White matter disease and cognitive impairment in *FMR1* premutation carriers

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ABSTRACT

Objective: This cross-sectional, observational study examined the role of white matter involvement in the cognitive impairment of individuals with the fragile X mental retardation 1 (*FMR1*) premutation.

Methods: Eight asymptomatic premutation carriers, 5 participants with fragile X tremor/ataxia syndrome (FXTAS), and 7 noncarrier controls were studied. The mean age of the asymptomatic premutation carriers, participants with FXTAS, and noncarrier controls was 60, 71, and 67 years, respectively. Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) were used to examine the middle cerebellar peduncles (MCP) and the genu and splenium of the corpus callosum in relation to executive function and processing speed. MRS measures were *N*-acetyl aspartate/creatine (NAA/Cr) and choline/creatine, and fractional anisotropy (FA) was used for DTI. Executive function was assessed with the Behavioral Dyscontrol Scale and the Controlled Oral Word Association Test (COWAT), and processing speed with the Symbol Digit Modalities Test.

Results: Among all 13 *FMR1* premutation carriers, significant correlations were found between *N*-acetyl aspartate/creatine and choline/creatine in the MCP and COWAT scores, and between FA in the genu and performance on the Behavioral Dyscontrol Scale, COWAT, and Symbol Digit Modalities Test; a correlation was also found between FA in the splenium and COWAT performance. In all regions studied, participants with FXTAS had the lowest mean FA.

Conclusion: Microstructural white matter disease as determined by MRS and DTI correlated with executive dysfunction and slowed processing speed in these *FMR1* premutation carriers. Neuroimaging abnormalities in the genu and MCP suggest that disruption of white matter within frontocerebellar networks has an important role in the cognitive impairment associated with the *FMR1* premutation. *Neurology*® 2015;84:2146-2152

GLOSSARY

CC = corpus callosum; **Ch/Cr** = choline/creatine; **COWAT** = Controlled Oral Word Association Test; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FMR1** = fragile X mental retardation 1; **FXS** = fragile X syndrome; **FXTAS** = fragile X tremor/ataxia syndrome; **MCP** = middle cerebellar peduncle; **MRS** = magnetic resonance spectroscopy; **NAA/Cr** = *N*-acetyl aspartate/creatine; **ROI** = region of interest; **TE** = echo time; **TR** = repetition time; **SDMT** = Symbol Digit Modalities Test.

Fragile X tremor/ataxia syndrome (FXTAS) is an inherited neurodegenerative disease in which dementia often accompanies motor and other clinical manifestations.¹ Although FXTAS can develop in women, the disease is more penetrant and severe in men.¹ FXTAS is caused by a CGG repeat expansion in the premutation range (55–200) of the fragile X mental retardation 1 (*FMR1*) gene, in contrast to the fragile X syndrome (FXS), which is caused by >200 CGG repeats.¹ Each disease has unique molecular pathogenetic features, with FXS related to transcriptional silencing with reduced or absent *FMR1* protein, and FXTAS characterized by increased *FMR1* messenger RNA,¹ which is thought to result in a toxic gain of function.

Executive dysfunction is the most notable cognitive deficit in the dementia of patients with FXTAS, and subtle executive impairment is also evident in *FMR1* premutation carriers without FXTAS.^{2–6} In FXTAS, both neuroimaging and neuropathologic evidence suggests preferential

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white matter involvement, potentially allying this disease with others in the category of white matter dementia.⁷ The characteristic MRI finding in FXTAS is hyperintensity within the middle cerebellar peduncle, known as the MCP sign (figure 1), and this abnormality is seen in about 60% of affected men.¹ Moreover, neuropathologic study has disclosed extensive cerebral and cerebellar white matter degeneration, with loss of myelin and axons, combined with preservation of frontal cortical thickness and neuronal density.⁸ Gray matter volume loss, however, has also been demonstrated in FXTAS using conventional MRI,^{9,10} suggesting a complex pathogenesis leading to the development of dementia. To examine the contribution of white matter disease to cognitive impairment in *FMRI* premutation carriers with and without FXTAS, we set out to assess the microstructure of cerebral white matter in relation to cognitive function.

METHODS **Standard protocol approvals, registrations, and patient consents.** The Colorado Multiple Institutional Review Board at the University of Colorado School of Medicine granted approval for this study. All participants underwent a brief neuropsychological examination followed by brain MRI. If CGG repeat expansion size was not already available for *FMRI* premutation carriers, blood was drawn and genetic assays were conducted in the laboratory of Dr. Berry-Kravis at Rush University.

Figure 1 The MCP sign

Axial fluid-attenuated inversion recovery MRI of a man with fragile X tremor/ataxia syndrome showing the middle cerebellar peduncle (MCP) sign (arrows designate bilateral hyperintensity of the MCP).

Participants. The sample consisted of 13 older men with the *FMRI* premutation, 5 of whom had FXTAS, and 7 noncarrier controls with a normal *FMRI* allele. Participant recruitment and participation occurred in the years 2009–2013 inclusive, and the sample sizes were determined by the availability of resources. *FMRI* premutation carriers were identified through the University of Colorado School of Medicine. Demographic and clinical data characterizing the sample are summarized in table 1. We attempted to match participants by age, but because the risk of asymptomatic premutation carriers developing FXTAS increases with age, individuals with FXTAS are typically older than asymptomatic premutation carriers. All participants selected for this study were educated at least through high school. All premutation carriers had previously been determined to have CGG repeat expansions in the premutation range (55–200), and all had been participants in previous research studies.² All of those with FXTAS had previously received a clinical diagnosis of definite FXTAS using current diagnostic criteria.⁹ Mean (SD) FXTAS stage¹¹ was 2.4 (1.14), ranging from 1 to 4. Comparison participants, recruited through the University of Colorado Denver listserv, had no history of neurologic disorder, psychosis, heavy alcohol use, or comorbid chronic illnesses that might affect cognition. Persons who had any contraindication to MRI were excluded.

Cognitive measures. Executive function was assessed with the Behavioral Dyscontrol Scale¹² and the Controlled Oral Word Association Test (COWAT),¹³ and information processing speed with the Symbol Digit Modalities Test (SDMT).¹⁴ Executive function and information processing speed were selected for testing because these domains are prominently affected in FXTAS^{2–6} and in many disorders characterized by white matter neuropathology.⁷ Before enrollment, all participants had been administered the Mini-Mental State Examination¹⁵ to generate a measure of general cognitive function.

Neuroimaging. Brain MRI and magnetic resonance spectroscopy (MRS) were performed on a GE 3T/94 scanner running version 15.M4 software (GE Healthcare, Waukesha, WI). Oblique axial (angled to the anterior and posterior commissures) T2 fluid-attenuated inversion recovery (repetition time [TR]/echo time [TE]/inversion time = 9,000/120/2,250 milliseconds, field of view 240 mm, thk/gap 3.0/0.0 mm, matrix 256 × 256) was performed on all participants to detect the MCP sign. MRS (GE's PROBE-P [PRESS], TR/TE = 3,000/30 ms, voxel size 15 × 15 × 15 mm, 128 averages) was used to examine the MCP, and diffusion tensor imaging (DTI) (TR/TE = 15,000/78 ms, field of view 24, thk/gap 2.6/0.0 mm, matrix 128 × 128, b = 1,000, 25 directions, b = 0, images = 1) was used to examine the MCP as well as the genu and splenium of the corpus callosum (CC). Spectra were processed using LCModel software.¹⁶ MRS measures were *N*-acetyl aspartate/creatine (NAA/Cr) and choline/creatine (Ch/Cr). NAA/Cr was measured as a marker of axonal integrity, and Ch/Cr to assess the state of myelin. Fractional anisotropy (FA) measures were obtained from the DTI data processed using GE's FuncTool package. Regions of interest (ROIs) were identified (by M.S.B.) to assess white matter of the MCP, genu, and splenium. Figure 2 shows the MRS voxel placement in the MCP and a representative spectrum with fit output from LCModel (fit shown in red) for an *FMRI* participant and a normal control. These areas were also those selected for MCP ROI with DTI. Figure 3 shows the DTI ROI placement for the measurement of FA in the genu and splenium.

Statistical analysis. Demographic, MRI, and neuropsychological data from the 8 asymptomatic premutation carriers were combined with those from the 5 participants with FXTAS,

Table 1 Demographic and clinical characteristics of the sample

	All premutation carriers (n = 13)	Participants with FXTAS (n = 5)	Asymptomatic premutation carriers (n = 8)	Noncarrier controls (n = 7)
Age, y	64.1 (11.1), 46–82	70.8 (6.9), 64–82	59.9 (11.5), 46–74	67.3 (7.5), 61–81
% Male	100	100	100	100
Education, y	15.0 (2.3), 12–19	14.6 (1.9), 13–18	15.2 (2.6), 12–19	18.4 (2.6), 15–22
MMSE score	28.6 (1.3), 26–30	28.6 (1.1), 27–30	28.6 (1.4), 26–30	29.4 (0.8), 28–30
CGG repeats	82.9 (16.3), 66–128	82.4 (13.0), 66–100	83.2 (19.0), 66–128	

Abbreviations: FXTAS = fragile X tremor/ataxia syndrome; MMSE = Mini-Mental State Examination. Data are mean (SD), range.

yielding a total of 13. The genetic abnormality common to these individuals justified the joint assessment of all premutation carriers as a single group to examine the effects of the *FMRI* premutation on white matter–behavior relationships. Statistical tests were conducted using SPSS version 22.¹⁷ The small sample size precluded multiple regression analyses to test the effect of covariates. Differences between groups were assessed by *t* test, and Pearson correlation coefficients were computed to assess the strength of association between variables. We selected a significance level of 0.05, using 1-sided significance values when we had hypothesized the direction of the relationship.

RESULTS The mean age difference between asymptomatic premutation carriers and participants with FXTAS was approximately 11 years, but fell just short

of significance ($p = 0.056$). As noted above, an age difference between these groups was not unexpected. The noncarrier control group did not differ in age from premutation carriers, but had more years of education ($p < 0.05$). The mean Mini-Mental State Examination score was very similar in all groups (*t* tests), ranging from 26 to 30 for all 20 participants. Axial fluid-attenuated inversion recovery MRI disclosed the MCP sign (figure 1) in 4 participants, including 1 of 8 asymptomatic *FMRI* premutation carriers and 3 of the 5 participants with FXTAS, while none of the noncarrier controls displayed this finding ($\chi^2 = 2.06$, not significant). CGG repeat size was not correlated with the imaging variables.

Figure 2 MRS voxel placement

Magnetic resonance spectroscopy (MRS) voxel placement in the middle cerebellar peduncle where it joins the cerebellar white matter in an *FMR1* participant (A), and a normal control (B). These voxels were also used for the diffusion tensor imaging region-of-interest placement. Also shown are the corresponding spectra from each participant (as output from LCModel, and with fits to the data shown in red).

Figure 3 Diffusion tensor imaging ROI placement

Color fractional anisotropy map of a normal control participant showing region-of-interest (ROI) placement in the genu (1) and splenium (2) of the corpus callosum.

Table 2 shows correlations between cognitive test results and microstructural white matter changes as determined by MRS and DTI. MRS data could not be obtained from one premutation carrier because of motion artifact. Regarding MRS of *FMRI* premutation carriers, better performance on the COWAT was associated with higher levels of NAA/Cr ($p = 0.02$) and Ch/Cr ($p = 0.04$) in the MCP. Figure e-1 on the *Neurology*[®] Web site at Neurology.org shows the relationship of COWAT raw score with MCP NAA/Cr in all 20 participants. From this figure, it can be seen that the relationship between COWAT and MCP NAA/Cr exists both

for participants with FXTAS and for asymptomatic premutation carriers.

As for DTI, among all premutation carriers, lower Behavioral Dyscontrol Scale, COWAT, and SDMT scores were correlated with decreased FA in the genu ($p = 0.002$, 0.02 , and 0.02 , respectively), while FA in the splenium was positively correlated with the COWAT ($p = 0.02$), and approached significance with SDMT ($p = 0.07$). None of the correlations between cognitive measures and FA in the MCP was significant. Among noncarrier controls, FA in the MCP was positively correlated with performance on the COWAT, and FA in both the genu and the splenium was positively correlated with SDMT performance. Table e-1 shows the mean FA by group, and for all regions examined, FA was lowest in participants with FXTAS.

DISCUSSION The results of this preliminary investigation demonstrate that dysfunction of the cerebral and cerebellar white matter may be important for the understanding of cognitive impairment in *FMRI* premutation carriers, and the dementia that can occur in those with FXTAS. Microstructural white matter abnormalities as determined by MRS and DTI correlated with executive dysfunction and slowed processing speed in these *FMRI* premutation carriers. Our data demonstrate a relationship between cognitive impairment and white matter abnormalities within frontal and cerebellar networks implicating tract disruption, reflected by decreased FA, and axonal loss, indexed by decreased NAA/Cr. Decreased Ch/Cr was also found in the MCP, plausibly representing dysmyelination, and was correlated with executive dysfunction. These results are consistent with cognitive deficits known to be

Table 2 Correlations of MRS and DTI white matter findings with cognition

	Executive function					
	BDS		COWAT		Processing speed, SDMT	
	Premutation carriers (n = 13)	Noncarrier controls (n = 7)	Premutation carriers (n = 13)	Noncarrier controls (n = 7)	Premutation carriers (n = 13)	Noncarrier controls (n = 7)
MRS						
MCP NAA/Cr			$r = 0.62$ (p = 0.02) ^a			
MCP Ch/Cr			$r = 0.53$ (p = 0.04) ^a			
DTI						
MCP FA			$r = 0.84$ (p = 0.009)			
Genu FA	$r = 0.74$ (p = 0.002)		$r = 0.57$ (p = 0.02)		$r = 0.60$ (p = 0.02)	$r = 0.70$ (p = 0.04)
Splenium FA			$r = 0.58$ (p = 0.02)			$r = 0.81$ (p = 0.027)

Abbreviations: BDS = Behavioral Dyscontrol Scale; Ch/Cr = choline/creatine; COWAT = Controlled Oral Word Association Test; DTI = diffusion tensor imaging; FA = fractional anisotropy; MCP = middle cerebellar peduncle; MRS = magnetic resonance spectroscopy; NAA/Cr = N-acetyl aspartate/creatine; SDMT = Symbol Digit Modalities Test.

One-sided significance levels were used, as we hypothesized a direction to the relationship. Empty cells represent nonsignificance.

^an = 12.

associated with the *FMRI* premutation,^{2,3,18} and with widespread white matter degeneration in FXTAS that includes loss of both myelin and axons.⁸ This is the first study to report white matter MRS data in association with cognitive dysfunction in *FMRI* premutation carriers. In addition, our DTI data are consistent with those of previous investigations of white matter microstructure using this technique in *FMRI* premutation carriers.¹⁹ The findings indicate that the role of white matter in the cognitive deficits observed in FXTAS, and among asymptomatic *FMRI* premutation carriers, merits further study.

While our main goal was to examine white matter microstructure, we also gathered MRI data to assess white matter macrostructure, and found the MCP sign in 60% of the participants with FXTAS, consistent with previous reports.¹ One of 8 asymptomatic premutation carriers also had the MCP sign, suggesting that preclinical disease may be under way in that individual. Past research has been inconclusive as to whether subtle executive function in asymptomatic premutation carriers reflects a neurodevelopmental phenotype among these individuals, or a neurodegenerative phenomenon affecting only a subset of carriers who are likely to progress to FXTAS. Our data are insufficient to answer this question, but do suggest that longitudinal study of asymptomatic premutation carriers is warranted.

This report provides initial MRS data in *FMRI* premutation carriers, and the findings, combined with parallel DTI data, extend the understanding of white matter dysfunction associated with this genotype. Because the microstructural abnormalities can occur in areas that appear normal on conventional MRI, our results suggest that subtle damage to myelin and axons develops before more obvious injury, although it is not clear which of these constituents of white matter is damaged first or more significantly. The MRS metabolites NAA/Cr and Ch/Cr cannot be used to define specific pathophysiologic mechanisms, but decreased NAA/Cr is thought to reflect axonal damage, while reduced Ch/Cr may suggest dysmyelination; these may both be early pathogenetic events. In autopsy studies of white matter in FXTAS, oligodendrocytes have not disclosed major abnormalities, but astrocytes, which are abundant in white matter and contribute to the maintenance of normal myelin,²⁰ have been found to be “dramatically” enlarged and to harbor more numerous intranuclear inclusions than neurons.⁸ A toxic effect of *FMRI* messenger RNA is thought to contribute to cellular dysfunction and death in FXTAS,^{1,21} and it is conceivable that astrocytes are a downstream target of this process. Toxicity could occur at the subcellular level via mitochondrial dysfunction and oxidative stress, which have been reported in FXTAS.^{22,23}

The DTI component of this study disclosed reduced FA in premutation carriers across all 3 white matter regions studied (table e-1), and correlations of these reductions with cognitive dysfunction (table 2). However, some correlations between FA and cognition were also found in noncarrier controls (table 2), a result that may be consistent with previous findings that both FA and volume decrease in white matter with normal aging,^{24–26} and are associated with a concomitant decline in executive function.²⁷

The syndrome of white matter dementia has been proposed to describe the dementia that can occur in patients with a wide variety of white matter disorders.⁷ This syndrome can result from diffuse or multifocal involvement of the brain white matter, and the clinical profile is determined more by the location and volume of neuropathology than its specific type. Damage to cerebral white matter has been most securely linked with cognitive dysfunction and dementia, but cerebellar white matter injury has also been implicated.^{28,29} In our participants, the *FMRI* premutation appears to produce clinically significant white matter disruption in the anterior CC as well as the MCP, suggesting that fronto-frontal and fronto-cerebellar involvement contributes to the cognitive dysfunction of FXTAS. The anterior CC is the major pathway connecting the frontal lobes, and disruption of anterior CC microstructure may underlie frontal lobe dysfunction; recent MRI studies of FXTAS have suggested that involvement of the splenium may also contribute to cognitive impairment.³⁰ Disruption of the MCP, the largest of the 3 cerebellar peduncles and responsible for conveying extensive input from the contralateral cerebral cortex via cortico-ponto-cerebellar fibers, is consistent with emerging understanding of the role of the cerebellum and its connections in cognition and emotion.^{28,29} Of note, recent studies of female *FMRI* premutation carriers have disclosed cognitive deficits consistent with involvement of nonmotor cerebellar networks.³¹ Executive dysfunction in our premutation carriers, therefore, could plausibly result from disruption of either the genu or the MCP, or both in combination.

Gray matter involvement is also seen in FXTAS and must be included in exploring the pathogenesis of cognitive dysfunction associated with the *FMRI* premutation. In addition to white matter changes, the neuropathology of FXTAS features intranuclear inclusions in hippocampal neurons and variable loss of Purkinje cells.⁸ MRI studies of FXTAS have disclosed volume loss in the cerebral cortex,^{9,10} cerebellar cortex,^{10,32} amygdala,¹⁰ and insula,¹⁰ and frontal cortical volume loss has been correlated with working memory impairment.¹⁰ Moreover, asymptomatic *FMRI* premutation carriers have been found to harbor gray matter changes in the hippocampus, cerebellum, thalamus, and basal ganglia.³³ Cognitive decline

could thus result from white matter damage or neuronal depletion, and the earliest neuropathologic features of this premutation remain unknown. Related to this question is the unresolved issue of whether structural brain changes represent a neurodevelopmental phenomenon or a neurodegenerative process leading to the appearance of FXTAS.³⁴

White matter, however, may deserve special consideration. White matter degeneration has been described as the most prominent neuropathologic characteristic of FXTAS,⁸ and the presence of normal frontal cortical thickness and neuronal density⁸ suggests that cortical degeneration is not the initial event leading to cognitive dysfunction. Moreover, the similarity of cognitive dysfunction in FXTAS^{2-6,18} to a host of known white matter disorders⁷ suggests that white matter damage may be a critical determinant of cognitive decline and dementia in this disease.⁴

An intriguing implication of this work is that dementia related to primary white matter dysfunction may occur in the setting of neurodegenerative disease. White matter dementia has been observed in a broad range of disease categories,⁷ but neurodegeneration has been considered a separate category in which white matter damage is regarded as secondary to, or coexistent with, primary gray matter degeneration.⁷ FXTAS may prove to be an example of a neurodegenerative dementia in which white matter degeneration is an early, or even the initial, neuropathologic event. If so, the concept of white matter dementia may be applicable to the category of neurodegenerative disease. Further study is needed to delineate in more detail the relationship between white matter damage and cognitive impairment and dementia in the *FMRI* premutation and FXTAS.

Limitations of this work include the small sample size, which precludes the comparison of white matter damage in *FMRI* premutation carriers with and without FXTAS, the lack of intra- and interrater reliability for ROI placement, the absence of gray matter analysis, and the cross-sectional study design. Our goal was to conduct a pilot study of white matter microstructure in an attempt to explore the pathogenesis of dementia in FXTAS. Study of a larger number of *FMRI* premutation carriers is warranted, as is the evaluation of more white matter regions in comparison with gray matter areas. The combined investigation of white and gray matter pathology will likely prove informative, particularly in areas where affected gray and white matter structures are closely related neuroanatomically. Candidate regions that appear most promising in this regard are the MCP in relation to the cerebellar gray matter, and the fimbria/fornix in relation to the hippocampus.³² Longitudinal studies of individuals with the *FMRI* premutation will also be critical in illuminating the earliest

manifestation of the genotype and the evolution to FXTAS in those destined to become affected.

AUTHOR CONTRIBUTIONS

Christopher M. Filley: study concept and design, analysis and interpretation of data, drafting and revising manuscript, study supervision. Mark S. Brown: data acquisition, analysis and interpretation of data, drafting and revising manuscript. Karen Onderko: data acquisition, analysis and interpretation of data, study management. Megan Ray: data acquisition, analysis and interpretation of data. Rachael E. Bennett: data acquisition, analysis and interpretation of data, study management. Elizabeth Berry-Kravis: data acquisition, analysis and interpretation of data. Jim Grigsby: study concept and design, analysis and interpretation of data, drafting and revising manuscript, study supervision.

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REFERENCES

1. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *J Investig Med* 2009;57:830–836.
2. Grigsby J, Brega AG, Engle K, et al. Cognitive profile of fragile X premutation carriers with and without fragile X-associated tremor/ataxia syndrome. *Neuropsychology* 2008;22:48–60.
3. Hunter JE, Sherman S, Grigsby J, Kogan C, Cornish K. Capturing the fragile X premutation phenotypes: a collaborative effort across multiple cohorts. *Neuropsychology* 2011;26:156–164.
4. Grigsby J, Cornish K, Hocking D, et al. The cognitive neuropsychological phenotype of carriers of the *FMRI* premutation. *J Neurodev Disord* 2014;6:28.
5. Seritan AL, Nguyen DV, Farias ST, et al. Dementia in fragile X-associated tremor/ataxia syndrome (FXTAS): comparison with Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B:1138–1144.
6. Kraan CM, Hocking DR, Georgiou-Karistianis N, et al. Impaired response inhibition is associated with self-reported symptoms of depression, anxiety, and ADHD in female *FMRI* premutation carriers. *Am J Med Genet B Neuropsychiatr Genet* 2014;165B:41–51.
7. Filley CM. White matter dementia. *Ther Adv Neurol Disord* 2012;5:267–277.
8. Greco CM, Berman RF, Martin RM, et al. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). *Brain* 2006;129:243–255.
9. Jacquemont S, Hagerman RJ, Leehey M, et al. Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging. *Am J Hum Genet* 2003;72:869–878.
10. Hashimoto R, Javan AK, Tassone F, Hagerman RJ, Rivera SM. A voxel-based morphometry study of gray matter loss in fragile X-associated tremor/ataxia syndrome. *Brain* 2011;134:863–878.

11. Bacalman S, Farzin F, Bourgeois JA, et al. Psychiatric phenotype of the fragile X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. *J Clin Psychiatr* 2006;67:87–94.
12. Grigsby J, Kaye K, Robbins LJ. Reliabilities, norms, and factor structure of the Behavioral Dyscontrol Scale. *Percept Mot Skills* 1992;74:883–892.
13. Spreen O, Benton AL. *Neurosensory Center Comprehensive Examination for Aphasia (NCCEA)*, revised edition. Victoria: University of Victoria Neuropsychology Laboratory; 1977.
14. Smith A. The Symbol Digit Modalities Test: a neuropsychologic test for economic screening of learning and other cerebral disorders. *Learn Disord* 1968;3:83–91.
15. Folstein MF, Folstein S, McHugh PR. “Mini-Mental State”: a practical method of grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
16. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med* 1993;30:672–679.
17. IBM Corp. *IBM SPSS Statistics for Macintosh*, version 22.0. Armonk, NY: IBM Corp.; 2013.
18. Brega AG, Goodrich G, Bennett RE, et al. The primary cognitive deficit among males with fragile X-associated tremor/ataxia syndrome (FXTAS) is a dysexecutive syndrome. *J Clin Exp Neuropsychol* 2008;30:853–869.
19. Hashimoto R, Srivastava S, Tassone F, Hagerman RJ, Rivera SM. Diffusion tensor imaging in male premutation carriers of the fragile X mental retardation gene. *Mov Disord* 2011;26:1329–1336.
20. Middeldorp J, Hol EM. GFAP in health and disease. *Prog Neurobiol* 2011;93:421–443.
21. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. *Lancet Neurol* 2013;12:786–798.
22. Ross-Inta C, Omanska-Klusek A, Wong S, et al. Evidence of mitochondrial dysfunction in fragile X-associated tremor/ataxia syndrome. *Biochem J* 2010;429:545–552.
23. Napoli E, Ross-Inta C, Wong S, et al. Altered zinc transport disrupts mitochondrial protein processing/import in fragile X-associated tremor/ataxia syndrome. *Hum Mol Genet* 2011;20:3079–3092.
24. Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn Reson Med* 2000;44:259–268.
25. Pagani E, Agosta F, Rocca MA, Caputo D, Filippi M. Voxel-based analysis derived from fractional anisotropy images of white matter volume changes with aging. *Neuroimage* 2008;41:657–667.
26. Ardekani S, Kumar A, Bartzokis G, Sinha U. Exploratory voxel-based analysis of diffusion indices and hemispheric asymmetry in normal aging. *Magn Reson Imaging* 2007; 25:154–167.
27. Grigsby J, Kaye K, Shetterly SM, Baxter J, Morgenstern NE, Hamman RF. Prevalence of disorders of executive cognitive functioning among the elderly: findings from the San Luis Valley Health and Aging Study. *Neuroepidemiology* 2002; 21:213–220.
28. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum: insights from the clinic. *Cerebellum* 2007;6:254–267.
29. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex* 2010; 46:831–844.
30. Apartis E, Blancher A, Meissner WG, et al. FXTAS: new insights and the need for revised diagnostic criteria. *Neurology* 2012;79:1898–1907.
31. Kraan CM, Hocking DR, Bradshaw JL, et al. Symbolic sequence learning is associated with cognitive-affective profiles in female FMR1 premutation carriers. *Genes Brain Behav* 2014;13:385–393.
32. Battistella G, Niederhauser J, Fornari E, et al. Brain structure in asymptomatic FMR1 premutation carriers at risk for fragile X-associated tremor/ataxia syndrome. *Neurobiol Aging* 2013;34:1700–1707.
33. Wang JY, Hagerman RJ, Rivera SM. A multimodal imaging analysis of subcortical gray matter in fragile X premutation carriers. *Mov Disord* 2013;28:1278–1284.
34. Berry-Kravis E, Hall DA. Executive dysfunction in young FMR1 premutation carriers: forme fruste of FXTAS or new phenotype? *Neurology* 2011;77:612–613.

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