EMBARGOED FOR RELEASE UNTIL 3 FEBRUARY 2008 @ 16:00:00 ET

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Eye blinks may help to identify children prenatally exposed to alcohol

- Not all children prenatally exposed to alcohol show distinctive facial anomalies usually associated with fetal alcohol syndrome (FAS).
- New findings indicate that deficits in eyeblink conditioning (EBC) can identify children with probable FAS.
- EBC may also serve to identify alcohol-exposed children who lack distinctive FAS features.

While children with fetal alcohol syndrome (FAS) have identifiable craniofacial abnormalities, children with alcohol-related neurodevelopmental disorder (ARND) can have significant cognitive impairments *without* facial anomalies. An important new study has found that a deficit in eyeblink conditioning (EBC) can identify children with probable FAS, and may also serve to identify alcohol-exposed children who lack distinctive FAS features.

Results are published in the February issue of *Alcoholism: Clinical & Experimental Research.*

"Eyeblink conditioning (EBC) is a Pavlovian paradigm that involves temporal pairing of a conditioned stimulus, [such as a] tone, with an unconditioned stimulus, [such as an] air puff," explained Sandra W. Jacobson, a professor in the department of psychiatry and behavioral neurosciences at Wayne State University School of Medicine, and first author of the study. "Animal studies have shown that binge consumption of alcohol during pregnancy impairs EBC. We [wanted] to see [if] we could [use the EBC paradigm to] identify underlying or subcortical deficits that are specifically affected by prenatal alcohol exposure [in children]."

"The present study provides the first documentation that clearly points to an FAS relationship because of the large sample size, the prospective follow-up of children from birth, and the careful measurement of prenatal exposure to alcohol and other drugs," said Lynn T. Singer, Deputy Provost and Vice President for Academic Programs at Case Western Reserve University. "Moreover, the deficits in EBC were not related to IQ or microcephaly, [which are] often confounding factors."

Jacobson knew from previous visits to the Western Cape Province of South Africa that there was an extremely high incidence of FAS in the region. In fact, the prevalence of FAS in the mixed-ancestry population is among the highest in the world. Although the traditional *dop* system – under which farm laborers were paid in part with wine – has been outlawed, heavy alcohol consumption persists in some regions, especially binge drinking on the weekends. Jacobson and her colleagues have been studying a group of women and their children since 1998, leading to this, the first prospective, longitudinal study of children with FAS.

The researchers administered three sessions of EBC to 98 five-year-olds born to mixed-ancestry women in Cape Town, pairing a tone with an air puff. Normally, after repeated pairings, a child as young as five months old will develop a conditioned eyeblink response. In addition to the EBC sessions, expert dysmorphologists assessed FAS status among the five-year-olds.

"Even knowing the high incidence of FAS that has been documented in rural areas of the Western Cape province, we were surprised to see the very high incidence of children born with FAS and partial FAS (PFAS) in this urban mixed-ancestry cohort," said Jacobson. "Twelve (18.8%) children born to the 64 heavy drinking mothers met criterion for FAS, and an additional 18 (28.1%) for PFAS. Not a single child with FAS at this age met criterion for

short-delay conditioning as contrasted with 75 percent of the controls. In addition, about two-thirds of the children with PFAS and two-thirds of the heavily exposed nonsyndromal children also did not meet criteria for conditioning within the two-three 50-trial (**UNCLEAR???**) sessions. [Given that we controlled for IQ and microcephaly,] these findings suggest that the EBC deficit does not reflect impaired intellectual ability but rather is a direct effect of the fetal alcohol exposure."

"[This study] clearly links one brain area to the learning deficits experienced by FAS children, whether or not they have physical manifestations of the condition, and thus can provide a basis for the development of remediation programs," said Singer. "Second, since normal human infants reach functional capacity on the EBC response by five months of age, and since the EBC deficit appears to be so sensitive, infants at risk can be identified early in life, [and] intervention programs can begin when the plasticity of the brain is greatest and have the strongest effect. Finally, [EBC] is a relatively simple assessment that could be incorporated easily into pediatric follow-up for high-risk children."

"[Our results show] that there was a dose-response relation between alcohol exposure and FASD diagnosis and that a fundamental element of learning is affected by prenatal alcohol exposure," said Jacobson. "We [next] need to extend the study of the EBC paradigm with fetal alcohol exposed children to see how this exposure impacts on children at different ages."

She and her colleagues have begun a pilot study to examine EBC in eight-to-11-year-old mixed-ancestry children in Cape Town to see whether the findings at five years of age are also apparent in older children. The researchers also hope to revisit the five-year-old group at 8.5 years of age to examine their EBC.

"It is also important to see whether additional conditioning sessions can lead to improved conditioning, especially in the heavily exposed nonsyndromal children," said Jacobson. "It has been difficult to identify specific CNS deficits that can be used to determine whether an alcohol-exposed child is affected by the exposure or not. Our present study demonstrates that a delay in EBC has a high sensitivity for identifying individuals with a diagnosis of probable FAS and that it may serve as a potential biomarker for diagnosis of exposed children lacking the distinctive FAS dysmorphology."

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Alcoholism: Clinical & Experimental Research (ACER) is the official journal of the Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. Co-authors of the ACER paper, "Impaired Eyeblink Conditioning in Children with Fetal Alcohol Syndrome," were: Mark E. Stanton of the Department of Psychology at the University of Delaware; Christopher D. Molteno and Nathaniel Khaole of the Department of Psychiatry at the University of Cape Town Faculty of Health Sciences, South Africa; Matthew J. Burden and Douglas S. Fuller of the Department of Psychiatry and Behavioral Neurosciences at Wayne State University School of Medicine; H. Eugene Hoyme of the Department of Pediatrics at Stanford University; Luther K. Robinson of the Department of Pediatrics at the State University of New York School of Medicine and Biomedical Sciences; and Joseph L. Jacobson of the Department of Psychiatry and Behavioral Neurosciences, and the Department of Obstetrics and Gynecology, at Wayne State University School of Medicine. The study was funded by the National Institute on Alcohol Abuse and Alcoholism, the National Institutes of Health Office of Research on Minority Health, the Foundation for Alcohol Related Research, Cape Town, South Africa, and the Joseph Young, Sr., Fund from the State of Michigan.

Journalists: A full copy of the manuscript may be obtained by contacting Mary Newcomb with the ACER Editorial Office at 317.375.0819 (mnewcomb-acer@earthlink.net), or by visiting http://www.blackwell-synergy.com/loi/acer.