Cerebral Growth in Fragile X Syndrome: Review and Comparison With Down Syndrome

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INTRODUCTION

The past decade of multi-disciplinary research efforts focusing on the neurobiology and functional sequelae of fragile X syndrome (FraX) has significantly advanced our understanding of the relation between gene, brain, and behavior in this disorder (Kaufmann and Reiss, 1999). However, in order to obtain a more comprehensive understanding of the pathophysiology of FraX, more specific information is needed regarding the way in which the FMR1 mutation affects the neuropathology of FraX, which include reductions in the posterior cerebellar vermis, age-dependent increases in hippocampal volume, and enlarged caudate nucleus and thalamus. Contrasting with these limbic and subcortical anomalies, much less is known about the neocortex in FraX. The present study attempted to examine cerebral and lobar-level volumetric changes in young males with FraX (2–7 years), by comparing groups of subjects with full mutation (FM) and mosaicism (Mos) with both age-matched controls and subjects with developmental language delay (DLD) and Down syndrome (DS). For this purpose, we used high resolution (i.e., SPGR) MRI scans and semi-automated methods for segmenting (tissue class) and parcellating (i.e., Talairach) the brain. In agreement with previous studies, we found no changes in overall brain or cerebrum size in FraX. Nevertheless, boys with FM FraX had relative reductions in temporal lobe volume (primarily gray matter) and relative preservation/enlargement of parietal white matter volume. While temporal lobe reductions were not specific, since they were also observed in DLD and DS subjects, parietal preservation/enlargement was only seen in FraX. The relevance of these preliminary findings was emphasized by comparisons between FraX groups, which revealed more marked changes in FM FraX than in Mos FraX (i.e., gene dosage). While cross-sectional analyses revealed marked age-dependent decreases in DS, a group showing marked global and lobar volumetric reductions, there were no changes over time in FraX. These neuroimaging data are discussed in the context of FraX neurobiology and other developmental disorders. Microsc. Res. Tech. 57:159–167, 2002. © 2002 Wiley-Liss, Inc.

KEY WORDS Fragile X; neuroimaging; cerebrum

ABSTRACT Neuroimaging studies have shown selective changes in brain size in Fragile X syndrome (FraX), which include reductions in the posterior cerebellar vermis, age-dependent increases in hippocampal volume, and enlarged caudate nucleus and thalamus. Contrasting with these limbic and subcortical anomalies, much less is known about the neocortex in FraX. The present study attempted to examine cerebral and lobar-level volumetric changes in young males with FraX (2–7 years), by comparing groups of subjects with full mutation (FM) and mosaicism (Mos) with both age-matched controls and subjects with developmental language delay (DLD) and Down syndrome (DS). For this purpose, we used high resolution (i.e., SPGR) MRI scans and semi-automated methods for segmenting (tissue class) and parcellating (i.e., Talairach) the brain. In agreement with previous studies, we found no changes in overall brain or cerebrum size in FraX. Nevertheless, boys with FM FraX had relative reductions in temporal lobe volume (primarily gray matter) and relative preservation/enlargement of parietal white matter volume. While temporal lobe reductions were not specific, since they were also observed in DLD and DS subjects, parietal preservation/enlargement was only seen in FraX. The relevance of these preliminary findings was emphasized by comparisons between FraX groups, which revealed more marked changes in FM FraX than in Mos FraX (i.e., gene dosage). While cross-sectional analyses revealed marked age-dependent decreases in DS, a group showing marked global and lobar volumetric reductions, there were no changes over time in FraX. These neuroimaging data are discussed in the context of FraX neurobiology and other developmental disorders.
brain regions that differentiate individuals with FraX from controls, including the contents of the posterior fossa (Guerreiro et al., 1998; Mostofsky et al., 1998; Reiss et al., 1988, 1991a,b), caudate nucleus (Murphy et al., 1999; Reiss et al., 1995), hippocampus (Jakala et al., 1997; Kates et al., 1997b; Reiss et al., 1994), and superior temporal gyrus (Reiss et al., 1994). Other studies have used FraX MRI data for developing and evaluating tissue segmentation (Reiss et al., 1998) and brain region parcellation (Aylward and Reiss, 1991; Kaplan et al., 1997; Kates et al., 1997b) protocols. The following is a bibliographic review of structural MRI studies in FraX according to specific brain regions.

CEREBRUM

In a study of 31 females and 18 males with FraX (age range, 2–28 years), compared to samples of IQ-matched (developmentally disabled) and normal controls, Reiss and coworkers (1995) reported significantly increased total cerebral volumes in FraX females, and a trend in the same direction for males with FraX, relative to unaffected controls. However, a more recent report from the same research group (Eliez et al., 2001) found no differences in total cerebral volume for either males or females with FraX. Since the samples for these two studies overlapped to some extent (Eliez et al., 2001), the source of these inconsistent findings is not evident, and warrants further investigation. In terms of cerebral lobar changes, the only region reported prior to the present study is the temporal lobe; Reiss and colleagues (1994) found age-related decreases in the volume of the superior temporal gyrus in a group of children and adolescents with FraX.

CEREBELLUM

Reiss and colleagues (1991a,b) found that the posterior cerebellar vermis region was reduced in both males and females with FraX compared to gender-matched controls (Fig. 1). In their initial study, in which 14 male subjects with FraX (age range, 2–43 years; mean age, 15.7) were compared to samples of 17 age- and IQ-matched individuals with development disabilities and 18 age-matched controls with normal IQs, Reiss and coworkers (1991a) reported that subjects with FraX demonstrated decreases in the posterior vermic lobules VI and VII (in absolute area as well as relative to intracranial area) and increases in the size of the fourth ventricle. In a complementary study of 12 females with FraX (age range, 6–27 years) and 13 age-and IQ-matched controls, lobules VI and VII were similarly decreased, and the fourth ventricle increased, in females with FraX (Reiss et al., 1991b), although the differences between females with FraX and controls were not as pronounced as those found between males with FraX and controls. As this “intermediate effect” of the mutation on females is expected in an X-linked disorder such as FraX, the decrease in lobules VI–VII of the vermis in these studies appeared to be a distinctive feature of FraX related to FMR1 mutation. A more recent study with a larger sample, by the same group (Mostofsky et al., 1998), confirmed the absolute and relative decrease in posterior vermis (lobules VI–X) size in males with FraX (n = 32) when compared with both normal (n = 38) and developmentally delayed (n = 28) controls. Although a similar comparison for females with FraX (n = 37) corroborated the posterior vermis hypoplasia when contrasted with 53 female controls, the specificity of the lobule VI–VII hypoplasia was not confirmed since similar comparisons between FraX males and developmentally delayed subjects were not significant (Mostofsky et al., 1998).

Associations between hypoplasia of the cerebellar vermis and behavioral and cognitive dysfunction in FraX have been reported in two studies. In an investigation of 30 school-age girls with FraX, Mazzocco and colleagues (1997) have described a significant negative correlation between the area of lobules VI and VII and parental ratings of frequency and severity of autistic behaviors, particularly in social communication and stereotypic behaviors. In the study cited above, Mostofsky et al. (1998) reported an association between posterior vermis size and performance on Full Scale, Verbal and Performance IQs, as well as on neuropsychological measures.

Fig. 1. Midsagittal MR images of (A) a male control patient and (B) a male with FraX. Borders are drawn around the anterior cerebellar vermis (lobules I to V), and lobules VI to VII and lobules VIII to X of the posterior cerebellar vermis. The area of the lobules comprising the posterior vermis appear smaller in the male with fragile X syndrome. Reproduced from Reiss et al. (1991a) with permission of the publisher.
chological measures traditionally associated with executive function. Knowledge of the functional neuroanatomy of the cerebellar vermis supports the notion that the vermis may be part of the circuits that underlie dysfunction in both behavioral regulation and cognition in FraX. The vermis plays a role in modulating sensory stimulation through its connections to the auditory and visual cortex, as well as a role in mediating higher-order cognitive function through its connections to the frontal lobe (Ivry, 1993).

HIPPOCAMPUS

Hippocampal anomalies have also been reported in FraX. In a study of 6 females and 9 males with FraX (age range, 6–27 years) and an unpaired sample of age- and IQ-matched controls, Reiss and colleagues (1994) found that both right and left hippocampal volumes were increased by approximately 20% in individuals with FraX (Fig. 2). A more moderate increase (7% left hippocampus, 13% right hippocampus) was found in a follow-up study, including five boys (age range, 3–12 years) and five girls (age range, 5–13 years) with FraX that were compared to unaffected age-matched control subjects (Kates et al., 1997b). However, in a sample of adults with FraX, Jakala et al. (1997) found no differences in hippocampal volume between FraX and control subjects. Given the small sample sizes, various age ranges, and inconsistent findings of these studies, the temporal lobe findings in FraX remain tentative.

SUBCORTICAL STRUCTURES

Abnormalities have also been reported in the caudate nucleus and thalamus. In their study, Reiss and colleagues (1995) found an increase in the volume of the caudate nucleus in both males and females with FraX, an increase in the volume of the lateral ventricles in males, as well as an increase in the volume of the thalamus in females (Fig. 3). In addition, Hjalgrim and coworkers (1999), using SPECT, reported resting frontal-subcortical hypofunction in individuals with FraX. The circuit that links the caudate nucleus and the prefrontal cortex has been associated with the regulation of impulse control and attention. Dysfunction of this neural circuit seems to be associated with hyperactivity, inattention and perseveration, which are all features of the FraX neurobehavioral phenotype (Kaufmann and Reiss, 1999).

In sum, several neuroanatomical structures appear to be anomalous in individuals with FraX, and are associated with the cognitive and behavioral features that characterize this disorder. However, there continue to be gaps in knowledge regarding FraX. Despite the inclusion of young subjects in several studies, there is a lack of systematic information about the ways in which the neuroanatomical phenotype is expressed in very young children with FraX. Accordingly, very little is known about the period of early postnatal brain development in this disorder. This is due to the fact that at the time that the earliest neuroimaging studies were conducted, children were often not identified with the syndrome until 4 or 5 years of age. Ethical issues have also prevented the recruitment of large numbers of very young control subjects. In addition to the limited understanding of neurodevelopment in very young children with FraX, very little is known about the ways in which the FMR1 mutation affects specific regions of the brain.
the neocortex. To date, the majority of anatomic imaging studies have focused on subcortical and limbic regions of the brain.

To increase knowledge in an understudied area, we report here the results of a study of young boys with FraX, ranging in age from 2 to 7 years, compared to both an age-matched sample of boys with developmental language delay (DLD) and boys with Down syndrome (DS). These contrast groups were chosen in order to provide comparative data from which to address the issue of the specificity of the neuroanatomic differences in FraX. A small sample of relatively young normal controls, recruited for other studies in our laboratory, was also included as a contrast group. Using recently developed, semi-automated methods for parcelling the brain into neurofunctional regions and segmenting these regions into tissue compartments according to a revised Talairach (Talairach and Tournoux, 1988), stereotaxic grid specifications, and cerebrospinal fluid (CSF) (Kaplan et al., 1997), we focused specifically on the measurement of the cerebral lobes in this study.

**METHODS**

**Sample**

The subjects consisted of 68 boys between the ages of 2 years 2 months and 8 years of age. The FraX mutation was confirmed by standard genetic (Southern blots) assays on all children with FraX. Children with full mutation FraX were grouped separately from children with *FMRI* mosaicism. The samples consisted of:

1. Full mutation (FM) FraX: N = 21; mean age, 4.89 (SD, 1.7); age range, 2.75–7.96; mean IQ, 50.5 (SD, 14.7); IQ range, 20–76.
2. Mosaic (Mos) FraX: N = 12; mean age, 4.96 (SD, 1.3); age range, 2.19–6.61; mean IQ, 59.8 (SD, 16.8); IQ range, 31–81.
3. Developmental language delay (DLD): N = 15; mean age, 5.18 (SD, 1.2); age range, 3.70–7.68; mean IQ, 64.7 (SD, 23.9); IQ range, 35–110.
4. Down syndrome (DS): N = 12; mean age, 5.94 (SD, 1.6); age range, 2.94–8.0; mean IQ, 31.1 (SD, 12.7); IQ range, 13–49.
5. Unaffected controls (NC): N = 8; mean age, 5.79 (SD, 1.7); age range, 3.02–7.39; mean IQ, 114.7 (SD, 8.7); IQ range, 102–126.

Children with FraX and DLD were recruited as part of a longitudinal study of development in young boys with FraX. Children with DS were recruited through the Down Syndrome Clinic of the Kennedy Krieger Institute. Unaffected controls were recruited for ongoing studies in our laboratory. Prior to recruitment, they were screened and excluded for the presence of neurological, learning, or psychiatric disorders. Informed consent was obtained from all parents and guardians, with a protocol that was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions.

**Image Acquisition and Processing**

Coronal, axial, and sagittal MRI images of each subject’s brain were acquired with a GE-Signa 1.5 Tesla scanner (General Electric, Milwaukee, WI). The sagittal T1-weighted scout was acquired with the following scan parameters: TR = 500–600, TE = 20, NEX = 1, matrix size = 256 × 256, field of view = 24 cm. Axial images were obtained using a double echo proton density T2-weighted sequence with the following parameters: TR = 3,000, TE = 30/100, NEX = 1/2, matrix size = 256 × 192, field of view = 24 cm. Coronal images were acquired with a 3-D volumetric radiofrequency spoiled gradient echo (SPGR) series with the following scan parameters: TR = 35–45, TE = 5–7, flip angle = 45, NEX = 1, matrix size = 256 × 128, field of view = 20–24. This SPGR series was partitioned into 124 1.5-mm contiguous slices.

Raw, GE-Signa formatted image data were transferred from the MRI scanner at Johns Hopkins Hospital to Apple Macintosh Power PC workstations via existing network connections. The SPGR image data were imported into the program BrainImage (Reiss, 1997) for visualization, processing, and quantitation (Subramaniam et al., 1997). The data were prepared for measurement by correcting for radiofrequency inhomogeneity artifacts, removing non-brain material, and reslicing the images to produce cubic voxel datasets (Subramaniam et al., 1997). The cubic voxel datasets were opened into the multiplanar visualization module of BrainImage, so that three orthogonal representations of the data could be viewed simultaneously.

**Image Measurement**

The isolated brain tissue was subdivided into cerebral lobes, subcortical, brainstem, and cerebellar regions according to a revised Talairach (Talairach and Tournoux, 1988) stereotaxic grid specific for measurement in pediatric study groups (Andreasen et al., 1996; Kaplan et al., 1997; Kates et al., 1999). Only cerebral lobe data, which have high levels of sensitivity and specificity (Kates et al., 1999), were used in this study. Each region was then segmented into gray, white, and CSF compartments using an algorithm that assigns voxels to one or more tissue categories based on intensity values and tissue boundaries (Reiss et al., 1998).
The segmentation method used was determined reliable for all gray matter, white matter, and CSF volumes (Reiss et al., 1998). All measurements were carried out by research assistants blind to the diagnosis of each subject.

**IQ Determination**

All children were administered the Bayley Scales of Infant Development-Second Edition (Bayley, 1993) and/or the Stanford-Binet Intelligence Scale-Fourth Edition (SB-IV) (Thorndike et al., 1986). The former test provides mental (MDI) and overall developmental (DQ) quotients. For all children whose abilities fell below the 2-year age level, the DQ was used to derive an IQ-equivalent score. For children who exceeded the mental age ceiling (>2 years) on this measure, or who had adequate language development, the SB-IV was used to obtain a full-scale IQ score.

**Statistical Analyses**

Linear regression analyses and Spearman rank correlations were used to determine the association between IQ and both age and tissue volumes. Univariate (ANCOVAs) and multivariate (MANCOVAs) analyses were used to compare whole brain and lobar volumes between study groups. In order to correct for multiple comparisons, post-hoc tests were conducted with the Bonferroni/Dunn statistic, with significance levels set at an alpha level of .005. In order to account for the dynamic nature of volumetric changes throughout early childhood, age was used as a covariate. Since preliminary analyses demonstrated an overall significant effect for whole brain volume, it was used as a covariate as well. Although study groups differed significantly in IQ scores, we did not use IQ as a covariate, since preliminary analyses revealed a nonlinear relationship between age and IQ for both the FraX and DLD groups. The sequence of analyses was decided a priori and consisted of:

2. Total white and gray cerebral volumes, as in step 1.
3. Individual lobar tissue volumes, as in step 1.
4. Gray and white matter volumes of lobes for which analyses in step 3 revealed significant group differences in lobar tissue volume.

**RESULTS**

**Volumetric Comparisons**

Differences in total brain volume, total cerebral volume, cerebral gray, and cerebral white matter were investigated with analysis of covariance (ANCOVA), with diagnosis as the grouping variable, age as the covariate, and cerebral gray and white matter volumes as the dependent variables. Differences in whole brain volume (F [df:4,1,62] = 12.41; P < .0001); cerebral tissue (F [df:4,1,62] = 9.76; P < .0001); cerebral gray (F [df:4,1,62] = 11.51; P < .0001) and cerebral white (F [df:4,1,62] = 6.63; P = .0002) were all significant. Post hoc analyses indicated that the total brain, total cerebral, and gray matter volumes of the DS study group were significantly smaller than the volumes of all other contrast groups, and the white matter volumes of the DS study group were significantly smaller than the volumes of the control and FM FraX groups (Table 1).

In order to investigate overall differences between study groups in regional lobar tissue volumes, a multiple analysis of covariance (MANCOVA) was carried out with diagnosis as the grouping variable, whole brain volume and age as the covariates, and lobar tissue volumes (frontal, parietal, temporal, and occipital) as the dependent variables. Diagnosis (Wilks’ Lambda = .51; F [df: 16, 138] = 2.12; P = .01) and whole brain volume (Wilks’ Lambda = .77; F [df: 4, 45] = 3.34; P = .02) were significant, as were interactions between diagnosis and age, diagnosis and whole brain volume, and age and whole brain volume. Analyses of variance for individual lobar regions indicated that the significance of the overall MANCOVA for diagnosis was accounted for by differences in parietal and temporal tissue volume. For the parietal lobe, a follow-up ANCOVA [df = 4,1,61] revealed that diagnosis (F = 2.90; P < .03) and whole brain volume (F = 295.14; P < .0001) were significant. Post-hoc analyses using the
Bonferroni/Dunn test indicated that the parietal tissue volumes of the DLD and DS groups were significantly smaller than either FraX or controls. For the temporal lobe, a follow-up ANCOVA [df = 4,1,1,61] indicated that diagnosis ($F = 2.94; P < .03$) and whole brain volume ($F = 282.77; P < .0001$) were significant. Post-hoc analyses revealed that temporal lobe tissue volumes were significantly reduced in all study groups (FM FraX, mosaic FraX, DLD, and DS) relative to controls.

Analyses of covariance were conducted to determine the contribution of gray and white matter compartments to the volumetric tissue differences found in the parietal and temporal lobes. Only the white matter compartment of the parietal lobe [df = 4,1,1,61] contributed to the lobar tissue differences; both diagnosis ($F = 5.55; P < .0007$) and whole brain volume ($F = 181.73; P < .0001$) were significant. Post-hoc analyses indicated that reduced parietal white volumes in both the DLD and DS study groups contributed to the findings, although mosaic FraX subjects demonstrated significant reductions relative to FM FraX subjects as well.

Both white and gray compartments contributed to differences in temporal lobe tissue volumes. For temporal gray [df = 4,1,1,61], both diagnosis ($F = 3.98; P < .006$) and whole brain volume ($F = 226.25; P < .0001$) were significant. Post-hoc analyses indicated that FM FraX, DLD, and DS (but not mosaic FraX) groups were significantly reduced relative to controls. For temporal white [df = 4,1,1,61], both diagnosis ($F = 2.59; P < .05$) and whole brain volume ($F = 108.20; P < .0001$) were significant. Post-hoc analyses indicated that the white matter volumes of DLD and DS groups were significantly reduced; however, volume reductions for the mosaic FraX group approached significance ($P = .0057$).

Cross-Sectional Effects of Age on Cerebral and Lobar Volumes

In order to investigate the relation between age and cerebral and lobar volumes, the four study groups (excluding controls) were group-matched by age. The groups consisted of 38 subjects: 8 with FM FraX, 10 with Mos FraX, 14 with DLD, and 6 with DS. All subjects were between 3.6 and 6.9 years of age. Controls were excluded from these analyses due to their skewed age distribution. The data were analyzed with the Spearman Rank Correlation. No significant correlations were found between age and cerebral tissue, parietal gray, or parietal white for the subjects with FM FraX, Mos FraX, or DLD. Cerebral tissue and cerebral white matter decreased significantly with age in the DS sample (Rho = -1.000; $P = .03$; Rho = -.94; $P = .03$, respectively). An inverse relation between age and cerebrocerebral gray matter approached significance (Rho = -.83; $P = .06$) (see Fig. 4).

No significant correlations were found between age and individual lobar gray and white matter volumes for the FM FraX, Mos FraX, or the DLD groups. In the DS sample, inverse relations were found between age and individual lobar gray and white matter regions, but (due to the small sample size) none reached significance with the exception of temporal gray matter (Rho = -.94; $P = .03$). The correlation between age and temporal white matter approached significance (Rho = -.83; $P = .06$).

**DISCUSSION**

Neuroimaging studies have shown selective changes in brain size in FraX. These include: reductions in the posterior cerebellar vermis (Mazzocco et al., 1997; Mostofsky et al., 1998; Reiss et al., 1991a,b), age-dependent increases in hippocampal volume (Kates et al., 1997b; Reiss et al., 1994), and enlarged caudate nucleus and thalamus (Reiss et al., 1995). Contrasting with these limbic and subcortical anomalies, much less is known about the neocortex in FraX. Data on cerebral volumes have been contradictory; although initial studies reported an enlarged cerebrum particularly in females (Reiss et al., 1995), a more recent publication did not replicate this finding (Eliez et al., 2001). At the lobar level, with the exception of an evaluation of the superior temporal gyrus, which showed age-related de-
creases in a group of children and adolescents (Reiss et al., 1994), no comprehensive examination of the cerebral cortex has been reported in FraX.

The results of the present study indicate that the brain and the cerebrum are not significantly altered in young males with FraX relative to controls (see Table 1). At the lobar level, only temporal lobe tissue volumes were different in FraX. Both FM FraX and Mos FraX subjects showed reductions with respect to controls. This temporal lobe volumetric change appeared to be predominantly influenced by decreases in gray matter, as evidenced in the FM FraX group when compared with controls. Parietal lobe changes were more subtle; parietal lobe tissue volumes in both FraX groups were larger than in DLD and DS boys, but comparable to normal controls. Moreover, analyses of tissue compartments revealed that, while FM FraX subjects had parietal white matter volumes comparable to controls, volumes of the Mos FraX group were reduced with respect to the FM FraX group.

With regard to the specificity of these findings, our MANCOVAs and ANCOVAs demonstrated that temporal lobe changes in FraX, which involved primarily gray matter, were not unique since boys with DLD and DS also demonstrated reduced temporal gray matter volumes. Nonetheless, the greater involvement of the FM FraX group suggests a gene dosage and, therefore, syndrome-dependent effect. On the other hand, the relative preservation/potential enlargement of parietal white matter seemed more specific to FraX. In contrast to the DLD and DS groups in which parietal (and temporal) volumes were reduced relative to controls, the parietal white matter in the FM FraX group was preserved relative to controls, and enlarged relative to subjects with Mos FraX. Accordingly, parietal preservation/enlargement is a potentially distinctive FraX feature that deserves further examination.

The preliminary cross-sectional volumetric analyses reported here, which only involved developmentally disabled individuals, demonstrated that, in the relatively short time interval under evaluation, only the DS group showed changes. In correspondence with the other volumetric comparisons, there was a significant age-dependent reduction in cerebral tissue, cerebral white matter, and temporal gray matter in DS. Similar findings, of lesser magnitude, were demonstrated for cerebral gray matter and temporal white matter in DS subjects. Cerebral gray matter reductions over time are concordant with quantitations of dendritic arborizations showing reductions beginning with early postnatal stages in DS (Becker et al., 1991). Nonetheless, the cross-sectional data reported here indicate that, during the period of late cerebral and synaptic development, there are no marked dynamic changes in FraX as those seen in DS.

Our findings of a relative preservation of brain and cerebral volumes in FraX are in agreement with the recent study by Eliez and colleagues (2001). Temporal lobe changes in FraX are not surprising; previous morphometric studies have shown an age-dependent decrease in superior temporal gyrus volume. Furthermore, a recent quantitative postmortem study demonstrated dendritic spine abnormalities in the temporal cortex (Irwin et al., 2001). However, the increase in density of dendritic spines and the long, immature morphology of the spines would predict an increase in temporal lobe volume, rather than the reduction we found. Moreover, neuronal counts of anterior superior temporal gyrus (Brodmann area 38) showed no differences between FraX subjects and controls (Hinton et al., 1991). Consequently, temporal gray matter volumetric reductions in FraX would be explained by decreases in dendritic arborizations, not yet reported in FraX. The latter is a suitable explanation considering that decreases in the size of dendritic trees are found in other developmental disorders (Kaufmann and Moser, 2000) and that, accordingly, temporal gray matter reductions were also found in the two contrast groups: DLD and DS. The lack of specificity of these findings further suggests that the temporal lobe is particularly vulnerable to genetic and environmental insults during development.

In light of the reductions in parietal white matter found in the DS, DLD, and Mos FraX study groups, the preservation and potential increase of parietal white matter volumes in the FM FraX group are intriguing, since the initial descriptions of abnormal dendritic spine morphology were based on parieto-occipital samples (Hinton et al., 1991). Accordingly, our data suggest that, in addition to the immature and elongated dendritic spines, there may also be changes affecting parietal cortical axons in FraX. As originally suggested by the knockout mouse data by Comery et al. (1997), the postulated axonal abnormalities could correspond to maturational and pruning failures. Potential alterations in the white matter of the parietal lobe are also
consistent with our knowledge of the cognitive deficits exhibited by individuals with this syndrome (Freund and Reiss, 1991). The deficits in visual spatial skills and working memory that have been described in children with FraX (Reiss et al., 1995) involve parietal lobe function. In addition, the present findings are supported by functional imaging studies of FraX females by Menon et al. (2000), who found a correlation between FMRP levels and activation of the frontal and parietal lobes during a visual spatial working memory task, and by Kwon et al. (2001), who reported that subjects with FraX failed to modulate frontal and parietal brain activation in response to increasing working memory demands.

In summary, integrating the results of the present study with those of previous reports, the apparent presence of both cortical and subcortical anomalies in the brains of FraX patients is consistent with Feng's finding of a widespread distribution of FMRP throughout the mammalian brain (Feng et al., 1997). Although we are not certain that widely distributed disruptions in FMRP levels will affect multiple regions in a similar way, the FraX phenotype, with a wide range of cognitive and behavioral features, is compatible with multiple anomalies in brain structure. Due to the limitations of sample size, age distribution, and other characteristics, our data on cerebral and lobar volumes should be considered preliminary in nature; however, the specificity of some findings warrants follow-up investigation. Future studies should include, in addition to larger samples with less skewed age and IQ distribution, an FMRP-based definition of FraX mosaic, analyses of sublobar regions, and correlations between volumetric and molecular and behavioral measures. In this way, we will gain a deeper understanding of gene-brain-behavior relations in young boys with FraX. Since the data reported here were drawn from an ongoing longitudinal study of young boys with FraX, analyses of longitudinal data will clarify, for example, the extent to which non-frontal white matter is preserved, or altered, in FM FraX. Finally, our findings also emphasize the importance of quantitative neuroimaging for the study of FraX. This type of research not only describes specific anatomical abnormalities, which complement the limited neuropathologic data on FraX, but also suggest abnormal developmental stages and processes (i.e., dendritic spine and axonal pruning) that advance our understanding of the neurobiology of FraX.

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