Brain dysmorphology in individuals with severe prenatal alcohol exposure

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Our previous studies revealed abnormalities on structural MRI (sMRI) in small groups of children exposed to alcohol prenatally. Microcephaly, disproportionately reduced basal ganglia volume, and abnormalities of the cerebellar vermis and corpus callosum were demonstrated. The present study used sMRI to examine in detail the regional pattern of brain hypoplasia resulting from prenatal exposure to alcohol using a higher resolution imaging protocol and larger sample sizes than reported previously. Fourteen participants (mean 11.4 years; eight females, six males) with fetal alcohol syndrome (FAS) and 12 participants (mean 14.8 years; four females, eight males) with prenatal exposure to alcohol (PEA) but without the facial features of FAS were compared to a group of 41 control participants (mean 12.8 years, 20 females, 21 males). Findings of significant microcephaly and disproportionately reduced basal ganglia volumes in the FAS group were confirmed. Novel findings were that in FAS participants, white matter volumes were more affected than gray matter volumes in the cerebrum, and parietal lobes were more affected than temporal and occipital lobes. Among subcortical structures, in contrast to the disproportionate effects on caudate nucleus, the hippocampus was relatively preserved in FAS participants. Differences between the PEA group and controls were generally non-significant; however, among a few of the structures most affected in FAS participants, there was some evidence for volume reduction in PEA participants as well, specifically in basal ganglia and the parietal lobe. There were no group differences in cerebral volume asymmetries. Severe prenatal alcohol exposure appears to produce a specific pattern of brain hypoplasia.

The damaging effects of heavy exposure to alcohol prenatally were first reported by Jones and Smith (1973) in the USA. A distinct pattern of facial malformations, growth retardation, and CNS dysfunction in children exposed to alcohol before birth comprise the fetal alcohol syndrome (FAS). This syndrome occurs in 1 of 1000 live births a year worldwide, and the prevalence of other alcohol-related neurodevelopmental disorders is even higher, making fetal alcohol exposure a serious problem (Abel 1995, Sampson et al. 1997). Prenatal exposure to alcohol reportedly causes abnormal morphological brain development including pathology of cortical invaginations, agenesis of various structures, and abnormal formation of the lateral ventricles (Konovalov et al. 1997). Anomalies of the corpus callosum, increased CSF in the brain, and other changes in brain regions including the cerebellum have also been reported in autopsy studies (Clarren and Smith 1978, Wisniewski et al. 1983). Studies of rats and mice exposed to alcohol before birth have demonstrated microcephaly, altered migration of neurons, and cerebellar abnormalities (Miller and Robertson 1993, Maier et al. 1999). Mattson et al. (1994) studied rats exposed to alcohol prenatally and demonstrated basal ganglia reduction and ventricular enlargement.

In our previous studies, structural MRI (sMRI) has been used to study the neuroanatomical effects of FAS in living children. The most striking findings of these studies have included evidence for microcephaly, callosal and vermal abnormalities, and disproportionately reduced volume of the basal ganglia (Riley et al. 1995, Mattson et al. 1996b, Sowell et al. 1996). Another study of FAS reported midline anomalies of the corpus callosum, ventriculomegaly, and the presence of cavum septi in seven of 10 participants (Swayze et al. 1997).

Alongside this neuroanatomical pattern, the neuropsychological deficits reported in children with FAS include deficits in verbal learning and explicit memory, attention, and planning abilities. These deficits are observable even in participants with FAS who have relatively unaffected overall IQ performance (Mattson et al. 1996a, Kerns et al. 1997, Olson et al. 1998). Children with histories of heavy prenatal exposure to alcohol (PEA) but in whom some criteria for the syndromic diagnosis of FAS are absent, demonstrate similar cognitive deficits. A neuropsychological study by Mattson et al. (1998, 1999) of FAS and PEA groups indicated that both groups were impaired on tests of language, verbal learning and memory, fine motor performance, and visual–motor integration. The current study expands our understanding of FAS dysmorphology and also includes an examination of brain morphology in this PEA group, as well as in a larger group of participants with FAS.

Methods

PARTICIPANTS

Fourteen young participants diagnosed with FAS (mean 11.4 years; eight females, six males), 12 participants with PEA (mean 14.8 years; four females, eight males), and 41 age-matched control participants (mean 12.8 years, 20 females, 21 males) were studied. Due to an artifact affecting some temporal lobe regions, some analyses included only 33 controls, 12 FAS and 11 PEA participants. All alcohol-exposed individuals were evaluated by a dysmorphologist. FAS participants met the following criteria: they had known prenatal exposure to alcohol, craniofacial anomalies consistent with FAS, prenatal

or postnatal growth deficiency or both, and CNS dysfunction. Participants in the PEA group were exposed to high levels of alcohol prenatally but did not meet the criteria necessary for a diagnosis of FAS; they displayed few or none of the facial features characteristic of FAS and did not show growth retardation. Individuals in the PEA group, as in the FAS group, were born to alcoholic women known to be using alcohol heavily during pregnancy, although specific data regarding dose and timing of alcohol exposure are not known. Neuropsychological assessment data are available on all of the alcohol-exposed participants except one of the PEA individuals. Both alcohol groups demonstrated neuropsychological deficits relative to controls but did not differ significantly from each other. Details of these data are reported elsewhere (Mattson et al. 1997, 1998), but full scale IQ scores are similar for both groups with FAS IQ, mean 79.7 (SD 17.7, range 40 to 103) and PEA IQ, 79.6 (SD 13.7, range 62 to 101).

FAS and PEA participants and some of the normal controls were recruited and evaluated by the Center for Behavioral Teratology at San Diego State University. Control participants were recruited from the Project in Cognitive and Neuronal Development at University of California, San Diego. Age- and sex-matched control participants were chosen to match the FAS group (Table I). Individuals were excluded from the control group if they had any history of head injury, learning disability, neurological or psychiatric disorder, significant medical condition, or substance abuse.

IMAGING PROTOCOL

Three whole-brain image series were collected for each participant. The first was a gradient–echo (SPGR) T1-weighted series with TR=24 ms, TE=5 ms, NEX=2, flip angle=45°, with contiguous 1.2 mm sections. The second and third series were fast spin–echo (FSE) acquisitions yielding two separate image sets: TR=3000 ms, TE=17 ms, ET=4; and TR=3800 ms, TE=102 ms, ET=8. Section thickness for the FSE series was 4 mm, no gaps (interleaved). For all series, the field of view was 24 cm.

IMAGE ANALYSIS

The image-analytic approach is similar to that used in our previous anatomical studies (Jernigan et al. 1990, 1991a; Jernigan and Ostergaard 1993), but represents a significant elaboration of these methods as described recently (Jernigan et al. 2001), and briefly below. Trained anatomists who were blind to participant diagnosis, age, sex, or any other identifying information subjected each image data set to the following image analysis procedures: (1) interactive isolation of intracranial regions from surrounding extracranial tissue, (2) three-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact, (3) reslicing of the volume to a standard orientation, (4) tissue segmentation using semi-automated algorithms, and (5) neuroanatomical region-of-interest analysis.

Brain was first isolated from extracranial areas in the image, i.e. from surrounding tissue that is in some instances contiguous with brain tissue and similar in signal value. The stripping operations were performed independently on six pairs of image volumes (obtained on different occasions); discrepancies in brain volume were small (mean 0.54%, range 0.03–1.25%).

Filtering was applied to reduce non-biological signal drift across the field of view, which is presumably due to field inhomogeneity and susceptibility effects. A three-dimensional, high-pass filter was applied, with two iterations, separately to the 'stripped' proton density (PD) weighted and T_2 weighted FSE image volumes. After filtering, image data sets were resectioned in a standard coronal plane defined relative to the decussations of the anterior and posterior commissures and the structural midline. The T1-weighted and FSE data sets are registered so that sections from all three data sets are available to the operators when attempting to resolve anatomical boundaries.

The tissue classification procedure is an interactive, supervised process. Operators designate the positions of three sets of tissue samples, one for each of the target tissues (gray, white, and CSF). Samples are selected in standard locations that appear to be homogeneous and free of signal abnormalities both in the section to be sampled and in the adjacent sections. In most cases, samples include 6 gray matter samples taken bilaterally in the caudate nucleus, putamen and pulvinar samples; 4 bilateral white matter samples in the suprasylvian region at the level of the pulvinar and at the level of the caudate/putamen; and 4 CSF samples taken within the frontal horns and posteriorly at approximately the level of the trigones of the cerebral ventricles. Sample voxel values are then analyzed using simple regression techniques to separate first all brain parenchymal voxels from CSF voxels, and then gray matter voxels from white matter voxels. The regression coefficients obtained in these simple analyses were then applied to classify each voxel within the volume as most similar to CSF, gray matter, or white matter. Interoperator reliability of total tissue volumes for independent tissue classification by two anatomists was estimated using 11 brain data sets, and was 0.92 for white matter, 0.95 for gray matter, and 0.99 for CSF.

Anatomists circumscribe regions on tissue-segmented images with standardized rules for delineating a set of subcortical structures and cortical regions. The region referred to as basomesial diencephalon includes septal nuclei, mamillary bodies, and other hypothalamic structures, the bed nucleus of the stria terminalis, and the diagonal band of Broca. The four major cortical lobes are drawn to include cortical gray matter, underlying white matter, and CSF. Volumes of each tissue are separately estimated within each lobe, and white matter and CSF volumes are also measured in a deep subcortical zone not within any of the cortical lobes. Gray matter and adjacent CSF of the cingulate cortex and insular cortex are defined separately. Representative fully processed images from a normal brain, illustrating the regional boundaries of brain structures, are shown in Figure 1.

For the present study the frontal lobe is defined as cortex

Table I: Participant demographics

	Controls	*FAS*	*PEA*
n	41	14	12
Age range, y	7–24	8–19	10–22
Age mean (SD), y	12.8 (4.8)	11.4 (3.3)	14.8 (4.4)
Sex, F/M	20/21	8/6	4/8

FAS, fetal alcohol syndrome; PEA, prenatal exposure to alcohol.

and underlying white matter anterior to the central sulcus and superior to the sylvian fissure (including cingulate cortex, but excluding insular cortex). Temporal lobe is defined as cortex and underlying white matter inferior to the sylvian fissure (also excluding insular cortex). Parietal lobe is defined as cortex and underlying white matter posterior to the central sulcus and anterior to the sylvian fissure. The posterior boundaries of both the temporal and parietal lobes are defined in part stereotactically on the standardized sections. Both lobes extend to the coronal section immediately anterior to the section containing the occipital notch. All cortex and underlying white matter posterior to this section is defined as occipital. Within sections at the intersection of the parietal, temporal, and occipital lobes, the parieto-occipital and the temporo-occipital sulci divide the respective lobes.

The deep subcortical zone is defined as that region lying mesially to the four lobes and including insular cortex, deep white matter, and the subcortical structures listed in Figure 1. The hippocampus and amygdala are excluded from the temporal lobe and measured separately as subcortical structures. The hippocampal region extends to the section immediately posterior to the pulvinar of the thalamus where it lies inferior to the corpus callosum. It extends anteriorly to (but not including) the section immediately posterior to the section in which the long columns of the fornix appear, i.e. the anterior boundary is defined in part stereotactically. The transition to the amygdala/entorhinal region occurs in this (immediately posterior) section behind the long columns of the fornix, and the region extends anteriorly to and including the section at which the temporal pole is entirely separated from the frontal lobe and the temporal stem is no longer visible. The inferior boundary of the hippocampus is defined by following the white matter through the bend in the parasubicular region, separating the subiculum from the entorhinal cortex.

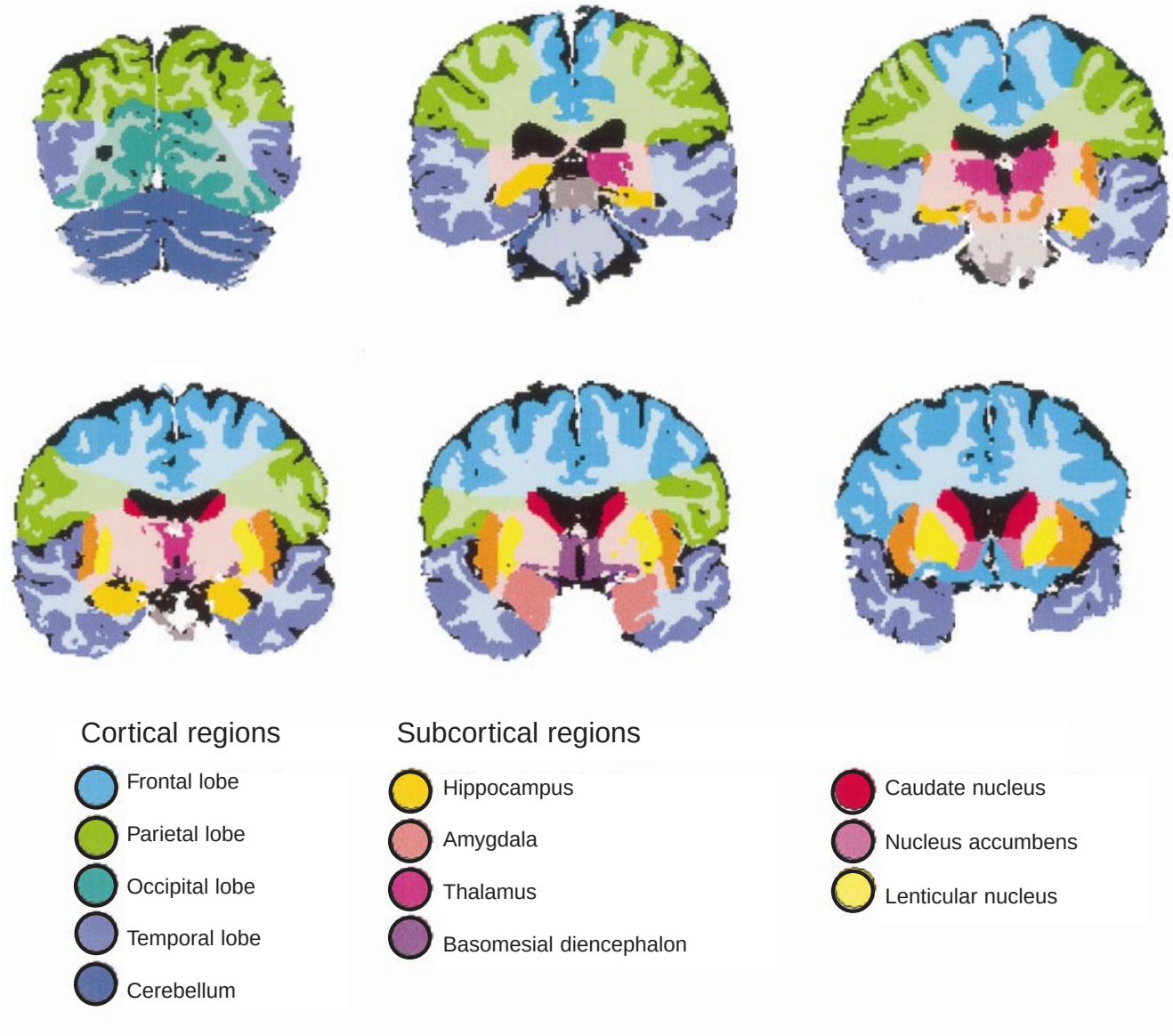

Figure 1: *Examples of six representative sections showing structural boundaries. White matter voxels are lighter color shades, gray matter voxels are darker colors, and CSF is coded black.*

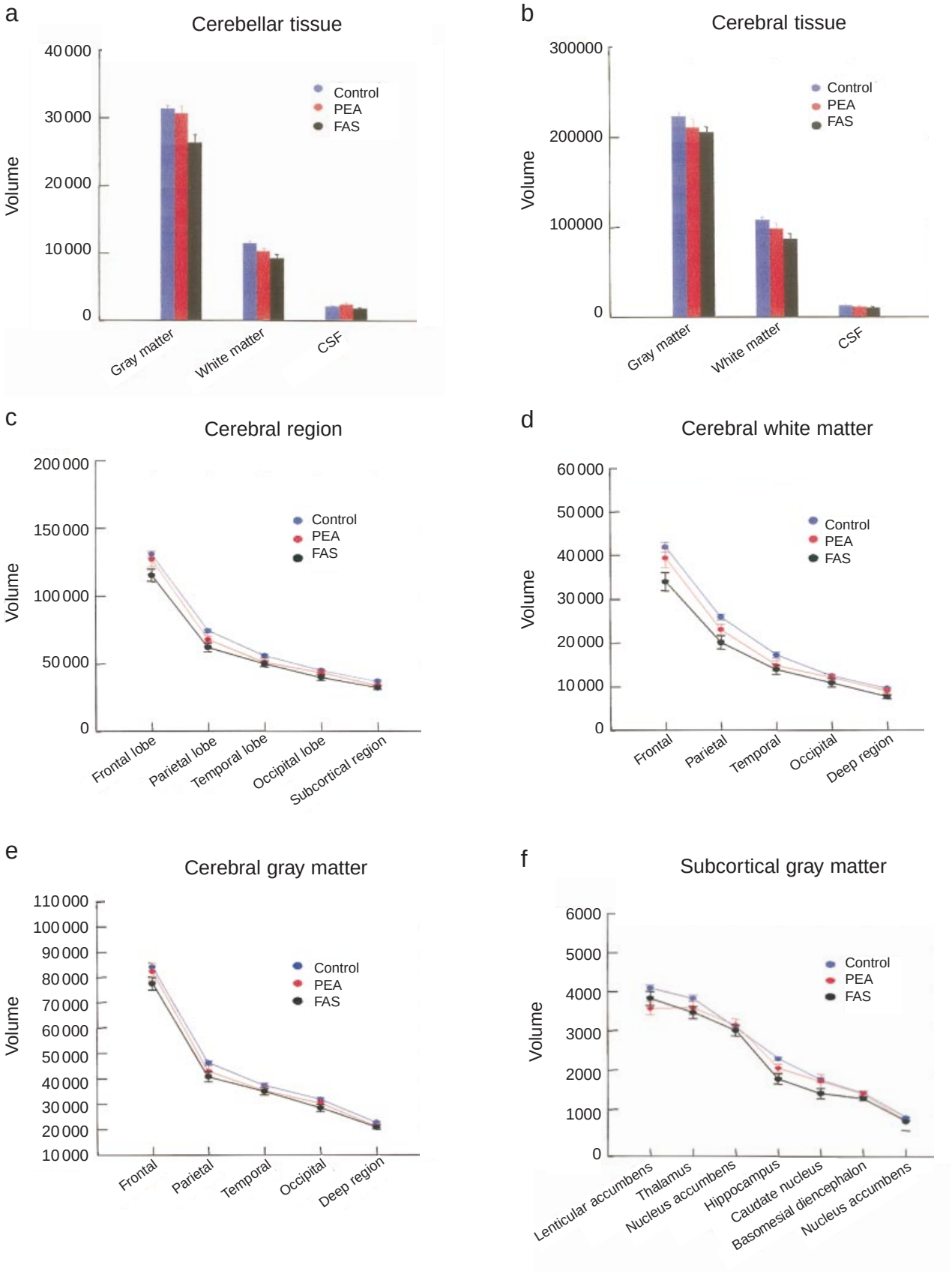

Figure 2: *Mean and standard errors of raw volumes in voxels for regions or tissue types. Regions are ordered by size on x-axis and line graphs connect group means. Comparisons (a) for each tissue type within cerebellum; (b) for each tissue type within cerebrum; (c) of total volumes of each cerebral region; (d) of white matter volumes of each cerebral region; (e) of gray matter volumes of each cerberal region; (f) of volumes of subcorical regions.*

The amygdala/entorhinal region includes amygdala, some very anterior hippocampus, contiguous entorhinal cortex, and the uncus (which includes perirhinal cortex). Interoperator reliability for estimated volumes of the primary gray matter structures, by analysis of 10 brain data sets, was performed independently by two anatomists. Results ranged from 0.88 to 0.99, with reliability for most measures exceeding 0.95. To summarize, the specific measures examined in the present study were gray matter, white matter, and CSF of each cerebral lobe and of the cerebellum; as well as gray matter volumes of the following subcortical structures: the hippocampus, amygdala, caudate nucleus, nucleus accumbens, lenticular nucleus, thalamus, and basomesial diencephalon.

Table II: Cerebral and cerebellar raw volume comparisons

Raw values	*Kruskal–Wallis (FAS, PEA, NC)*	*p*	*Mann–Whitney U (FAS vs NC)*	*p*
Total cranial vault	10.8	0.005	460	0.001
Cerebral cranial vault	10.2	0.006	460	0.001
Cerebral gray matter	5.3	0.069	282	0.031
Cerebral white matter	8.3	0.017	309	0.004
Cerebral CSF	1.0	0.619	232	0.383
Cerebellar cranial vault	13.7	0.001	475	0000
Cerebellar gray matter	12.9	0.002	471	0.000
Cerebellar white matter	10.4	0.005	439	0.003
Cerebellar CSF	4.6	0.100	369	0.113

FAS, fetal alcohol syndrome; PEA prenatal exposure to alcohol; NC, control participant.

Table III: Control versus FAS comparisons of proportional region volumes

Proportional measures	*Mann–Whitney U FAS vs NC*	*p*
a. Proportion of cranial vault		
Cerebellar cranial vault	381	0.069
b. Proportion of lobe sum		
Frontal lobe	168	0.441
Parietal lobe	302	0.008
Temporal lobe	135	0.106
Occipital lobe	144	0.166
c. Proportion of cerebrum		
Cerebral white matter	284	0.031
d. Proportion of cerebellum		
Cerebellar white matter	367	0122
e. Proportion of cortex		
Frontal cortex	146	0182
Parietal cortex	291	0.017
Temporal cortex	166	0.411
Occipital cortex	164	0.383
f. Proportion of white matter sum		
Frontal lobe white	204	0.878
Parietal lobe white	289	0.020
Temporal lobe white	167	0.426
Occipital lobe white	127	0.068
g. Proportion of subcortical structures		
Caudate nucleus	321	0.002
Lenticular nucleus	137	0.117
Basomesial diencephalon	197	0.980
Thalamus	150	0.218
Hippocampus	122	0.050
Amygdala	260	0.122
Nucleus accumbens	212	0.719

FAS, fetal alcohol syndrome; NC, control participants.

STATISTICAL ANALYSES

Because of the modest sample sizes in the alcohol-exposed groups, and concern about skewing in the distributions, the nonparametric Kruskal–Wallis and Mann–Whitney *U* tests were used to compare groups. The group effects were examined hierarchically, with global structure comparisons preceding regional comparisons. Groups were first compared on volume of the overall cranial vault. Groups that differed were then compared on proportional loss of supratentorial versus infratentorial structures. Groups differing in cerebrum volume were also compared on the proportional losses across the major cerebral lobes. Groups differing in either compartment were then compared on proportional loss of gray versus white matter within that compartment. When there was evidence that gray and white matter were affected differentially, lobar analysis was conducted separately for each tissue compartment. Finally, comparisons of the proportional losses among subcortical structures were made.

Results

Significant group differences were observed for volume estimates of the cranial vault, the cerebral (supratentorial) vault, the cerebellar (infratentorial) vault, cerebral gray matter (Fig. 2b), cerebral white matter (Fig. 2b), cerebellar gray matter (Fig. 2e), and cerebellar white matter (Fig. 2d). These results are summarized in Table II. Groups did not differ on estimates of the volume of cerebral CSF (Fig. 2b) or cerebellar CSF (Fig. 2a). Post hoc comparisons of the groups revealed that in all cases the effects of group were mediated by significant volume reductions (hypoplasia) in the FAS group relative to the control group. In no case did the PEA group differ significantly from the controls on these global volumes. Secondary analyses attempted to define the pattern of brain hypoplasia present in FAS participants.

The first set of secondary analyses compared the FAS and control groups on proportionalized brain volumes of different structures and regions (Table III). First, in order to determine

Table IV: Post hoc PEA versus control comparisons of parietal and caudate effects

	Mann–Whitney U (PEA vs NC)	*p*
Raw values		
Parietal lobe sum	334	0.061
Parietal lobe white matter	337	0.054
Parietal lobe gray matter	313	0.154
Caudate nucleus	294	0.125
Proportions		
Parietal lobe sum	229	0.198
Parietal lobe white matter	216	0.350
Parietal lobe gray matter	235	0.147
Caudate nucleus	246	0.080

PEA, prenatal exposure to alcohol; NC, control participants.

whether the cerebrum and cerebellum were affected to comparable degrees, volume of the cerebellar (infratentorial) cranial vault was expressed as a proportion of the volume of the total cranial vault (infratentorial plus supratentorial). The group difference on this proportion approached significance, suggesting that cerebellar hypoplasia may exceed cerebral hypoplasia (Table IIIa). Next, within the cerebrum, each lobe (gray and white matter combined) was expressed as a proportion of the total cerebral volume (gray and white combined), and the groups were then compared on these proportions (Table IIIb). Only group difference on the parietal lobe proportion reached significance, and this difference revealed that the parietal lobe was disproportionately reduced in volume in FAS participants relative to controls.

To examine the possibility that either gray matter or white matter was disproportionately affected in FAS participants, we computed, separately for the cerebrum and cerebellum, the proportion of brain volume that was white matter (Table IIIc,d). A significant proportional reduction of white matter was observed in the cerebrum, while a smaller proportional white matter reduction in the cerebellum did not reach significance. Thus it appears that, at least within the cerebrum, white matter hypoplasia is more severe than gray matter hypoplasia in FAS participants.

This discrepancy in the magnitude of the group differences between cerebral gray and white matter volumes prompted comparison of the different lobes by tissue type (Table IIIe,f). That is, the cortex of each of the four cerebral lobes was expressed as a proportion of the sum of the cortex in the four lobes and the groups were compared on these proportions. Similarly, the white matter of each lobe was expressed as a proportion of the total cerebral white matter volume in the four lobes groups were compared on these proportions. The groups differed significantly on the proportional parietal cortex volume.

Proportional measures of both parietal and occipital white matter volumes approached significance. Both parietal lobe gray matter and parietal lobe white matter were disproportionately reduced in FAS participants relative to controls, while the difference on the occipital lobe measure was a result of proportionally larger volumes in the FAS group which may reflect relative sparing of the occipital lobe white matter in FAS participants.

Finally, the pattern of hypoplasia across subcortical structures was examined (Table IIIg). Each volume was expressed as a proportion of the sum of the subcortical structure volumes. The two groups differed on the proportional measures for the caudate and hippocampus. There was disproportionate reduction of caudate nucleus volume in FAS participants, with disproportionate sparing of hippocampal volume in an otherwise hypoplastic brain. Pattern differences are illustrated in Figure 2a–f.

Since the brains of FAS participants seemed to differ most strikingly from the brains of their controls in caudate nuclei and parietal lobe volumes, we conducted post hoc comparisons of the PEA and control groups on measures from these regions (Table IV). The rationale was that differences might be present between the PEA and control groups in these regions if PEA participants had suffered similar but more moderate effects on brain development. The comparisons of estimated raw volumes of these structures did not reveal significant reductions in the PEA participants relative to controls, although a reduction in the total parietal lobe and parietal lobe white matter volumes approached significance. Group differences on the proportional measures of caudate volume (relative to total subcortical gray volume) also approached significance (Table IV). Thus these findings, while far from conclusive, raise the possibility that a similar, but milder, pattern of brain hypoplasia exists in some PEA participants.

Discussion

These results confirm and extend our previous observations describing the effects of prenatal alcohol exposure on cerebral morphology. They provide additional information about brain structures not previously examined separately, such as the hippocampus, the amygdala, and the nucleus accumbens; they also include a systematic comparison of the effects across the major tissues and lobes.

Since the major effects were due to hypoplasia in the FAS participants, these results are most relevant to those individuals in whom the full syndrome is present. In such cases, generalized hypoplasia of the brain occurs, but at least within the cerebrum, white matter is more severely affected than gray matter. This pattern could be caused by a disproportionate effect on the process of myelination. Other investigators have examined the effects of prenatal alcohol exposure on astroglial development in the rat brain and conclude that effects on important precursor radial glial cells may lead to alterations of axon growth and subsequent dysmorphology of the corpus callosum and other white matter tracts (Guerri et al. 1997). Since myelination of cerebral white matter, particularly in frontal and parietal lobes, continues well into adulthood, it is possible that the effects observed here are due in part to developmental delays. Ongoing longitudinal studies may reveal whether myelination is proceeding normally in these participants.

Whatever the cause of disproportionate white matter hypoplasia in the cerebrum of FAS participants, it does not result in the same pattern of loss in the cerebellum. This may be due to the specific sensitivity of cerebellar neurons, particularly Purkinje cells but also granule cells, to the teratogenic effects of alcohol (Bonthius and West 1991, Maier et al. 1999). It may be that the damaging effects of prenatal alcohol exposure on white matter development affect cerebrum and cerebellum similarly, but that the disproportionate loss of cerebellar neurons alters the balance of gray and white matter hypoplasia in the two structures. The fact that both neuronal and glial populations within the cerebellum are particularly vulnerable to fetal alcohol exposure may account for the trend toward more severe cerebellar than cerebral hypoplasia overall.

Lobar analysis of cerebral hypoplasia in FAS indicates most severe effects on the parietal lobe in both white and gray matter compartments. A series of MRI studies of normal development have shown that maturation and growth of frontal and parietal lobes continues well into adulthood, and longer than in other parts of the cerebrum, in association with late myelination (Jernigan et al. 1991b; Sowell et al. 1998, 1999a,b). Therefore, one question that arises is whether the young people with FAS in the present study will show normal progressive changes in brain development, and whether the degree of hypoplasia in parietal lobes observed relative to age peers will increase or decrease as they, and their controls, reach adulthood.

The pattern of effects on subcortical structures in this

sample of young people with FAS is striking, with no evidence of any reduction in hippocampal volume, but severe effects on the caudate nucleus. Although other subcortical structures are also reduced in volume, i.e. other basal ganglia structures and diencephalic structures, these appear to be affected to approximately the same degree as cerebral gray matter overall. The relative sparing of the hippocampus is puzzling: it is unclear whether this results from a lack of vulnerability of hippocampal cell populations, or from incomplete maturational 'pruning' within the structure, due, for example, to reduced neural interaction with more heavily affected structures elsewhere in the brain.

These results suggest that the effects on the brain that accompany FAS include not only generalized growth retardation of the brain as reflected in microcephaly, but a characteristic alteration of the shape of the maturing brain due to disproportionate effects on the growth of specific tissues and brain structures relative to others. The case for cerebral dysmorphology in PEA cases that do not meet criteria for FAS, based on the present findings, is marginal. However, it may be important that in PEA, as in FAS, some evidence was found for relative reductions in basal ganglia and parietal lobe volumes. These suggestive findings in the PEA group may result from similar but more modest effects on brain growth in these participants, or may be due to the inclusion of some 'affected' and some 'unaffected' individuals in this group. The pattern of the changes in brain volumes may be central to behavioral and neuropsychological features common to these two alcohol-exposed groups. Further studies are needed to resolve this question.

Accepted for publication 17th October 2000.

Acknowledgements

This work was supported by NIH grants AA10417 (EP Riley), P50 NS22343 (E Bates), and RO1 HD 23854 (DA Trauner), and by the Medical Research Service of the Department of Veterans Affairs (PI: TL Jernigan).

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