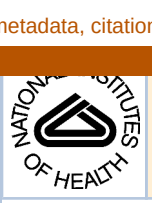

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Early white-matter abnormalities of the ventral frontostriatal pathway in fragile X syndrome

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Abstract

AIM—Fragile X syndrome is associated with cognitive deficits in inhibitory control and with abnormal neuronal morphology and development.

METHOD—In this study, we used a diffusion tensor imaging (DTI) tractography approach to reconstruct white-matter fibers in the ventral frontostriatal pathway in young males with fragile X syndrome (*n*=17; mean age 2y 9mo, SD 7mo, range 1y 7mo–3y 10mo), and two age-matched comparison groups: (1) typically developing (*n*=13; mean age 2y 3mo, SD 7mo, range 1y 7mo–3y 6mo) and (2) developmentally delayed (*n*=8; mean age 3y, SD 4mo, range 2y 9mo–3y 8mo).

RESULTS—We observed that young males with fragile X syndrome exhibited increased density of DTI reconstructed fibers than those in the typically developing (*p*=0.001) and developmentally delayed (*p*=0.001) groups. Aberrant white-matter structure was localized in the left ventral frontostriatal pathway. Greater relative fiber density was found to be associated with lower IQ (Mullen composite scores) in the typically developing group (*p*=0.008).

INTERPRETATION—These data suggest that diminished or absent fragile X mental retardation 1 protein expression can selectively alter white-matter anatomy during early brain development and, in particular, neural pathways. The results also point to an early neurobiological marker for an important component of cognitive dysfunction associated with fragile X syndrome.

Investigating neuroanatomical abnormalities in individuals with known genetic etiologies can advance our understanding of the relationship between specific genes and the development of the nervous system. Fragile X syndrome is most commonly caused by a trinucleotide repeat (CGG) mutation of the fragile X mental retardation 1 (*FMR1*) gene on chromosome Xq27.3, resulting in diminished or absent production of the *FMR1* protein (FMRP). *FMR1* mutations of approximately 200 or more CGG repeats result in the clinical features of fragile X syndrome and are referred to as 'full' mutations. Reduced FMRP levels in both humans and the knockout mouse are associated with increased dendritic spine density,[1] abnormal axonal guidance,[2] and an overall immature neuronal morphology.[3] In humans, fragile X syndrome is associated with a host of symptoms that include delays and qualitative abnormalities in cognitive development. One cognitive function known to be particularly deficient in fragile X syndrome is inhibitory

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control.[4] The current study was designed to investigate the neuroanatomical correlates of cognitive deficits associated with the *FMR1* full mutation during early brain development. To accomplish this goal, we studied a sample of very young males with fragile X syndrome (age ~1–3y) to assess early white-matter development of selected pathways associated with cognitive deficits such as inhibitory control.

The ability to inhibit one's behavior or cognitions effectively (i.e. cognitive inhibition) is thought to be a primary function of the ventral frontostriatal pathway. Indeed, previous neuroimaging studies of adolescents and adults with fragile X syndrome have reported abnormal blood-oxygen-related dependent signals[5] and fractional anisotropy[6] in regions that constitute this pathway. Recent advances in neuroimaging techniques, such as diffusion tensor imaging (DTI) tractography, allow for increased specificity in quantitative metrics of white-matter anatomy. In the current study, we used a tractography approach to dissociate ventral from dorsal frontostriatal fibers and to assess the integrity of these pathways by using fractional anisotropy and relative fiber density DTI metrics. Based on previous studies indicating ventral frontostriatal dysfunction in adolescents and adults with fragile X syndrome,[5] we predicted that we would observe evidence of atypical white-matter development in affected male infants and toddlers in the ventral but not the dorsal frontostriatal pathway. Further, based on studies showing that mutations of the *FMR1* gene are associated with abnormal dendritic and synaptic density and delayed white-matter development,[3] we predicted that we would observe abnormal relative fiber density and fractional anisotropy in the ventral frontostriatal pathway in affected male infants and toddlers compared with the comparison groups.

METHOD

Participants

Participants were 17 males with fragile X syndrome (mean age 2y 9mo, SD 7mo, range 1y 7mo–3y 10mo), 13 typically developing males (mean age 2y 3mo, SD 7mo, range 1y 7mo–3y 6mo), and eight males with idiopathic developmental delay (mean age 3y, SD 4mo, range 2y 9mo–3y 8mo). All participants were recruited by Stanford University, CA, or by the University of North Carolina, USA. The protocol was approved by the institutional review boards of both universities. Informed consent was obtained from the families of all participants. There was no statistical difference in the proportion of diagnoses as a function of recruitment location.

Participants in the group with developmental delay (Mullen composite standard scores <85) included children with developmental delay of unknown cause who did not exhibit symptoms indicative of an autism spectrum disorder. Exclusion criteria for all groups included preterm birth (<34 wk), low birthweight (<2000g), evidence of a genetic condition or syndrome (except fragile X), sensory impairments, and any serious medical conditions affecting development. Exclusion criteria were assessed by means of a standardized interview with the parent(s) of each participant. Participants were given a standard battery of measures which included the Mullen Scales of Early Learning.[7] Measures of behavior were assessed by parental report using the Vineland Adaptive Behavior Scales[8] and the Child Behavior Checklist.[9]

Genetic analysis

DNA testing for the typical *FMR1* expansion mutation was performed to confirm the presence of the full mutation in all participants with fragile X syndrome or to rule out the mutation in participants with developmental delay. FMRP expression in fragile X syndrome was ascertained by calculating the percentage of peripheral lymphocytes containing FMRP using immunostaining techniques. The mean percentage of peripheral lymphocytes containing FMRP in the group with fragile X syndrome was 5.6%.

Diffusion tensor fiber tractography

Detailed description of DTI acquisition and processing procedures are provided in supporting Methods (supporting information published online). All analyses were performed using DtiStudio[10] blinded to participant group. Fiber tracking was performed using the Fiber Assignment by Continuous Tracking method.[10] Briefly, tracing was initiated from a seed voxel from which a line was propagated in both retrograde and orthograde directions according to the eigenvector at each pixel. As in previous studies, the tracking was terminated (thresholded) when it reached a voxel with a fractional anisotropy value lower than 0.15, or when the turning angle was greater than 40°. In order to reconstruct branching patterns, tracking was performed from every voxel inside the brain, though only fibers that were identified to be within either the ventral or dorsal frontostriatal pathway were retained.

Fibers encompassing the frontostriatal pathway were identified by restricting all fibers to those that penetrated through regions of interest defined by anatomical landmarks. First, we used an automated technique to segment the caudate nucleus from the rest of the brain[11] on each participant's high-resolution spoiled gradient echo (image dimension: 256 × 256 × 256; voxel size: 0.78125 × 0.78125 × 0.78125mm). Second, to isolate ventral and dorsal frontostriatal fibers separately, regions of interest were created and positioned directly anterior to the ventral caudate nucleus for ventral fibers and directly anterior to the dorsal-posterior caudate nucleus for dorsal fibers (supporting Methods and Fig. S1, supporting information, published online).[12] For the ventral frontostriatal fibers, reconstructed fibers were excluded that extended posteriorially relative to the posterior limb of the internal capsule and those that extended to the contralateral hemisphere (Fig. 1).[13] For the dorsal frontostriatal fibers, reconstructed fibers were excluded that extended inferiorially relative to the most inferior slice that intersected both the genu and the splenium of the corpus callosum and those that extended to the contralateral hemisphere. Mean fractional anisotropy values and relative fiber density (mean number of fibers per voxel) were collected for each reconstructed fiber bundle, for each participant. Fractional anisotropy is a metric that corresponds to the proportion of linear movement of water molecules within a voxel, and relative fiber density is a metric that serves to indicate the density of white-matter fibers projecting through a voxel.[14] Mean relative fiber density is calculated by averaging the number of fibers that project through each of the voxels that a particular fiber bundle encompasses. Statistical comparisons were made between the group with fragile X syndrome and the combined comparison groups (typically developing and developmentally delayed) as well as between the group with fragile X syndrome and each of the comparison groups separately by using independent sample *t*-tests and a statistical threshold of $p=0.05$ (two-tailed). In addition, we performed a whole-brain tract-based spatial statistical (TBSS) analysis[15] to study between-group differences in fractional anisotropy (see supporting Methods). Last, we performed a correlation analysis between each of the cognitive and behavioral measures and each of the DTI metrics (fractional anisotropy and relative fiber density).

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Supporting methods:

Figure S1: Region of Interest (ROI) definition. Each participant's caudate was segmented using an automated method (blue). Ventral (green) and dorsal (red) ROIs were delineated on axial views on each participant's high resolution spoiled gradient recalled image. Boundaries for each ROI were defined by anatomical landmarks of each caudate.

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RESULTS

Cognitive and behavioral measures

Mullen composite standard scores (M) were significantly lower in the fragile X syndrome group (M=55.59, SD 11.05) than in the combined control group ($p<0.001$) and the typically developing group (M=111.08, SD 19.90; $p=0.001$), but not the developmentally delayed group (M=57.62, SD 11.35; $p=0.87$). Vineland Adaptive Behavior composite standard scores were significantly lower in the fragile X syndrome group (M=61.94, SD 7.62) than in the combined control group ($p=0.004$) and the typically developing group (M=95.92, SD 13.5; $p<0.001$), but not the developmentally delayed group (M=64.00, SD 6.80; $p=0.84$). The fragile X syndrome group exhibited more attentional problems (M=64.62, SD 8.45) (as measured by the Child Behavior Checklist) than the combined comparison group ($p=0.001$) and the typically developing control group (M=52.00, SD 5.43; $p=0.0001$). However, the difference in attentional problems between the fragile X syndrome and developmentally delayed groups (M=60.86, SD 7.00) did not reach statistical significance ($p=0.31$).

Fractional anisotropy: fragile X versus comparison groups

We compared fractional anisotropy values for each reconstructed fiber tract between the fragile X syndrome and the combined comparison group (typically developing and developmentally delayed) as well as between the fragile X syndrome group and each of the comparison groups independently. These analyses showed no significant between-group difference ($p>0.10$) in mean (SD) fractional anisotropy values: left ventral: fragile X syndrome 0.318 (0.024), typically developing 0.315 (0.025), developmentally delayed 0.319 (0.026); right ventral: fragile X syndrome 0.328 (0.028), typically developing 0.325 (0.031), developmentally delayed 0.335 (0.023); left dorsal: fragile X syndrome 0.290 (0.035), typically developing 0.291 (0.031), developmentally delayed 0.300 (0.029); right dorsal: fragile X syndrome 0.293 (0.022), typically developing 0.291 (0.021), developmentally delayed 0.302 (0.021). We further explored between-group differences in fractional anisotropy by performing a whole-brain TBSS analysis (see supporting Methods).[15] This analysis confirmed that there was no between-group difference in fractional anisotropy in the ventral or dorsal frontostriatal pathway.

Relative fiber density: fragile X versus comparison groups

We then compared relative fiber density for each reconstructed fiber tract between the group with fragile X syndrome and the comparison groups as described above. These analyses indicated that the fragile X syndrome group exhibited greater relative fiber density in the left ventral frontostriatal pathway than the combined control group (fragile X syndrome > typically developing and developmentally delayed group: $t(36)=4.36$; $p=0.0001$; Fig. 2). Significantly greater relative fiber density in the left frontostriatal pathway was observed in the fragile X syndrome group than in the typically developing (fragile X syndrome > typically developing: $t(28)=3.80$; $p=0.001$) and developmentally delayed groups independently (fragile X syndrome > developmentally delayed: $t(23)=4.23$; $p<0.001$). There was no significant between-group difference in relative fiber density in the right ventral frontostriatal pathway (mean [SD]: fragile X syndrome 6.36 [1.06], typically developing 5.71 [1.51], developmentally delayed 5.86 [1.31]), or within the left (fragile X syndrome 4.00 [1.313], typically developing 3.82 [1.39], developmentally delayed 4.14 [1.07]) and right (fragile X syndrome 3.4 [1.32], typically developing 4.51 [1.72], developmentally delayed 5.09 [1.13]) dorsal frontostriatal pathways (all p values >0.10). The difference in left ventral frontostriatal relative fiber density between groups remained significant after controlling for the volume of the left ventral region of interest used to initiate the tractography (fragile X syndrome > combined controls: $t(35)=3.64$, $p=0.004$; fragile X syndrome > typically developing: $t(27)=3.88$, $p=0.001$; fragile X syndrome > developmentally delayed $t(22)=3.16$, $p=0.005$).

Cognitive behavioral measures and DTI metrics: exploratory correlation analysis

We performed correlation analyses between each of the cognitive behavioral measures (Mullen composite standard score,[7] Vineland Adaptive Behavior,[8] and attentional problems subscale of the Child Behavior Checklist)[9] and each of the DTI metrics (fractional anisotropy and relative fiber density) across groups and within each group. Across all experimental groups, lower Mullen composite standard scores were significantly correlated with higher relative fiber density in the left ventral frontostriatal pathway (r=−0.34; p=0.04; 95% confidence interval [CI] = −0.04 to −0.60). There was no significant association between any of the cognitive behavioral measures and any of the DTI metrics in any of the other pathways (all p values >0.05). Within each group, we observed that the relationship between lower Mullen composite standard scores and higher relative fiber density in the left ventral frontostriatal pathway was significant in the typically developing group (r=−0.70; p=0.008; CI=−0.24 to −0.90; Fig. 3) but not in the fragile X syndrome or developmentally delayed group.

DISCUSSION

In this study, we observed that the *FMR1* full mutation was associated with increased relative density of reconstructed white-matter fibers but not reduced fractional anisotropy during early human brain development. Further, we show that increased relative fiber density is localized to a white-matter pathway which is important to the development of inhibitory control, a cognitive domain known to be particularly impaired in those with fragile X syndrome. These findings indicate that neuroanatomical abnormalities in the ventral frontostriatal pathway are present during an early stage (~1–3y of age) of brain development in fragile X syndrome.

Research using cell cultures and animal models of fragile X syndrome indicates that diminished FMRP expression significantly alters the translation of specific mRNAs involved in neuronal development and function. For example, FMRP is expressed in developing axons and growth cones[2] and within myelin-producing oligodendrocytes during early development.[16] *FMR1* knockout mice exhibit abnormalities in neuronal architecture such as increased spine density[1] and longer dendritic spines[17] as well as an overall relatively immature morphology.[18] FMRP is thought to regulate synaptogenesis[19] and to modulate the pruning of synapses throughout development.[18] These neuronal and synaptic morphometric abnormalities found in *FMR1* knockout mice vary as a function of developmental stage.[20] Taken together, these studies indicate that reduced or absent FMRP expression alters the structural integrity of neurons and affects neurodevelopmental processes such as synaptic pruning, axon development,[2] and, perhaps, myelination.[16]

DTI provides a method for interrogating the anatomy of white-matter pathways by characterizing the orientational properties of water diffusion. Fractional anisotropy is a metric that corresponds to the proportion of linear movement of water molecules within a voxel. Assessing the extent of diffusion as measured by fractional anisotropy has helped to identify aberrant white-matter pathways in clinical conditions such as multiple sclerosis and Parkinson disease, and in female adolescents with fragile X sydrome.[6] Relative fiber density is a metric indicative of the density of white-matter fibers projecting through a voxel.[14] It has been used to study pathological brain states such as in glioblastoma[14] and normal brain structure.[21] The fact that we observed a difference in relative fiber density but not fractional anisotropy indicates that these metrics are likely to represent different cytoarchitectural properties of white matter. Fractional anisotropy varies as a function of a number of microstructural characteristics and, in particular, is sensitive to the extent to which axons are myelinated. In terms of development, rapid increases in axon myelination occur throughout the first few years of life and continue beyond childhood and late into adolescence. Maturation of myelinated axons has been reported to correspond with measurable age-related increases in fractional anisotropy.[22] However, relative fiber density shows an opposite pattern, such that this index decreases with age.[22] The

fact that axon myelination occurs in a robust manner late into adolescence and early adulthood, particularly in prefrontal pathways, might help to explain why in a previous study of older females (13–22y) with fragile X syndrome we observed a difference in fractional anisotropy[6] whereas in the present study of very young males we did not. Our findings also are consistent with histoanatomical research demonstrating that reduced FMRP levels are associated with overall immature neuronal morphology,[17] and that these alterations are most pronounced during early stages of brain development.[20]

Mutation of the *FMR1* gene leading to fragile X syndrome is typically associated with a general delay in cognitive development that prominently includes, but is not limited to, deficits in working memory, set shifting, divided and sustained attention, and inhibitory control. Because the *FMR1* gene mutation is X-linked, effects on cognitive development are typically more severe in males than females. Males with fragile X syndrome exhibit profound deficits in tasks that involve the inhibition of repetitious behavior. For example, males with fragile X syndrome committed more false-alarm errors during a continuous performance task,[4] and were less able to withhold motor responses to auditory stop cues[23] than mental-age-matched controls. Inhibitory control is a complex and multifaceted construct which involves many brain structures, including the prefrontal cortex, the posterior cortical regions, and the basal ganglia. The study presented here was focused on regions constituting the frontostriatal pathway; however, there may be other brain regions and circuits that contribute to deficient inhibitory control in fragile X syndrome. Additionally, inhibitory control was not explicitly measured in our research participants (age ~1–3y). The aberrant frontostriatal anatomy reported in this study may, therefore, be an early marker of general cognitive impairment and not specifically poor inhibitory control.

The results of the exploratory correlation analysis indicated that, across all experimental groups, lower IQ (as measured by the Mullen composite standard score) was associated with greater relative fiber density in the left ventral frontostriatal pathway. However, when investigated within each group, the relationship between IQ and relative fiber density was found to be significant only in the typically developing group, and not in the developmentally delayed or fragile X syndrome groups. This finding is consistent with the results of the group comparison between the fragile X syndrome and typically developing groups. In both analyses, we observed that lower IQ measures were associated with greater relative fiber density. The fact that the correlation was significant only in the typically developing group may in part be because of basal levels of IQ in the fragile X syndrome and developmentally delayed groups and/or differences in the variance of IQ scores within each group (typically developing: SD=19.90; developmentally delayed: SD=11.35; fragile X syndrome: SD=11.05).

We observed structural abnormalities in fragile X syndrome in the ventral but not the dorsal frontostriatal pathway. The ventral pathway is thought to govern behavioral inhibition and impulsivity, whereas the dorsal pathway is thought to contribute to relatively higher-order executive functions and basic motor processes. This dissociation is consistent with a recent DTI study in which white matter microstructure variation in the ventral frontostriatal pathway was associated with the recruitment of inhibitory cognitive control in healthy participants aged 7 to 31 years.[13] Furthermore, aberrant structural integrity of regions constituting the ventral frontostriatal pathway has been reported in other disorders characterized by poor inhibitory control, such as attention-deficit-hyperactivity disorder[24] and Tourette syndrome.[25]

In summary, these data provide evidence that reduced FMRP affects the development of white-matter tracts in a localized anatomical fashion and support the utility of using genetic analyses, advanced brain imaging techniques, and developmental approaches for studying complex gene-brain-behavior relationships. Such interdisciplinary research approaches hold particular

promise for facilitating the development of new treatments for those with genetic disorders such as fragile X syndrome.

LIST OF ABBREVIATIONS

DTI, Diffusion tensor imaging; FMR1, Fragile X mental retardation 1 gene; FRMP, Fragile X mental retardation 1 protein; rFD, Relative fiber density; TBSS, analysis Tract-based spatial statistical analysis.

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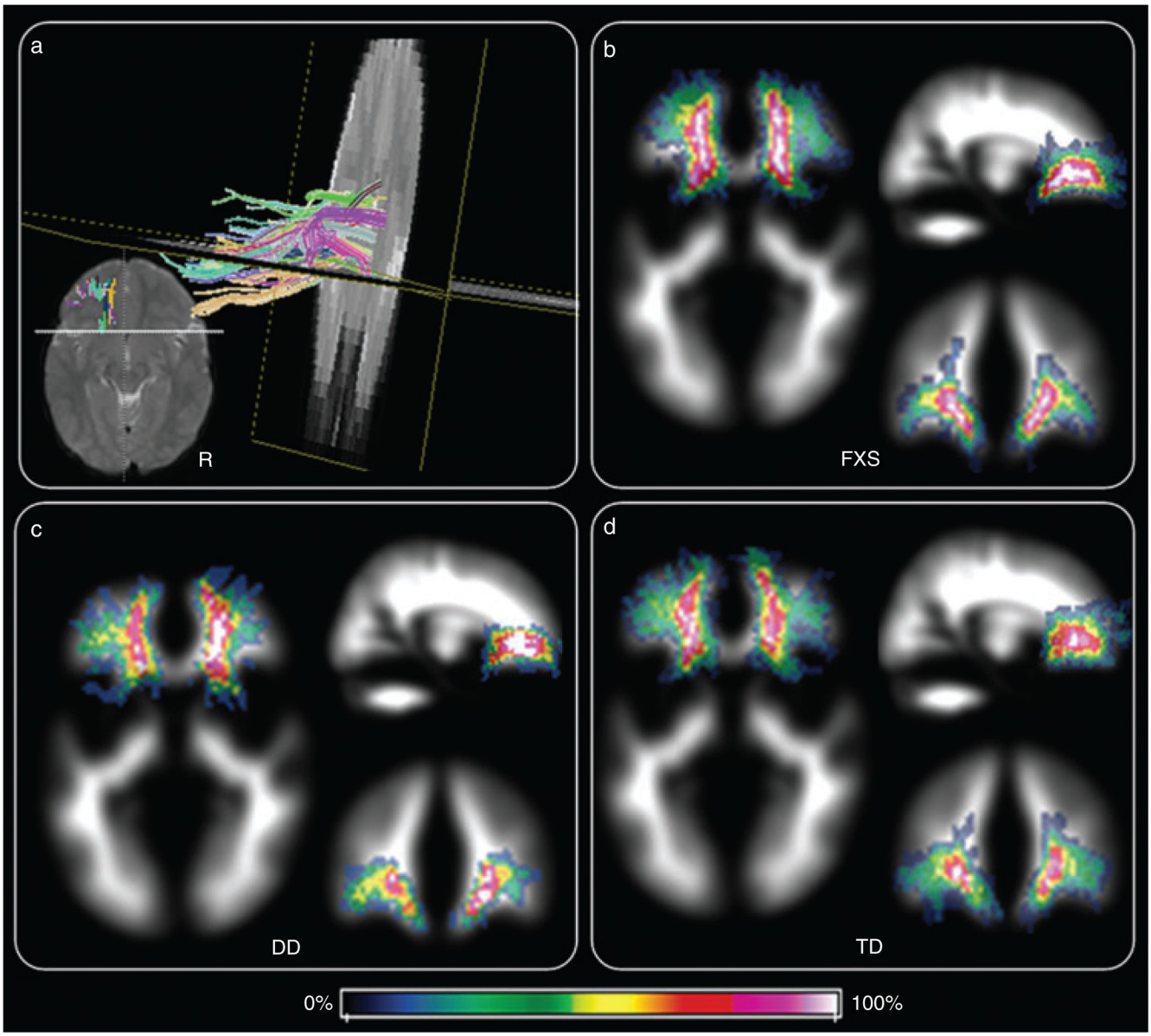

Figure 1.

Ventral frontostriatal tractography. Reconstructed left ventral frontostriatal fibers for (a) one representative typically developing participant. Fibers were reconstructed that projected anteriorally relative to the ventral portion of the caudate (Method section). Probabilistic maps of the left and right reconstructed ventral frontostriatal pathways within each of the experimental groups (b, fragile X; c, typically developing; and d, developmentally delayed). Color coded trajectories are overlaid upon a standard segmented white matter template. The represented range between 0% and 100% corresponds to the likelihood that a reconstructed fiber tract was localized within that particular voxel. R, right; FXS, fragile X syndrome; DD, developmentally delayed; TD, typically developing.

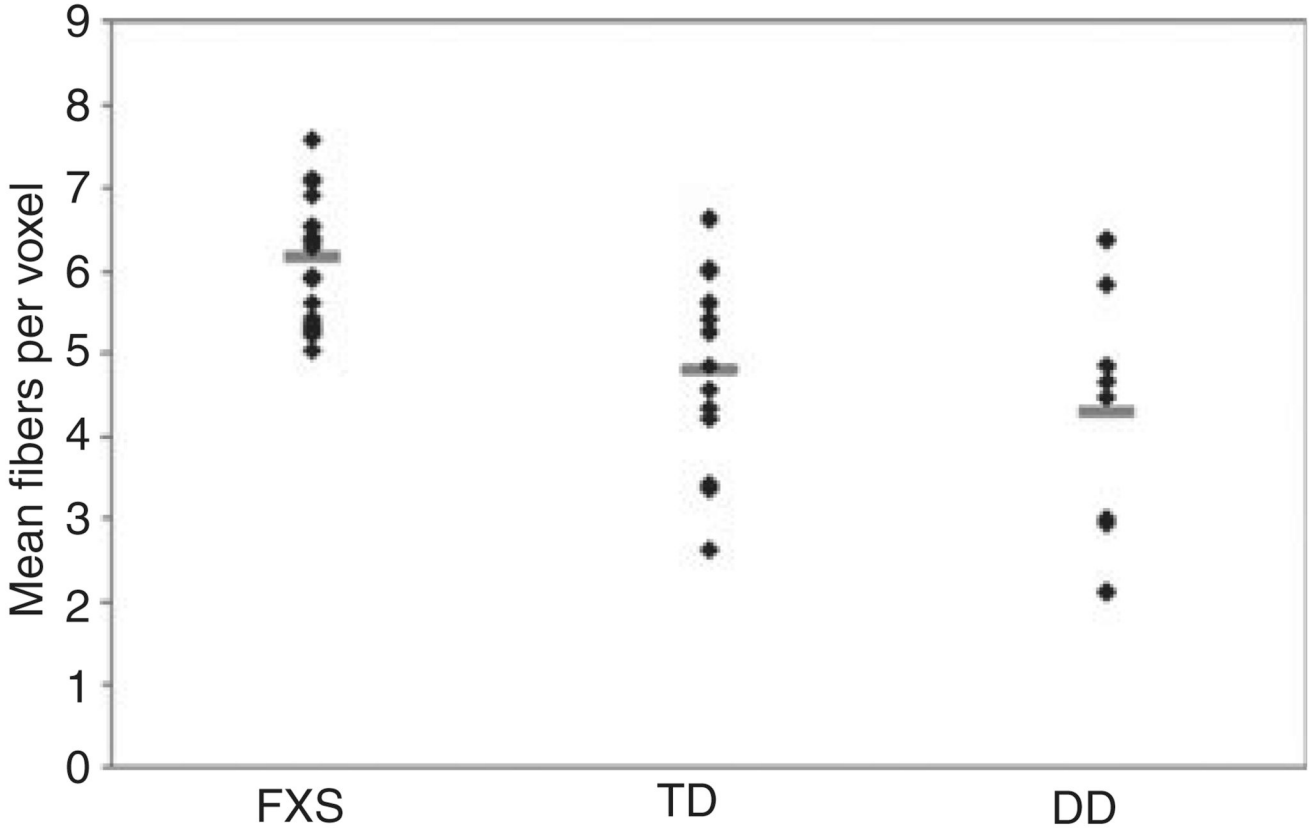

Figure 2.
Dot plot of relative fiber density (mean fibers per voxel) for each reconstructed left ventral frontostriatal pathway in each of the experimental groups. Each data point is representative of one participant in each group. Gray horizontal lines are representative of group means: fragile X syndrome (FXS), 6.14; typically developing (TD), 4.79; and developmentally delayed (DD), 4.28.

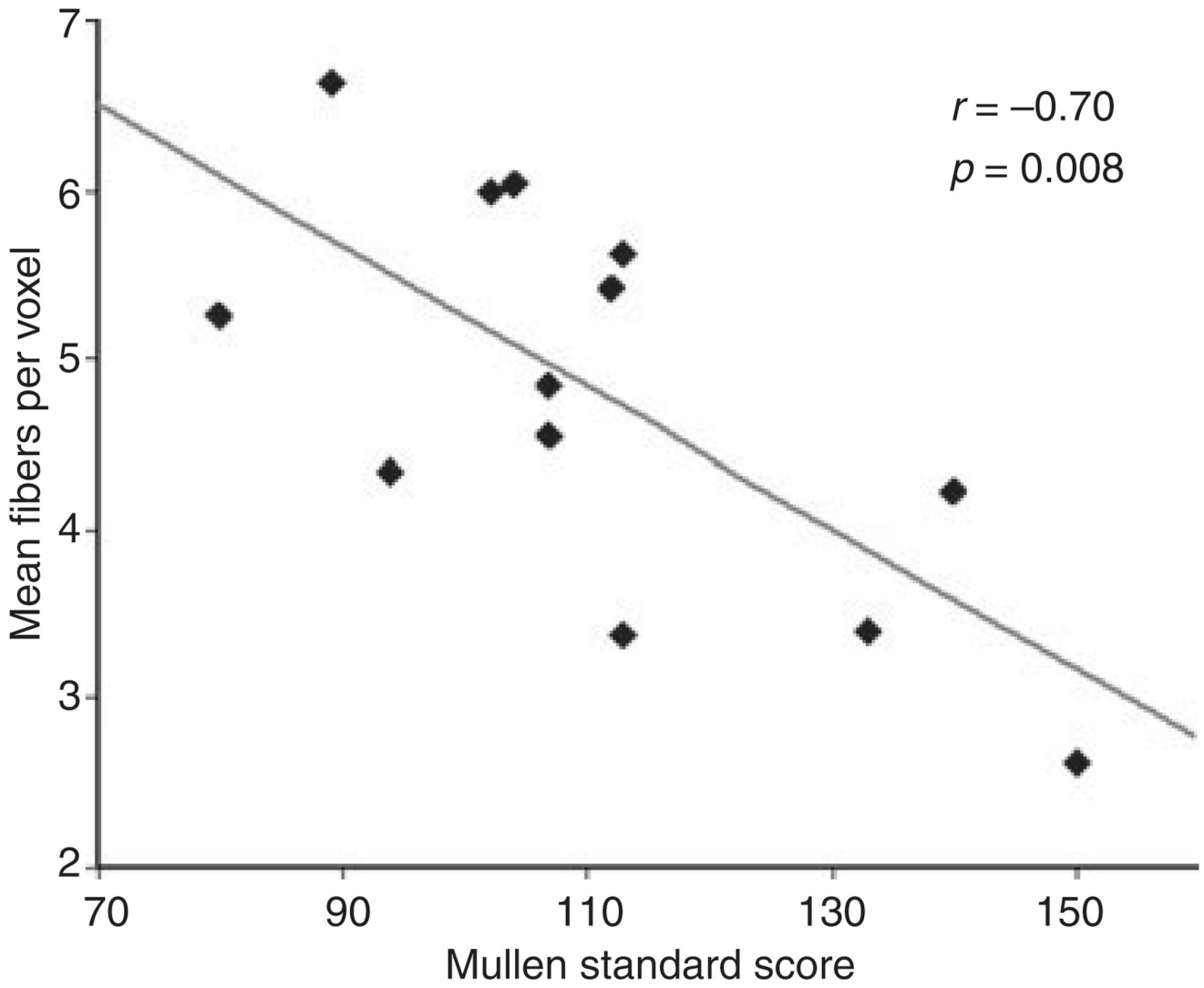

Figure 3.
Scatterplot of Mullen composite standard scores (*x* axis) and relative fiber density (mean fibers per voxel in the left ventral frontostriatal pathway) (*y* axis) within the typically developing control group.