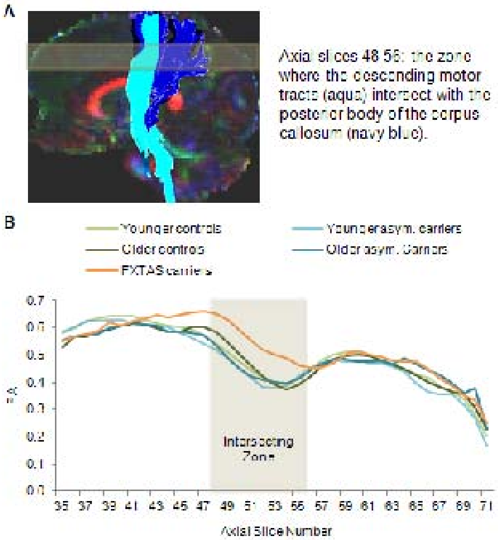
Supplementary Online Content

Wang JY, Hessl D, Schneider A, Tassone F, Hagerman RJ, Rivera SM. Fragile X–associated tremor/ataxia syndrome: influence of the FMRI1 gene on motor fiber tracts in males with normal and premutation alleles. *JAMA*. Published online June 10, 2013. doi:10.1001/jamaneurol.2013.2934.

eFigure. Fractional anisotropy (FA) elevation in the descending motor tracts in the fragile X-associated tremor/ataxia syndrome (FXTAS) carriers.

eAppendix. Least Absolute Shrinkage and Selection Operator (LASSO) using measurements of motor fiber tracts to predict motor test scores.

This supplementary material has been provided by the authors to give readers additional information about their work.



eFigure. FA elevation in the descending motor tracts in the FXTAS carriers. (A) The overlay of the descending motor tracts (aqua) and the posterior body (navy blue) of the corpus callosum on a midsagittal view of the DTI color-coded map. The shaded area shows the axial slices 48-56 where the two fiber tracts interact. (B) Slice-wise group mean FA values of the descending motor tracts. The slices from the midbrain and above are shown. Age 50 years was used as the cutoff for dividing the younger and older groups. The descending motor tracts from individual brains are aligned with the most superior axial slice showing the fibers. Average FA was calculated for axial slices from 48 to 56. In multiple linear regression using age as a covariate, the carriers with FXTAS showed significantly higher FA relative to the older healthy controls (mean/SD 0.53/0.08 vs. 0.45/0.03, df = (2, 48), $\beta = 0.08$, $p < 0.001$) while no difference in FA was observed comparing asymptomatic premutation carriers to healthy controls (mean/SD 0.43/0.04 vs. 0.45/0.03, df = (2, 57), $\beta = -0.02$, *ns*).

eAppendix. LASSO Using Measurements of Motor Fiber Tracts to Predict Motor Test Scores

Methods: Least Absolute Shrinkage and Selection Operator (LASSO) is a type of penalized regression for variable reduction. LASSO finds a set of coefficients by minimizing the mean squared errors under the condition that the sum of the absolute values of the coefficients is less than a constant. We used a Matlab program for performing LASSO: *glmnet* (http://www-stat.stanford.edu/~tibs/glmnet-matlab/), and wrote additional Matlab scripts for performing leave-one-out cross validation for the predicted motor test scores.

Specifically, we first transformed the DTI dataset into ranks, took out samples one by one, and used the remaining samples to estimate the regulatory parameter, λ. The selection of λ itself utilizes a cross validation procedure across 10 λ values in glmnet. In this case, we performed 10-fold cross validation to find the λ value that provided the minimum mean squared error for one particular set of (n — 1) samples. This step was repeated for each of the sample. Then the average value of λ was calculated and subsequently used for constructing of the glmnet models to predict the behavioral outcome scores of the taken-out samples. We preferred leave-one-out cross validation over 10-fold cross validation in this step because of the small sample size especially for the FXTAS- group (n = 26).The coefficients for the 12 tractography measurements were estimated using the complete dataset. Finally, we computed Pearson correlations between the actual and predicted behavioral scores to compare the performance of glmnet with PLS regression.

Results: While glmnet performed similarly to PLS regression for predicting behavioral regulation and dexterity in the FXTAS-positive group (r = 0.49 and 0.61, respectively; p = 0.003 and <0.001, respectively), none of the predictions for the control and FXTAS-negative groups were significant at p = 0.05. In contrast, PLS regression was able to predict behavioral regulation in the control group at 5% false discovery rate and the FXTAS-negative group at 10% false discovery rate. The sets of tractography measurements important for the predictions were generally consistent between the two methods in the FXTAS-positive group although glmnet used less numbers of tractography measurements. Measurements from the middle and superior cerebellar peduncles and corpus callosum anterior body were important for predicting the behavioral outcomes in the FXTAS-positive group. The descending motor fiber tract, which was important for predicting behavioral regulation and dexterity in the FXTAS-positive group in PLS, was no longer important using LASSO.

We reasoned that by finding the covariance between the dependent and independent variables, PLS regression might outperform LASSO for small datasets, in which the noise from the non-useful variables for predictions was not substantial. To assess whether LASSO outperforms PLS regression in a large dataset, we tested glmnet using a DTI dataset with 168 tractography measurements. The images were acquired from 23 patients within 2 weeks of traumatic axonal injury. The neuropsychological tests were conducted at least 6 months after the injury. In this case, glmnet produced more similar results to PLS regression.