or excitation to enduring neurobehavioral dysfunction in prenatal alcohol-exposed offspring. These results may also be a clue to potential pharmacological therapies for fetal alcohol effects.

The next three chapters (chapters 6–8), continuing in part from the groundwork laid in chapter 5, discuss the genetic, ontogenetic, neural, and behavioral influences on responsivity to alcohol. These studies bear on clinical issues in the development of alcoholism by investigating the factors affecting the initiation and maintenance of alcohol

drinking, as well as the factors affecting the reinitiation of drinking after brief periods of abstinence. Clues from basic research in these areas may prove vital in devising effective clinical treatments for alcoholism and relapse.

Chapter 7 (McKinzie, McBride, Murphy, Lumeng, & Li) presents a series of studies assessing differences in biobehavioral responses to challenge doses of alcohol in rats bred for differential preferences for consuming alcohol, that is the alcohol-preferring (P) and non-alcohol-preferring (NP) rats, and low alcohol drinking (LAD) and high alcohol drinking (HAD) rat lines. This new research assesses these line-dependent differences in alcohol preference in adolescent animals, an age of heightened susceptibility to the psychotropic effects of alcohol and other drugs. Analogous to the critical periods analyses by Goodlett and Johnson in chapter 4, studies of the type used by McKinzie and colleagues illustrate how systematic evaluation of line- and age-dependent pharmacologic responses can provide insights into the processes and factors affecting initiation of alcohol drinking behavior.

In contrast to alcohol preferences in rats, the research described in chapter 6 by Dudek, Tritto, Case, Caldarone, and Clarke targets a different response to alcohol—the biphasic, dose-dependent activational effects of acute alcohol doses in mice. These authors assessed locomotor activation in several strains of mice to assess the genetic bases of differential responses to these effects of alcohol. The combination of choosing a precisely defined behavioral-biological response to alcohol and a sophisticated genetic analysis allows estimation of the numbers of genes controlling CNS effects of alcohol, and forms the basis (and justification) for other ongoing gene mapping research using quantitative trait loci (QTL) techniques.

Heyser, Schulteis, and Koob (chapter 8) describe an animal model assessing a critical aspect of alcoholism: the enhanced response to a first drink after a period of abstinence. The exaggerated magnitude of this response to a first re-exposure to alcohol, called the "alcohol deprivation effect," may explain the great risk people with alcoholism face in trying to drink socially or intermittently. As in chapter 7, a developmental analysis is used to help analyze the phenomenon.

The next two chapters can be viewed as integrating two earlier themes in this volume: prenatal alcohol exposure and early responses to alcohol. How does fetal or early infant exposure to alcohol affect later responsivity to alcohol? In chapter 9, Mennella discusses research on the behavioral sensitivity of human infants to very small levels of alcohol in breast milk. This sensitivity appear to be mediated by responses to the altered sensory qualities of the milk (i.e., alcohol-adulterated odor and/or taste). Mennella's research results imply that even very young infants will learn something about alcohol even when exposed to low, nonpharmacological levels. In chapter 10, the research by Molina, Domingues, López, Pepino, and Faas with rats suggests that fetuses and infants given early experience with the sensory qualities of alcohol can learn a preference for alcohol. These authors review an extensive series of studies using an animal model assessing the same issues raised by Mennella and that detail the impact of nonpharmacologic levels of alcohol exposure during the prenatal and early neonatal periods. These exposures can increase subsequent alcohol intake and affect later learning involving alcohol.

In chapter 11, Smith, Meyers, and Waldorf compare the features of three comprehensive alcoholism treatment regimens incorporating brief motivational enhancement therapies, together with direct community and/or family involvement in the treatment. The strategies described by Smith and her colleagues are relevant to a wide number of substanceabusing populations, including pregnant women and adolescents.

Finally, in the concluding chapter, Goodlett describes his vision of the potential future directions and value of multidisciplinary work that is energized by effective communication among basic and clinical researchers.

This volume began as a symposium at Binghamton University in June 1996. Almost all of the primary authors trained as graduate students or postdoctoral fellows at Binghamton University during the last 20 years, or had trained with current Binghamton University faculty at other institutions. Although there was a tradition of alcohol research at Binghamton University, particularly regarding behavior genetics, the confluence of eventual interest in alcohol research for many of these authors was not by some grand design. These scientists, trained in varied disciplines at Binghamton and elsewhere, all chose over the years to bring their multidisciplinary approaches to bear on *Alcohol and Alcoholism: Effects on Brain and Development*.

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REFERENCES

Hannigan, J.H. (1996). Of mice and women and alcohol: A fractal history of fetal alcohol syndrome research. *Developmental Psychobiology, 29,* 398–400.

Vorhees, C.V. (1986). The principles of behavioral teratology. In: E.P.Riley & C.V. Vorhees, (Eds.), *The Handbook of Behavioral Teratology* (pp. 23–48). New York: Plenum Press.

Alcohol and Alcoholism

Effects on Brain and Development

1
Prenatal Exposure to Alcohol: Effects on Brain Structure and Neuropsychological Functioning

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Prenatal alcohol exposure can have devastating and long-lasting effects on the exposed individual. These effects include physical anomalies and cognitive and behavioral impairments with outcomes ranging in severity from perinatal death to subtle behavioral problems. One clearly defined outcome of heavy prenatal alcohol exposure is fetal alcohol syndrome (FAS), which is characterized by pre- and/or postnatal growth deficiency, craniofacial anomalies, and evidence of central nervous system (CNS) dysfunction (Jones & Smith, 1973). It is estimated that FAS affects approximately 0.29 to 0.48 per 1,000 live births, with incidences increasing to 2.99 per 1,000 in certain socioeconomic and ethnic groups (Abel & Sokol, 1991). Importantly, these estimates include only the subset of alcohol-exposed individuals who meet the clinical criteria for a diagnosis of FAS. They do not include persons exposed to alcohol prenatally with some, but not all, of the effects required for a diagnosis of FAS. Although this second group of individuals may not display all or any of the physical features of FAS, they often exhibit behavioral and cognitive impairments very similar to those seen in "full blown" cases of FAS. Therefore, the impact of prenatal alcohol exposure may be more subtle and far-reaching than once believed.

The behavioral and cognitive impairments seen in individuals with FAS are most likely the manifestations of underlying structural or functional changes in the brain. However, the specific relationship between brain pathology and behavioral and cognitive alterations in these children is still unclear, highlighting the necessity for a more thorough understanding of alcohol's specific effects on brain and behavior. Additionally, because the threshold for alcohol-related effects is not known and because some of these effects may be extremely subtle (e.g., Goldschmidt, Richardson, Stoffer, Geva, & Day, 1996), it is important to elucidate the pattern of brain anomalies and behavioral and cognitive deficits in alcohol-exposed children, both with and without the diagnosis of FAS. Recent data obtained using brain imaging and neuropsychological testing are helping to clarify the specific nature of these anomalies. This chapter summarizes recent work from our laboratory using magnetic resonance imaging (MRI) and neuropsychological testing to examine groups of children with FAS and, where applicable, groups of children with histories of heavy prenatal alcohol exposure but without the full syndrome of FAS. These children are referred to here as having prenatal exposure to alcohol (PEA).

NEUROANATOMICAL FINDINGS

Animal models provided much information about alcohol's specific effects on the brain (see Miller, 1992 for an overview of this research). However, research with these animal models may have limited generalizability to humans, leaving much to be learned about how alcohol uniquely affects the developing human brain. Much of the earliest information about alcohol's effects on the human brain came from autopsy reports of children with FAS. These children were exposed to heavy amounts of alcohol in utero and usually died due to complications resulting from this exposure. Jones and Smith (1973) published the first report of an autopsy on a child with FAS. Their results revealed microencephaly and a uniformly thinned and disorganized cortex underlying a massive neuroglial leptomeningeal heterotopia. Additionally, the corpus callosum and other midline commissures were absent, and the cerebellum was underdeveloped and poorly formed.

Since this initial report, there have been about 25 additional autopsy reports in the literature. (For a detailed review of these studies, see Clarren, 1986, and Mattson & Riley, 1996). In general, these subsequent reports of autopsied brains documented a wide range of structural problems, the most common being microencephaly and malformations, consistent with a failure or interruption in neuronal migration (Clarren, 1981). However, there was extreme variability in the types of abnormali-ties found in these brains; thus the basic conclusion from these studies was that there is no specific pattern of brain malformation that occurs following prenatal alcohol insult (Clarren, 1986; Peiffer, Majewski, Fischbach, Bierich, & Volk, 1979). However, it should be noted that there are limitations in using these studies to generalize to the larger population of individuals with FAS. First, these autopsy studies reflect a skewed sample of only very severe cases of children with FAS. Furthermore, although no obvious pattern of brain deficits was found, autopsy studies may not be sensitive or systematic enough to detect a more subtle pattern of brain abnormalities.

More recently, MRI techniques allowed researchers to learn about the brains of surviving children with FAS. Because MRI analysis is safe and noninvasive, it allows researchers to compare specific brain structures in individuals with histories of prenatal alcohol exposure to those of other normally and abnormally developing persons. Although clinical assessments of these images often do not reveal obvious structural abnormalities, the use of more detailed quantitative analysis allows researchers to examine specific brain structures, determine their volumes, and systematically compare them to brain structures in normal subjects. The use of MRI combined with quantitative analysis is bringing researchers closer to understanding the nature of alcohol's effects on the developing human brain.

Recent work in our laboratory examined the effects of heavy prenatal alcohol exposure on specific brain structures. Although the amount of alcohol that our subjects were exposed to in utero is difficult to quantify, the mothers of these children would typically be classified as abusive drinkers; that is, they drank excessive amounts of alcohol in a fairly regular or binge drinking pattern throughout their pregnancies. Our MRI studies revealed reductions in the volumes of both the cerebral and cerebellar vaults and increases in the cortical and subcortical fluid in children with FAS when compared to nonexposed children (Mattson & Riley, 1996). These findings suggest an overall decrease in the development of brain tissue in children prenatally exposed to alcohol. Detailed results of these MRI studies follow.

Corpus Callosum

As determined by both autopsy and MRI studies, the developing corpus callosum appears to be particularly sensitive to the effects of alcohol. This structure, which is composed of 200 to 800 million nerve fibers, is the major connection between the neocortical hemispheres. It processes interhemispheric information and provides interhemispheric cooperation necessary for actions and movements of the body (Kolb & Whishaw, 1990). FAS autopsy reports detailed cases of complete agenesis or absence of the corpus callosum (Jones & Smith, 1973; Peiffer et al., 1979; Wisniewski, Dambska, Sher, & Qazi, 1983), partial agenesis (Kinney, Faix, & Brazy, 1980), and cases with a significantly thinned but present corpus callosum (Clarren, Alvord, Sumi, Streissguth, & Smith, 1978; Coulter, Leech, Schaefer, Scheithauer, & Brumback, 1993). Additionally, the anterior commissure, which forms a second, much smaller pathway between the right and left cerebral hemispheres, was reported to be missing in some cases (Clarren et al., 1978; Peiffer et al., 1979) and underdeveloped in another case (Coulter et al., 1993).

MRI studies provided more information about the specific areas of the corpus callosum that are affected by prenatal alcohol exposure, along with additional data about the frequency of callosal agenesis in children with FAS. The incidence of agenesis of the corpus callosum found in the general population is 0.3% and in other developmentally delayed populations is 2.3% (Jeret, Serur, Wisniewski, & Fisch, 1986; Jeret, Serur, Wisniewski, & Lubin, 1987). In our initial MRI study examining brain structures in children with FAS within our limited sample of individuals in San Diego, we reported one child with a moderately hypoplastic corpus callosum and another with agenesis of the corpus callosum (Mattson et al., 1992). A subsequent MRI study, specifically looking at abnormalities of the corpus callosum, found another case of agenesis and mentioned a third case that although not evaluated for that study, was known to have callosal agenesis (Riley et al., 1995). At the time that study was conducted, 44 alcohol-exposed individuals in the San Diego area had been evaluated, providing an agenesis incidence rate of nearly 7%. In addition, Jeret and Serur (1991) speculated that prenatal alcohol exposure might be a leading cause of corpus callosum agenesis. More recently, Johnson, Swayze, Sato, and Andreason (1996) examined nine cases of FAS, and agenesis of the corpus callosum was noted in three. In our study, we examined the size of the corpus callosum in 10 children with either FAS or PEA by measuring the overall midsagittal area along with the area for each of five equiangular regions. These children were found to have reductions in the overall area and in four of the five equiangular regions when compared to matched controls. Because children with FAS are typically microcephalic, overall brain size was controlled for to determine if the reductions seen in the corpus callosum were disproportionate to the reductions seen in the rest of the brain. Three of five regions remained significantly different from those in control subjects after accounting for overall brain size. These affected areas correspond approximately to the genu (which links the prefrontal areas), the portion of the corpus callosum just anterior to the splenium (which primarily links sensory areas), and the splenium (which primarily links the visual areas) (Kolb & Whishaw, 1990). Interestingly, these results are similar to those found in a separate MRI study examining the corpus callosum in children with attention deficit hyperactivity disorder (Hynd et al., 1991). These callosal anomalies might be related to the behavioral similarities (e.g., hyperactivity, impulsivity, and attentional difficulties) reported between these two groups of children.

Basal Ganglia

The basal ganglia are a collection of nuclei whose primary input comes from the cerebral cortex, with output directed through the thalamus and back to the prefrontal, premotor, and motor cortices. These structures are traditionally considered part of the motor system, although they may also play a role in some forms of cognitive functioning (Côté & Crutcher, 1991). Furthermore, diseases with known pathology in these areas (e.g., Parkinson's disease and Huntington's disease) frequently have cognitive components (Cummings & Benson, 1992). Autopsy studies of children with FAS reported several cases with evidence of damage to the basal ganglia (Peiffer et al., 1979; Ronen & Andrews, 1991; Wisniewski et al., 1983). MRI studies specifically examining the basal ganglia and diencephalon revealed that these areas may be especially sensitive to the teratogenic effects of alcohol. A study examining children with FAS found reductions in the size of the basal ganglia and diencephalon, even after controlling for overall brain size (Mattson et al., 1992).

A subsequent MRI study examining the basal ganglia and diencephalon in two children with PEA found similar reductions in the volume of the basal ganglia as well as in the diencephalon, although when brain size was accounted for, the volume of the diencephalon was similar in comparison to nonexposed controls (Mattson et al., 1994). These results suggest that the basal ganglia, like the corpus callosum, may be especially sensitive to the effects of alcohol exposure in utero. These results also support the notion that specific brain structures might be more susceptible to anomalous changes than others, and that brain changes can occur in the absence of the facial features on which a diagnosis of FAS is dependent.

A subsequent study examined six children with FAS and again found that the basal ganglia and diencephalon were reduced when compared to nonexposed controls. Follow-up analyses, dividing the basal ganglia into the caudate and the putamen, found that these structures were also reduced. However, when overall brain size was accounted for, the basal ganglia, and, more specifically, the caudate were the only structures that remained significantly reduced in volume in the FAS children (Mattson, Riley, et al., 1996). In contrast to the earlier study of children with FAS (Mattson et al., 1992), the diencephalon was not proportionately reduced. However, the earlier study included more severe cases of FAS.

Cerebellum

The cerebellum is composed of an outer layer of gray matter that covers a white core of connecting fibers and is attached to the brain stem at the level of the pons. It is indirectly involved in regulating movement, balance, and posture (Ghez, 1991). Numerous FAS autopsy studies reported cases with abnormalities of the cerebellum ranging from cerebellar dysgenesis (Clarren et al., 1978; Coulter et al., 1993; Jones & Smith, 1973; Peiffer et al., 1979; Wisniewski et al., 1983) and the presence of cerebellar heterotopic cell clusters (Clarren et al., 1978; Peiffer et al., 1979), to hypoplasia (Wisniewski et al., 1983) or agenesis of the cerebellar vermis (Peiffer et al., 1979).

Results from our MRI studies suggest that the cerebellum is also particularly sensitive to alcohol's teratogenic effects. We reported reductions in the cerebellar vault in children with FAS (Mattson et al., 1992) and in children with PEA (Mattson et al., 1994). Our

more recent MRI study, specifically examining the effects of alcohol on the cerebellar vermis, revealed that the area of the anterior regions (lobules I to V) was reduced but the posterior and remaining regions were not (Sowell et al., 1996). Previous findings from an animal model similarly found abnormal development of the anterior region with apparent sparing of the posterior vermis in rats exposed prenatally to alcohol (Goodlett, Marcussen, & West, 1990).

NEUROPSYCHOLOGICAL FINDINGS

Prenatal alcohol exposure has long been associated with subsequent cognitive and behavioral changes. In fact, FAS is reported to be among the leading known causes of mental retardation in the Western world (Abel & Sokol, 1987). Whether prenatal alcohol exposure produces a global deficit in intellectual functioning or whether individuals with such histories show a specific cognitive and/or behavioral profile of spared skills and weaknesses is still unresolved and under study. Furthermore, there is a tremendous need for additional research examining threshold effects for such cognitive and behavioral impairments (Jacobson & Jacobson, 1994) and the extent to which persons with PEA exhibit cognitive impairments similar to those seen in FAS. In an attempt to answer these questions, studies from our lab examined behavioral and cognitive abilities in children with the formal diagnosis of FAS and in children known to have heavy prenatal exposure to alcohol (PEA), but who lack the physical features of FAS. These children were typically referred for evaluation for FAS, but were found to be structurally normal and neither microcephalic nor growth retarded. Following is a review of our recent findings that illustrates some of the affected behavioral and cognitive domains in alcohol-exposed children.

Intellectual Functioning

Because alcohol's effects on cognitive functioning might be considered one of its most devastating consequences, it is important to estimate the cognitive potential of alcohol-exposed children. There have been numerous studies of cognitive ability in children with FAS, including both individual case reports and group studies. These studies typically report IQs ranging from Intellectually Deficient to Average, with these measures of IQ appearing to be relatively stable over time (Streissguth, Herman, & Smith, 1978). For a review of studies assessing the intellectual functioning in alcohol-exposed children, the reader is referred to Mattson and Riley (1998).

A recent study from our laboratory using the Wechsler intelligence scales (Wechsler, 1974; Wechsler, 1989) to examine the intellectual functioning of children prenatally exposed to alcohol found that when compared to a normal control group matched for age, gender, and ethnicity, both the FAS and PEA groups showed deficits in overall IQ and on most subtest scores (Mattson, Riley, Gramling, Delis, & Jones, 1997). Overall, the PEA group's scores were marginally higher than the FAS group's, but few significant differences were found between the two alcohol-exposed groups on the individual subtests. These results demonstrate that high levels of prenatal alcohol exposure can lead to impairments in overall intellectual functioning. Furthermore, although these data do

not aid in the establishment of a threshold for alcohol-related effects, it is important to note that intellectual deficits can occur in children who do not meet the full criteria for FAS.

Language

Because children with FAS are often sociable, friendly, and outgoing, and appear younger than their chronological age, their language abilities may seem unimpaired. However, previous research showed that these children tend to have lower verbal abilities than non-exposed children (Abel, 1990; Abkarian, 1992; Conry, 1990). Recent findings from our lab found that children with FAS performed significantly lower than control children did on measures of word comprehension and naming ability, as measured by the Peabody Picture Vocabulary Test-Revised and the Boston Naming Test, respectively (Mattson, Riley, Gramling, Delis, & Jones, 1998). Similarly, children with PEA were found to have poor performances on these tests in comparison to the normal controls. Although the PEA children tended to have higher scores than the FAS children, these differences were not statistically significant. Thus, these findings are similar to those found for intellectual functioning and indicate that children exposed to alcohol without overt physical effects may nevertheless suffer from impairments in language functioning.

Verbal Learning and Memory

A recent study from our lab demonstrated deficits in verbal learning and memory in children with FAS when compared to nonexposed controls matched for age, gender, and ethnicity (Mattson, Riley, Delis, Stern, & Jones, 1996). Children were administered the California Verbal Learning Test-Children's Version (CVLT-C), a learning task that assesses immediate and delayed recall and recognition memory for a word list. Children with FAS learned fewer words over five acquisition trials and subsequently had difficulty remembering words after a delay period of 20 minutes. These children also had increased numbers of intrusion and perseverative errors. That is, they tended to respond with words not on the original target list and also to repeat words already said. They were also less accurate in distinguishing target words from distracter words on a test of recognition memory and tended to make an increased number of false-positive errors.

These results suggest that children with FAS failed to benefit from repeated exposure to the material. Whereas children in the control group improved their ability to remember the words across five trials, children in the FAS group seemed to show improvement only between the first two trials with little new learning on trials 3 through 5. However, although the FAS group tended to recall fewer words on the recall trials, there were no group differences on a retention measure for previously learned words. That is, although children with FAS initially recalled fewer words than did controls, they exhibited normal forgetting rates and were able to remember what they learned as well as controls did. These findings suggest that the memory impairment in the FAS group may be at the encoding level rather than at the retrieval level.

Additionally, when compared to a control group matched for mental age (MA), children with FAS were similar to controls on learning and free recall measures, but were less able to discriminate the target words from distracters, made more false-positive

errors, and made more perseverative errors. In summary, there were few differences between the FAS and MA matched groups, suggesting that learning and memory deficits are related in part to an overall global intellectual deficit. However, the pattern of deficits that continued to exist when MA was controlled suggests that children with FAS may have specific problems with encoding and response inhibition that are unique to the disorder.

Children with PEA also display impaired performance on the CVLT-C (Mattson, Riley, Gramling, et al., 1998). When compared to normal controls, group differences were found in learning and recall errors, but not on retention of learned information. Importantly, the FAS and PEA groups showed a similar pattern of impaired learning, and both demonstrated average retention of verbal material. Both alcohol-exposed groups made increased numbers of intrusion errors and had difficulty distinguishing target words from distracter words, but only the FAS group made more perseverative errors on recall and more false-positive errors on recognition testing. These results indicate qualitatively similar patterns of deficits in verbal learning and memory between the FAS and PEA children.

Academic Skills

Given their deficits in learning and overall intellectual ability, one might predict that children prenatally exposed to alcohol would also display impairments in academic skills. Previous studies showed decreased academic achievement and increased rates of learning problems in children exposed to alcohol prenatally (Streissguth, Barr, & Sampson, 1990). We (Mattson, Riley, Gramling, et al., 1998) recently examined the performances of children with FAS and PEA on the Wide Range Achievement Test-Revised (WRAT-R), a screening measure designed to assess academic skills, including reading, spelling, and arithmetic. Findings revealed that in all three academic areas, both groups of alcohol-exposed children (FAS and PEA) had significantly lower scores than control children. These results suggest that children with PEA may suffer from similar academic problems to those faced by children with FAS. From a practical point of view, it must be stressed that although children with PEA may suffer many of the same academic difficulties as children with FAS, in fact, they may be less likely to receive the same type of remediation because educators may not realize that these difficulties are related to prenatal alcohol exposure.

Fine-Motor Skills

Previous studies showed that prenatal alcohol exposure affects the developing motor system (Marcus, 1987). Children of alcoholic mothers were described as having poor motor development, fine-motor dysfunction, and delayed gross-motor performance (Jones, Smith, Ulleland, & Streissguth, 1973). Studies reported deficits in fine- and gross-motor skills along with inferior coordination in children exposed to alcohol prenatally (Barr, Streissguth, Darby, & Sampson, 1990; Kyllerman et al., 1985). Animal studies also described motor dysfunctions such as gait disturbance (Hannigan & Riley, 1989) and poor balance (Meyer, Kotch, & Riley, 1990). Recently, fine-motor speed and coordination was assessed in children with FAS and PEA using the Grooved Pegboard.

Results revealed that both alcohol-exposed groups showed impaired performance on this test when compared to nonexposed controls (Mattson, Riley, Gramling, et al., 1998). These results, combined with past research, suggest that motor development might be sensitive to the effects of prenatal alcohol exposure.

Visuospatial Abilities

Visuospatial deficits in children with FAS were also reported, although relatively few studies examined this area. The few previous studies showed that children with FAS show deficits in visual-motor integration (Conry, 1990; Janzen, Nanson, & Block, 1995; Uecker & Nadel, 1996). We recently tested visual-motor integration skills in children with FAS and PEA using the Beery Developmental Test of Visual-Motor Integration (VMI). Both alcohol-exposed groups displayed poorer performance than did normal controls (Mattson, Riley, Gramling, et al., 1998). Again, these results indicate that children with PEA show patterns more similar to children with FAS than to normal control children.

In another study examining specific visuospatial abilities, we found that children with FAS displayed deficits in the processing of hierarchical stimuli (Mattson, Gramling, Delis, Jones, & Riley, 1996). Visuospatial abilities were assessed using the global-local test, in which a large stimulus (the global feature) composed of smaller stimuli (the local features) is presented to the child. The alcohol-exposed children had difficulty recalling the local features of the stimulus, but showed no deficits in recalling the global or configural features of the stimulus. These deficits in local processing were found to be distinct from memory impairments because the same performance pattern was found when children were asked to copy the hierarchical stimuli. Therefore, the results suggest a specific impairment in processing of local features of hierarchical visual stimuli.

Nonverbal Problem Solving

Like visuospatial abilities, the problem-solving skills of alcohol-exposed children have received little attention. There is some evidence that children prenatally exposed to alcohol have difficulty planning and tend to perseverate on incorrect strategies when approaching problem-solving tasks (Kodituwakku et al., 1992). Recently we examined the performance of alcohol-exposed children on a test of nonverbal problem solving. A combined group of children with FAS and PEA was administered the Wisconsin Card Sorting Test (WCST), which requires nonverbal problem solving and cognitive flexibility. Previous research using this task with alcohol-exposed children, although limited, demonstrated that children exposed to alcohol prenatally display decreased accuracy (Carmichael Olson, Feldman, Streissguth, & Gonzalez, 1992), achieve fewer categories, and make more perseverative errors (Kodituwakku et al., 1992) than do normal controls. Findings from our data reveal that although alcohol-exposed children performed more poorly than normal controls on the WCST, their performance was better than expected based on their overall level of cognitive ability (Mattson, Roebuck, & Riley, 1996). These findings support the suggestion that alcohol exposure does not produce a unitary decline in functioning but, instead, some processes may be more affected than others.

SUMMARY AND CONCLUSIONS

Our findings using MRI techniques revealed that children with FAS have specific volumetric reductions in their overall brain size, cerebellum, basal ganglia, diencephalon, and corpus callosum. When overall brain size is taken into account and results from a sample of PEA children are included in the analyses, the basal ganglia and specifically the caudate, the anterior vermis of the cerebellum, and specific areas of the corpus callosum all appear to be disproportionately affected by gestational alcohol exposure. These findings provide some of the first evidence that prenatal alcohol exposure produces a specific pattern of structural anomalies in the human brain.

Our current studies examining the cognitive profile of children with FAS documented impairment in overall intellectual functioning as well as a pattern of relative weaknesses and spared skills in some distinct areas. Specifically, children with FAS show deficits in verbal learning, although verbal retention appears to be less affected. Children with FAS show deficits in processing hierarchical stimuli and exhibit specific weaknesses in the processing of local versus global features. Although it appears that nonverbal problem-solving skills are impaired when compared to normal controls, their performance is actually better than expected based on their overall level of intellectual functioning. These findings suggest that children with FAS exhibit overall deficits in cognitive functioning as assessed by standardized IQ tests, although further neuropsychological testing reveals a cognitive profile consisting of specific strengths and weaknesses. Therefore, although the reported cognitive deficits in alcohol-exposed children may reflect a general decline in overall intellectual ability, they do not correspond to an overall unitary decline in neuropsychological functioning.

Much is known about the cognitive and behavioral abilities of children with FAS, although less is known about these abilities in children with PEA. Current findings suggest that the cognitive abilities of children with PEA are qualitatively similar to those of FAS children, although they show a tendency to be somewhat less impaired. It should be noted, however, that our results might be biased by the fact that some of the PEA children were ascertained retrospectively and may have been referred because of behavioral problems. However, the majority of our PEA subjects were identified prospectively or in the newborn period, before any behavioral or cognitive problems developed. We noted no systematic difference as a result of these different ascertainment procedures. Most importantly, our results indicate that, at the very least, a subset of children with PEA may suffer from effects of prenatal alcohol exposure even though overt physical signs are absent.

This chapter provides an overview of recent work assessing alcohol's effects on the developing brain in humans and the resulting behavioral and cognitive impairments that may ensue. Numerous studies showed cognitive and behavioral impairments in children diagnosed with FAS. However, it is not yet clear how brain malformations are related to cognitive functioning. Understanding the specific effects of alcohol on the developing brain may provide insight into the cause and nature of these cognitive and behavioral deficits. Given that there is still much to learn about these brain anomalies, corresponding deficits in brain functioning are under study.

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REFERENCES

Abel, E.L. (1990). *Fetal alcohol syndrome.* Oradell, NJ: Medical Economics Company, Inc.

Abel, E.L., & Sokol, R.J. (1987). Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies. *Drug and Alcohol Dependence, 19,* 51–70.

Abel, E.L., & Sokol, R.J. (1991). A revised conservative estimate of the incidence of FAS and its economic impact. *Alcoholism: Clinical and Experimental Research, 15,* 514–524.

Abkarian, G.G. (1992). Communication effects of prenatal alcohol exposure. *Journal of Communicative Disorders, 25,* 221–240.

Barr, H.M., Streissguth, A.P., Darby, B.L., & Sampson, P.D. (1990). Prenatal exposure to alcohol, caffeine, tobacco, and aspirin: Effects on fine and gross motor performance in 4-year-old children. *Developmental Psychology, 26(3),* 339–348.

Carmichael Olson, H., Feldman, J.J., Streissguth, A.P., & Gonzalez, R.D. (1992). Neuropsychological deficits and life adjustment in adolescents and adults with fetal alcohol, syndrome. *Alcoholism: Clinical and Experimental Research, 16,* 380.

Clarren, S.K. (1981). Recognition of fetal alcohol syndrome. *Journal of the American Medical Association, 245(23),* 2436–2439.

Clarren, S.K. (1986). Neuropathology in fetal alcohol syndrome. In J.R.West (Ed.), *Alcohol and brain development* (pp. 158–166). New York: Oxford University Press.

Clarren, S.K., Alvord, E.C., Sumi, M., Streissguth, A.P., & Smith, D.W. (1978). Brain malformations related to prenatal exposure to ethanol. *Journal of Pediatrics, 92(1),* 64–67.

Conry, J. (1990). Neuropsychological deficits in fetal alcohol syndrome and fetal alcohol effects. *Alcoholism: Clinical and Experimental Research, 14(5),* 650–655.

Côté, L., & Crutcher, M.D. (1991). The basal ganglia. In E.R.Kandel, J.H.Schwartz, & T.M.Jessell (Eds.), *Principles of neural science* (pp. 647–659). Norwalk, CT: Appleton & Lange.

Coulter, C.L., Leech, R.W., Schaefer, G.B., Scheithauer, B.W., & Brumback, R.A. (1993). Midline cerebral dysgenesis, dysfunction of the hypothalamic-pituitary axis, and fetal alcohol effects. *Archives ves of Neurology,* 50(July), 771–775.

Cummings, J.L., & Benson, D.F. (1992). *Dementia: A clinical approach* (2nd Ed.). Boston: Butterworth-Heinemann.

Ghez, C. (1991). The cerebellum. In E.R.Kandel, J.H.Schwartz, & T.M.Jessell (Eds.), *Principles of neural science* (pp. 626–646). Norwalk, CT: Appleton & Lange.

Goldschmidt, L., Richardson, G.A., Stoffer, D.S., Geva, D., & Day, N.L. (1996). Prenatal alcohol exposure and academic achievement at age six: A nonlinear *fit. Alcoholism: Clinical and Experimental Research, 20,* 763–770.

Goodlett, C.R., Marcussen, B.L., & West, J.R. (1990). A single day of alcohol exposure during the brain growth spurt induces brain weight restriction and cerebellar Purkinje cell loss. *Alcohol, 7,* 107–114.

Hannigan, J.H., & Riley, E.P. (1989). Prenatal ethanol alters gait in rats. *Alcohol, 5,* 451–454.

Hynd, G.W., Semrud-Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., & Lyytinen, H. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: Morphometric analysis of MRI. *Journal of Learning Disabilities, 24(3),* 141–146.

Jacobson, J.L., & Jacobson, S.W. (1994). Prenatal alcohol exposure and neurobehavioral development: Where is the threshold? *Alcohol Health & Research World, 18,* 30–36.

Janzen, L.A., Nanson, J.L., & Block, G.W. (1995). Neuropsychological evaluation of preschoolers with fetal alcohol syndrome. *Neurotoxicology and Teratology, 17(3),* 273–279.

Jeret, J.S., & Serur, D. (1991). Fetal alcohol syndrome in adolescents and adults [Letter to the editor]. *Journal of the American Medical Association, 266(8),* 1077.

Jeret, J.S., Serur, D., Wisniewski, K., & Fisch, C. (1986). Frequency of agenesis of the corpus callosum in the developmentally disabled population as determined by computerized tomography. *Pediatric Neuroscience, 12,* 101–103.

Jeret, J.S., Serur, D., Wisniewski, K.E., & Lubin, R.A. (1987). Clinicopathological findings associated with agenesis of the corpus callosum. *Brain Development, 9,* 225–264.

Johnson, V.P., Swayze II, V.W., Sato, Y., & Andreasen, N.C. (1996). Fetal Alcohol Syndrome: Craniofacial and central nervous system manifestations. *American Journal of Medical Genetics, 61,* 329–339.

Jones, K.L., & Smith, D.W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet, 2,* 999–1001.

Jones, K.L., Smith, D.W., Ulleland, C.N., & Streissguth, A.P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet, 1,* 1267–1271.

Kinney, H., Faix, R., & Brazy, J. (1980). The fetal alcohol syndrome and neuroblastoma. *Pediatrics, 66(1),* 130–132.

Kodituwakku, P.W., Handmaker, N.S., Cutler, S.K., Weathersby, E.K., Handmaker, S.D., & Aase, J.M. (1992). Specific impairment of self regulation in FAS/FAE: A pilot *study. Alcoholism: Clinical and Experimental Research, 16(2),* 381.

Kolb, B., & Whishaw, I.Q. (1990). *Fundamentals of human neuropsychology.* (3rd ed.). New York: W.H.Freeman.

Kyllerman, M., Aronson, M., Sabel, K.-G., Karlberg, E., Sandin, B., & Olegard, R. (1985). Children of alcoholic mothers: Growth and motor performance compared to matched controls. *Acta Paediactrica Scandinavica, 74,* 20–26.

Marcus, J.C. (1987). Neurological findings in the fetal alcohol syndrome. *Neuropediatrics, 18(3),* 158–160.

Mattson, S.N., Gramling, L., Delis, D.C., Jones, K.L., & Riley, E.P. (1996). Global-local processing in children prenatally exposed to alcohol. *Child Neuropsychology, 2(3),* 165–175.

Mattson, S.N., & Riley, E.P. (1996). Brain anomalies in fetal alcohol syndrome. In E. L.Abel (Ed.), *Fetal alcohol syndrome: From mechanism to prevention* (pp. 51–68). New York: CRC Press.