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COMMENTARY

Brain Imaging in FAS

Commentary on the article by Malisza *et al.*

SUSAN Y. BOOKHEIMER, AND ELIZABETH R. SOWELL

Department of Psychiatry and Biobehavioral Sciences [S.Y.B.] and Department of Neurology [E.S.], UCLA School of Medicine, Los Angeles, CA 90095

Fetal alcohol syndrome (FAS) is caused by maternal consumption of alcohol during pregnancy, though it is not clear how much alcohol is required to result in the syndrome. Children with FAS exhibit a wide range of symptoms such as severe growth restriction, facial dysmorphology (*i.e.*, smooth philturm, thin upper lip, small palpebral fissures), and intellectual disability. It affects 0.2 to 1.5 individuals per 1000 births across various populations and is at comparable or increased rates relative to other neurodevelopmental disorders such as Down syndrome. The relatively high incidence of FAS in the US is of considerable social concern given that it is a leading cause of preventable developmental disabilities (1). Further, children with all required features to obtain a diagnosis of FAS are not the only ones negatively affected; those with severe prenatal alcohol exposure, but without facial dysmorphology required for the FAS diagnosis have also exhibited neurocognitive deficits (2) and brain abnormalities (3,4). The brain is particularly vulnerable to the teratogenic effects of prenatal alcohol exposure. Microcephaly was among the first noted gross neural abnormalities in children born to alcohol abusing mothers (5) and has been consistently confirmed in postmortem and *in vivo* studies (6).

The paper by Maluszic and colleagues (7) used structural and functional MRI (fMRI), finding differences in brain activation during working memory (WM) tasks in children and adults with fetal alcohol spectrum disorders (FASD) including FAS, partial FAS, and alcohol related neurodevelopmental disorder (ARND). The maintenance of structural brain changes into adulthood described above raises the specter of potentially permanent functional changes following prenatal exposure to alcohol. Although the study is preliminary, it is the first published study thus far to examine brain function in FASD using fMRI, and hopefully will encourage further study into this disorder using advanced imaging methods.

Designing and performing fMRI studies in children is challenging under the best circumstances, and there are particular difficulties of interpretation when one population is impaired in the function studied, as is the case in these FASD subjects. The authors suggest that FASD children and adults show increased functional activation at a low-level working memory task in inferior and middle frontal cortices which decreased with task difficulty, while control children and adults showed the opposite pattern. Interpretation of results must remain very cautious for several reasons. The first involves performance differences between groups. Because both accuracy and reaction times were lower in the FASD groups than in controls, it is difficult to determine whether differences in activation between groups reflect more general factors related to performance or are specific to task-group effects. When tasks become very difficult subjects tend to disengage or focus on irrelevant features of the task; when challenging but within reach, brain regions involved in effortful processing tend to be engaged regardless of task or population (8,9). Other approaches to handling the problem of group performance differences include parametric designs; (8,10) performance matched comparisons, (11) and separate covariance analysis of the effects of performance on brain activation (9). Future fMRI studies of FASD incorporating these approaches would bolster the significance of the present findings.

A second problem with interpretation involves the nature of the comparisons. While group averaged maps of FASD or control subjects may appear different visually, direct statistical comparisons of group effects are required to determine whether there are reliable group effects. Limited power and different N's may produce group-activation maps that appear to show group differences but which reflect primarily differences in the power to detect activations. Such power is often limited by increased variability in clinical populations.

Finally, while control children and adults may both show areas of activity within the same lobe, the precise areas of activation do not appear to overlap in this study, which would be testable by direct group comparisons. Although children and adults tend to differ in magnitude of fMRI activation, in general children and adults have shown similar patterns of engagement in DLPFC and intraparietal cortex in working memory tasks, (11,12) which are not seen consistently in the present studies. In part this is likely due to the relatively small numbers of subjects. While individual subjects may show the expected

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Correspondence: Susan Y. Bookheimer, Ph.D., Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, 205 Brain Mapping Cntr, BOX 957085. Los Angeles, CA 90095; email: sbook@ucla.edu

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activation patterns (such as in Fig. 2, Fig. 3, Fig. 4, Fig. 5), these cannot be interpreted to reflect group trends.

The structural brain abnormalities observed in FASD individuals in previous studies may also be helpful in interpreting the pattern of functional effects observed here. Localized brain size reduction on orbito-frontal regions have been observed in children, adolescents and young adults with FASD, (13) and this region showed activation abnormalities during the WM task in both children and adults with FASD in this study. The increased activity in orbital frontal cortex in FASD relative to control subjects could be related to biologic aspects of the structural abnormality, or it could result from misregistration of images in brain regions that do not match normative brain anatomy. While quantitative measures of brain anatomy were not included in this report, it is possible that localized decreased orbito-frontal volumes in the FASD subjects were over-compensated in the spatial registration process, resulting in an apparent increased spatial extent of activation in this region during WM.

The effects of prenatal alcohol exposure on brain structure are not always observable upon gross inspection of magnetic resonance imaging (MRI) data. Subtler effects in brain morphology have been revealed only through quantitative comparisons of MRI data from groups of individuals with and without prenatal alcohol exposure (6). Most recently, our group has shown brain shape and cortical tissue density abnormalities that persist into adolescence, long after the teratogenic exposure of alcohol to the developing brain. Parietal, frontal and temporal lobe abnormalities were prominent in the results (13) and these effects were observable only through new brain mapping technology which allowed detailed computerized assessment with much greater localizing ability than was previously possible.

Future investigations of FASD would benefit from integration of functional and structural imaging data to help disentangle potential artifacts from structural abnormalities from the functional signal. Nonetheless, this study marks an important new approach to studying the effects of alcohol exposure on the structure and function of the developing brain and underscore the need to pursue them through adulthood.

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