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# Cognitive Profile of Fragile X Premutation Carriers With and Without Fragile X-Associated Tremor/Ataxia Syndrome

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Fragile X-associated tremor/ataxia syndrome (FXTAS) develops in a subset of fragile X premutation carriers and involves gait ataxia, action tremor, Parkinsonism, peripheral neuropathy, autonomic disorders, and cognitive impairment. The study was designed to define the nature of cognitive deficits affecting male premutation carriers with and without FXTAS. A sample of 109 men underwent motor, cognitive, genetic, and neurologic testing, as well as brain magnetic resonance imaging. Subjects were classified into 3 groups: (a) asymptomatic premutation carriers, (b) premutation carriers with FXTAS, and (c) normal controls. Men with FXTAS performed worse than controls on mental status, intelligence, executive cognitive functioning (ECF), working memory, remote recall of information, declarative learning and memory, information processing speed, and temporal sequencing, as well as 1 measure of visuospatial functioning. Language and verbal comprehension were spared. Asymptomatic carriers performed worse than controls on ECF and declarative learning and memory. This comprehensive examination of cognitive impairment in male premutation carriers suggests that FXTAS involves substantial executive impairment and diffuse deficits in other cognitive functions. Longitudinal research currently underway will provide insight into the progression of the disorder.

*Keywords:* fragile X, premutation, cognition, trinucleotide repeats, executive cognitive function

The fragile X mental retardation 1 (*FMR1*) gene may expand to produce either of two phenotypically distinct allelic variants. These are referred to as the *premutation* and the *full mutation*. In both mutations, the gene locus becomes unstable and undergoes expansion by adding a number of nucleotide triplets consisting of one purine (cytosine [C]) and two pyrimidines (guanine [G])—or CGG. Mutations of the *FMR1* gene are classified as premutations or full mutations based on the size of the CGG trinucleotide repeat expansion (Oberlè et al., 1991; Verkerk et al., 1991). Expansions involving more than 200 CGG repeats are known as the full mutation and usually undergo some combination of methylation with transcriptional silencing and inefficient translation (Primerano et al., 2002). The consequent reduction or absence of *FMR1* protein gives rise to fragile X syndrome, the most common heritable form of mental retardation.

Individuals with 55 to 200 CGG repeats have the fragile X premutation. Until recently, persons with the premutation (known as carriers of fragile X) were thought to have an essentially normal cognitive phenotype. It is now clear, however, that some carriers have a subtle phenotype consisting of mild physical, cognitive, and emotional problems (Cornish et al., 2005; Dorn, Mazzocco, & Hagerman, 1994; Franke et al., 1998; R. J. Hagerman & Hagerman, 2002; R. J. Hagerman et al., 1996; Hessl et al., 2005; Loesch et al., 2003; Loesch, Hay, & Mulley, 1994; Mazzocco, Pennington, & Hagerman, 1993; Moore, Daly, Schmitz, et al., 2004; Murphy et al., 1999; Reiss, Freund, Abrams, Boehm, & Kazazian, 1993). Moreover, some female carriers have subtle anomalies of brain structure (Riddle et al., 1998; Smits et al., 1994; Tassone, Hagerman, Loesch, et al., 2000; Tassone, Hagerman, Taylor, et al., 2000), and a sizable percentage (between about 13% and 20%) experience premature ovarian failure (Allingham-Hawkins et al., 1999; Hundscheid, Braat, Kiemeney, Smits, & Thomas, 2001; Marozzi et al., 2000; Sherman, 2000).

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The fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that affects some individuals with premutation repeat expansions. This recently identified disorder is characterized by gait ataxia, action tremor, Parkinsonism, and cognitive impairment. Affected persons frequently also have peripheral neuropathy and autonomic disorders (R. J. Hagerman, Leehey, et al., 2001; Jacquemont et al., 2003; Leehey et al., 2003).

The prevalence of FXTAS increases with age, and a significant percentage of carrier men develop FXTAS in their 50s, 60s, or 70s (Berry-Kravis et al., 2003; Brussino et al., 2005; R. J. Hagerman et al., 2004; Jacquemont et al., 2004; Loesch, Churchyard, Brotchie, Marot, & Tassone, 2005; Rogers, Partington, & Turner, 2003). A small number of persons experience the onset of tremor and/or ataxia while in their 40s (Jacquemont, Leehey, Hagerman, Beckett, & Hagerman, 2006). An initial study of prevalence found that approximately 17% of men in their 50s, ascertained through known fragile X syndrome families, had developed FXTAS, whereas 75% of male carriers age 80 years or older were affected (Jacquemont et al., 2004).

Women with the premutation are less likely to develop FXTAS, and the phenotype may differ somewhat from that observed in men (Berry-Kravis, Potanos, Weinberg, Zhou, & Goetz, 2005; P. J. Hagerman & Hagerman, 2004; R. J. Hagerman et al., 2004; Jacquemont et al., 2006). In part, this sex difference in prevalence is related to X-inactivation in women. Leehey et al. (in press) have observed that the activation ratio (i.e., the percentage of cells with X chromosomes having an active normal allele) is a determinant of the penetrance and severity of ataxia among women with FXTAS.

Histologically, FXTAS is characterized by the presence of intranuclear astrocytic and neuronal inclusion bodies throughout the cortex and subcortical areas, especially in the hippocampus (Greco et al., 2002, 2006). Study of the composition of the inclusions has led to the identification of a large number of proteins, including lamin A/C and several other intermediate neurofilament proteins, two variants of αB-crystallin, and myelin basic protein (Arocena et al., 2005; Iwahashi et al., 2006). Magnetic resonance imaging and pathology studies both demonstrate generalized atrophy of the cerebellum, brainstem, and cerebral hemispheres, with extensive Purkinje cell loss in the cerebellum. T2-weighted magnetic resonance imaging, especially with fluid-attenuated inversion-recovery sequences, demonstrates hyperintensities in the middle cerebellar peduncles in a majority of patients (Brunberg et al., 2002; Jacquemont et al., 2003), reflecting spongiform neuropathologic changes in those regions.

In addition to neurologic features, FXTAS is characterized by a progressive impairment of cognition (Bacalman et al., 2006; Bourgeois et al., 2006; Grigsby, Brega, et al., 2006; Grigsby et al., 2007; Grigsby, Leehey, et al., 2006). Preliminary research suggests that the cognitive phenotype is noteworthy for the presence of significantly impaired executive cognitive functioning (ECF; (Grigsby, Brega, et al., 2006; Grigsby et al., 2007; Grigsby, Leehey, et al., 2006), but the range of neuropsychological measures administered to date has been somewhat limited. Nevertheless, consistent deficits have been observed on nonverbal IQ, speed of information processing, behavioral self-regulation, verbal fluency, and working memory.

Cognitive deficits have been demonstrated in a knock-in mouse model with a $(CGG)_{98}$ repeat (Van Dam et al., 2005; Willemsen et al., 2003). The knock-in mice also develop intranuclear inclusions, although one remarkable finding is that the hippocampus is only mildly affected relative to the number of inclusions found in the human hippocampus. Two additional distinctions between the mouse and human neuropathology are noteworthy: A large number of inclusions is found in the mammillary bodies, which are relatively spared in humans (Willemsen et al., 2003), and only neurons (and not astroglia) contain inclusions. Older $(CGG)_{98}$ mice were found to have deficits in specific aspects of memory (e.g., spatial learning but not passive avoidance), and there were impairments on some motor tasks (e.g., accelerating rotarod and stationary beam).

The purpose of the present study was to characterize the spectrum of cognitive deficits experienced by men with the fragile X premutation. Given our hypothesis that FXTAS produces cognitive impairment similar to that seen in frontotemporal dementias, spinocerebellar ataxias, and related disorders (see discussion in Grigsby, Leehey, et al., 2006), we anticipated that subjects with FXTAS would perform worse than controls on all measures associated with, or affected by, the executive cognitive functions. We expected that verbal reasoning, language comprehension and articulation, and simple visuospatial functioning would be relatively unaffected. We further anticipated that performance on most cognitive measures would be similar across the asymptomatic carrier and control groups. However, given previous research indicating that some asymptomatic premutation carriers may suffer mild cognitive impairment (R. J. Hagerman & Hagerman, 2002; R. J. Hagerman et al., 1996; Loesch et al., 2003; Mazzocco et al., 1993; Moore, Daly, Schmitz, et al., 2004), especially of the ECFs, we expected that asymptomatic carriers would perform worse than controls on a subset of these measures.

## Method

The protocol for this longitudinal study was reviewed and approved by the institutional review boards of the University of Colorado at Denver and Health Sciences Center and the University of California, Davis, Medical Center. All subjects provided written informed consent and Health Insurance Portability and Accountability Act authorization prior to participating in the study.

### *Subjects*

#### *Description of Sample*

The subjects were 109 men 41–89 years of age. The vast majority of subjects were White (93.4%). One subject was African American, 1 was American Indian/Alaska Native, and 3.7% of subjects identified themselves as Hispanic or Latino. For all subjects, English was the first language.

Each subject was classified into one of three groups: (a) premutation carriers not meeting diagnostic criteria for FXTAS (i.e., "asymptomatic carriers"), (b) FXTAS, or (c) control (i.e., normal allele). Of the 70 premutation carriers enrolled, 28 (40%) did not meet criteria for definite or probable FXTAS and, thus, were classified in the asymptomatic premutation carrier group. The FXTAS group comprised 42 male premutation carriers who met diagnostic criteria for definite or probable FXTAS (see Jacquemont et al., 2003). One member of the FXTAS group was a mosaic, having two distinct CGG repeat values in the premutation range (73 and 87). For the purposes of analysis, this subject's mean

CGG repeat value was used (80). The control group included 39 men with normal *FMR1* alleles. Three study subjects having a "smear" of CGG repeat values ranging across categories (e.g., ranging from gray zone [45–54 CGG repeats] into the full mutation range) were excluded from the analyses reported in this article.

Throughout enrollment, an attempt was made to match the three study groups on the key sociodemographic characteristics of age and education. Descriptive analyses indicated that age differed somewhat by group. Asymptomatic carriers ($M = 59.1$) and FXTAS subjects ($M = 68.1$) did not differ significantly in age from the control group ($M = 63.5$). However, the FXTAS group was significantly older than the asymptomatic premutation group ($t = -4.12$, $p = .0001$). Because all eligible premutation carriers were enrolled and later classified on the basis of molecular, radiologic, and clinical findings, the age difference between the two premutation groups supports earlier observations of age-dependent penetrance in FXTAS (Jacquemont et al., 2004; Tassone et al., 2007). Younger men in the asymptomatic group may have not yet begun to show symptoms of FXTAS. Given this significant age difference, we controlled for age at the time of assessment in all analyses examining dependent measures that were not already age adjusted.

The three study groups were well matched with regard to educational attainment. Although years of education was somewhat lower among FXTAS subjects ($M = 15.3$) and asymptomatic carriers ($M = 15.6$) than control subjects ($M = 16.9$), these differences were not significant Although educational status did not differ significantly across groups, we controlled for years of education in all adjusted analyses related to cognitive functioning.

### *Subject Recruitment*

The majority of FXTAS subjects and asymptomatic carriers were identified as a result of their involvement in earlier pedigree studies conducted at the participating institutions. Other premutation carriers were ascertained through their participation in biannual meetings of the National Fragile X Foundation, local and regional fragile X-related support groups, or through the clinical practices of study coinvestigators. Control subjects were recruited from the families of subjects with the fragile X premutation and through other recruitment approaches (e.g., recruitment advertisements sent to the University of Colorado at Denver and Health Sciences Center's employee e-mail distribution list).

Prior to enrollment, subjects were screened to confirm eligibility. Subjects were required to be English-speaking men over the age of 40 years. Women were not included in the study because female premutation carriers develop FXTAS at a substantially reduced rate and severity than do their male counterparts (Berry-Kravis et al., 2005; P. J. Hagerman & Hagerman, 2004; R. J. Hagerman et al., 2004; Jacquemont et al., 2004, 2006). Potential subjects were excluded from the study if they had neurologic conditions other than FXTAS or were undergoing medical treatments that had the potential to impair cognitive or emotional functioning, or otherwise to restrict their ability to participate in the study. Exclusion criteria included the following: sensory/language deficit or medical condition making participation impossible (e.g., severe deconditioning); medical condition or treatment with the potential to adversely affect cognitive or emotional functioning (e.g., concurrent corticosteroids or opiates); head injury involving more than momentary loss of consciousness; medically intractable or surgically treated epilepsy; definitively diagnosed movement disorders other than FXTAS; stroke; history of schizophrenia, manic episodes, or psychotic depression; history of toxic encephalopathy, encephalitis, or bacterial meningitis; and delirium associated with an acute medical condition. In addition, because information about each subject's functional status was obtained from the subject as well as a family member or friend, only men with an available informant who was knowledgeable about the potential subject's functional status were enrolled in the study.

### *Procedures*

The baseline examination involved administration of a thorough battery of cognitive and neuropsychological tests, a neurological evaluation conducted by a physician experienced in the diagnosis of movement disorders and FXTAS, and a blood draw. In the current report, baseline data regarding motor and neuropsychological functioning are presented.

### *Motor Functioning*

Two tests of fine motor functioning were conducted. In the Purdue Pegboard Test (Tiffin & Asher, 1948), the subject rapidly inserts small metal pegs into holes on a pegboard, first using the right hand, then the left hand, and finally both hands simultaneously. The number of pegs inserted during each 30-s trial serves as a measure of fine motor functioning. The Finger Tapping Test (Reitan, 1969) requires repetitive tapping of the index finger on a device that records the number of taps made in 10 s. Subjects completed three trials using the dominant hand and the nondominant hand separately (with additional trials as necessary when one of the three fell more than 10% above or below the mean of the other two trials). The mean score across trials for each hand was calculated for analysis. Because FXTAS subjects were expected to perform poorly on these measures, we administered them largely for use as covariates in the analysis of other tests that involved the manipulation of stimulus materials.

### *Cognitive Testing*

Study subjects were assessed with an extensive battery of cognitive tests covering a wide variety of skills: general mental status, intelligence, ECF, working memory, remote declarative memory, declarative verbal learning and memory, verbal reasoning and comprehension, language, speed and capacity of information processing, visuospatial functioning, visual attention, and temporal sequencing.

*Mental status.* Mental status was measured with the Mini-Mental State Examination (MMSE), a reliable and widely used assessment of general mental status (Folstein, Folstein, & McHugh, 1975). Total scores less than 24 on this 30-point scale are suggestive of clinically significant cognitive impairment; scores less than 20 typically are taken to indicate dementia.

*General intellectual functioning.* The Wechsler Adult Intelligence Scale—Third Edition (WAIS–III; Wechsler, 1997a) is the most widely used test of general intelligence. We used the Verbal and Performance (nonverbal) IQ—VIQ and PIQ, respectively—scores, which are adjusted for subject age, as measures of general intellectual functioning.

*ECF.* Scores on two tests of ECF were combined to compute a composite ECF score: the Behavioral Dyscontrol Scale (BDS) and the Controlled Oral Word Association Test (COWAT). The BDS is a an extensively validated measure of the capacity for behavioral self-regulation involving deliberate control of simple voluntary motor behavior (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Grigsby, Kaye, Eilertsen, & Kramer, 2000; Grigsby, Kaye, & Robbins, 1992; R. J. Hagerman, Greco, et al., 2001; Kaye, Grigsby, Robbins, & Korzun, 1990). Although it involves motor functioning, the BDS is administered and scored in such a way that scores are minimally affected by tremor. The BDS, a nine-item instrument yielding scores ranging from 0 to 27 (scores $\leq$14 indicate impairment), measures the capacity to use intentions to guide the performance of goal-directed, purposeful activity. Seven items involve motor performance, one involves the capacity to shift attention (alphanumeric sequencing; Grigsby, Kaye, & Busenbark, 1994), and one is a rating, by the examiner, of the patient's insight into the accuracy of his/her performance.

A subtest of the Neurosensory Center Comprehensive Exam for Aphasia (Spreen & Benton, 1977), the COWAT is a highly reliable measure of verbal fluency (desRosiers & Kavanaugh, 1987), which is considered to be a component of ECF as it involves the ability to generate information actively. The total number of words generated on the COWAT and the total BDS score were converted to *z* scores and averaged to compute an ECF composite score. Larger numbers on the composite index reflect better executive functioning.

*Working memory.* Working memory is associated with ECF in that it serves to maintain plans and intentions in short-term memory so the executive system can use these plans and intentions to organize behavior in a coherent, goal-directed manner (Baddeley, 1990; Fuster, 2000; Levy & Goldman-Rakic, 2000). Previous studies have suggested that men with FXTAS may experience impairment of working memory (Grigsby, Brega, et al., 2006; Grigsby et al., 2007; Grigsby, Leehey, et al., 2006). The Working Memory Index of the WAIS–III, which is adjusted for age, was used as a measure of working memory capacity.

*Remote recall of information.* The Information subtest of the WAIS–III examines the extent of an individual's general cultural knowledge. The age-adjusted score on this subtest was used as a measure of remote declarative memory.

*Declarative verbal learning and memory.* Our observations of individuals with FXTAS suggest that they may experience impairment of declarative verbal learning and memory (e.g., the case reported in Grigsby, Leehey, et al., 2006). Two commonly used clinical measures of verbal learning were included in the study to examine such memory disturbances. The Logical Memory Test (LMT) of the Revised Wechsler Memory Scale—Third Edition (WMS–III) measures declarative verbal memory based on the subject's ability to recall the details of a short story read aloud by the examiner (Wechsler, 1997b). Three LMT-derived measures were examined: (a) the total number of story elements recalled immediately after the story was read, (b) the number of elements recalled after a 30-min delay, and (c) the number of elements recalled after the delay as a percentage of the immediate recall score.

The Rey Auditory Verbal Learning Test (RAVLT; Spreen & Strauss, 1998) consists of a list of 15 unrelated concrete nouns repeated five times (the learning trials). Three measures were computed on the basis of the RAVLT: (a) the number of words correctly recalled on the final learning trial, (b) the total number of words correctly recalled across all five learning trials, and (c) a delayed recall percentage score, with the number of words recalled after a 20- to 30-min delay in the numerator and the number of words recalled after the fifth learning trial in the denominator.

*Verbal reasoning and comprehension.* Three measures of the capacity for verbal reasoning and comprehension were obtained from the WAIS–III (Wechsler, 1997a): the Similarities, Comprehension, and Vocabulary subtests. Age-adjusted scores were used for all subtests.

*Language.* Two instruments were used to examine language function among the study subjects. The Boston Diagnostic Aphasia Exam (BDAE) is a reliable and comprehensive test of a wide range of language functions, including aspects of comprehension, expression, and articulation (Davis, 1993; Goodglass & Kaplan, 1983; Spreen & Strauss, 1998). We examined subjects' scores on 12 subtests of the BDAE. Subjects' scores on the 15-item short form of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1978) were used as a measure of confrontation naming.

*Speed and capacity of information processing.* Three tests provided measures of the speed and capacity of information processing. The Symbol Digit Modalities Test (SDMT) is a reliable measure of processing speed that can be administered orally (Smith, 1968), eliminating any confound with motor impairment. Subjects' total scores (i.e., the number of correct responses minus the number of errors during a 90-s trial) were examined as a measure of processing speed. Subjects' age-adjusted scores on the Symbol Search subtest of the WAIS–III also were used to measure speed of information processing, as were subjects' raw scores on the word-reading and color-naming components of the Stroop Test (Stroop, 1935), which reflect the number for words read or colors named, respectively, during a 45-s trial.

*Visuospatial functioning and visual attention.* Two WAIS–III measures were used to examine visuospatial functioning: the Block Design and Object Assembly subtests. Performance on the Picture Completion subtest was examined as a measure of visual attention. For all tests, age-adjusted scores were used.

*Temporal sequencing.* The Picture Arrangement subtest of the WAIS–III provides a measure of subjects' capacity for sequential reasoning. Subjects' age-adjusted scores on this subtest were used to examine group differences in temporal sequencing.

### *Neurologic Examination*

In addition to completing the battery of motor and cognitive tests, each subject underwent a thorough neurologic examination conducted by a physician experienced in the diagnosis of movement disorders and FXTAS. The neurologic exam focused on key features of FXTAS, including tremor, cerebellar dysfunction, signs of parkinsonism, reflexes and sensation. On the basis of the neurologic evaluation, CGG repeat status, and neuroradiologic findings, the physician assigned premutation carriers either to the asymptomatic premutation group or the FXTAS group according to the diagnostic criteria established by Jacquemont et al. (2003).

### *Molecular Assays*

At the baseline visit, each subject provided a blood sample for determination of CGG status and *FMR1* mRNA level. We isolated

genomic DNA and total RNA from peripheral blood leucocytes (5 ml of whole blood) using standard methods (Puregene and Purescript Kits; Gentra Inc., Minneapolis, MN). Southern blot and PCR-based genotyping and *FMR1* mRNA quantification were performed as described previously (Tassone et al., 2007; Tassone, Hagerman, Loesch, et al., 2000; Tassone, Hagerman, Taylor, et al., 2000). For Southern blot, 5–10 μg of isolated DNA was digested with EcoRI and Nrul. The hybridization probe used was the *FMR1*-specific probe labeled StB12.3. PCR amplification of genomic DNA used primers c and f as described by Saluto et al. (2005). We conducted analysis and calculation of trinucleotide expansion size for both Southern blot and PCR analysis using an Alpha Innotech FluorChem 8800 Image Detection System (Alpha Innotech Corporation, San Leandro, CA).

### *Data Analysis*

Descriptive analyses were conducted to examine the demographic characteristics, motor functioning, and cognitive performance of the study sample. For all variables, the mean, minimum and maximum values, and standard deviation were computed. Ordinary least squares regression models were used to compare subjects' demographic characteristics and test performance across groups. For each dependent variable, separate models examined the impact of three group comparison variables: (a) asymptomatic premutation carrier (1) versus FXTAS (0), (b) asymptomatic premutation carrier (1) versus control (0), and (c) FXTAS (1) versus control (0). Given the large number of statistical tests performed, a conservative alpha value ($p \leq .01$) was used.

### *Covariates*

Regression analyses controlled for important factors that had the potential to confound the group differences under examination. As FXTAS is believed to be a progressive neurodegenerative disorder, analyses of motor functioning controlled for subject age at the time of assessment. In addition, although group differences in educational status were not detected, all models examining cognitive test performance controlled for years of education, as is customary in the analysis of cognitive functioning. Because group differences in age were detected, it was important to control for the effects of age in the regression analyses. For dependent measures that were not already age adjusted (i.e., all measures except those derived from the WAIS–III), age at the time of assessment also was included as a covariate. Finally, because the WAIS–III Block Design, Object Assembly, and Picture Arrangement subtests involve a motor component, the dominant hand score on the Purdue Pegboard Test was included as a covariate in all analyses related to these tests.

## Results

### *Study Sample*

### *Molecular and Clinical Findings*

Trinucleotide repeat expansions were somewhat larger in the FXTAS group than the asymptomatic carrier group, although this difference fell just short of significance ($t = -2.34$, $p = .02$). Although the range of CGG repeat values in the two carrier groups was similar, men in the FXTAS group had an average CGG value of 93.4 (range = 60–142), whereas members of the asymptomatic carrier group had an average CGG value of 82.5 (range = 57–150). Within the control group, CGG repeat values ranged from 15 to 47, with an average value of 30.9. Although the majority of control subjects had CGG repeat values in the normal range, 2 fell into the gray (intermediate) zone (i.e., 45–54). Neither of the gray zone subjects showed clinical signs of FXTAS. As the CGG repeat values for these individuals (45 and 47, respectively) were well below the premutation range, which starts at 55 (some investigators consider 60 to be the low end of the premutation range), both were classified as controls.

Of men diagnosed with FXTAS, 81% had both tremor (postural or intention) and ataxia (34 of 42). Three additional subjects (7%) had tremor without ataxia, and 5 (12%) had ataxia without tremor. The prevalence of these signs was less common in the asymptomatic premutation group. Of the 28 asymptomatic carriers, 20 (71%) showed no evidence of either tremor or ataxia on neurologic exam. Four asymptomatic carriers (14%) had tremor without ataxia, and 3 (11%) had ataxia without tremor. Of the 39 control subjects, 3 (8%) showed evidence of tremor, and 2 (5%) had both tremor and ataxia.

Men in the FXTAS group typically developed signs of tremor and/or ataxia in their late 50s. For the 24 FXTAS subjects for whom age of onset data were available, tremor became apparent at 59.5 years of age, on average. Ataxia developed at 59.7 years of age, on average ($n = 30$). The range of ages at which these symptoms developed was quite wide. FXTAS subjects developed tremor anywhere between the ages of 48 and 79 years, and they developed ataxia between the ages of 47 and 78 years. Too few age-of-onset data were available for subjects in the asymptomatic carrier and control groups to permit comparisons with FXTAS subjects.

### *Motor Functioning*

Five measures of motor functioning (from the Purdue Pegboard Test and Finger Tapping Test) were compared across groups. (Table 1 provides unadjusted means and significance values, as well as partial $R^2$ statistics, which identify the proportion of the variance in a dependent variable that is explained by a given independent variable, over and above the variance explained by age.) Given that tremor is a major component of the diagnosis, subjects with FXTAS were expected to perform poorly on tests of motor functioning in comparison with their counterparts in the asymptomatic carrier and control groups. Controlling for age, FXTAS subjects scored significantly worse than control subjects on all measures of motor functioning (Purdue dominant hand: $t = -5.97$, $p < .0001$; Purdue nondominant hand: $t = -4.99$, $p < .0001$; Purdue both hands: $t = -5.44$, $p < .0001$; Finger Tapping dominant hand: $t = -5.34$, $p < .0001$; and Finger Tapping nondominant hand: $t = -5.00$, $p < .0001$). Performance in the FXTAS group was significantly worse than in the asymptomatic carrier group on four of the five measures (Purdue dominant hand: $t = 4.06$, $p = .0001$; Purdue both hands: $t = 2.99$, $p < .01$; Finger Tapping dominant hand: $t = 3.07$, $p < .01$; and Finger Tapping nondominant hand: $t = 2.59$, $p = .01$). No significant differences between asymptomatic carriers and control subjects were identified.

Table 1
*Motor Test Performance: FXTAS Subjects Versus Asymptomatic Carriers and Controls*

| Motor functioning | FXTAS *M* ($n$ = 42) | Asymptomatic premutation *M* (Partial $R^2$) ($n$ = 28)[a] | Control *M* (Partial $R^2$) ($n$ = 39)[b] |
|---|---|---|---|
| Purdue Pegboard—Dominant hand | 8.4 | 12.0*** (.16) | 12.0*** (.28) |
| Purdue Pegboard—Nondominant hand | 8.4 | 10.8 (.04) | 11.7*** (.20) |
| Purdue Pegboard—Both hands | 6.8 | 9.4* (.10) | 9.8*** (.22) |
| Finger Tapping Test—Dominant hand | 43.4 | 53.4* (.10) | 54.1*** (.26) |
| Finger Tapping Test—Nondominant hand | 40.2 | 49.4* (.07) | 51.0*** (.23) |

*Note.* Table 1 presents the results of separate regression analyses comparing fragile X-associated tremor/ataxia syndrome (FXTAS) subjects to asymptomatic carriers and controls. No significant differences between asymptomatic carriers and controls were identified.
[a] FXTAS subjects versus asymptomatic carriers. [b] FXTAS subjects versus controls.
* $p \leq .01$. *** $p \leq .0001$.

### *Cognitive Functioning*

Risk-adjusted regression analyses showed significant impairment of cognitive functioning among men diagnosed with FXTAS. (Table 2 presents raw scores by group for all cognitive measures, significance values, and partial $R^2$ values for the comparison of the premutation groups with the control group. When differences between the two premutation carrier groups emerged, this information is provided in the text.)

#### *Mental Status*

There were no differences between asymptomatic premutation carriers and subjects in either the FXTAS or control groups on the MMSE. However, men diagnosed with FXTAS had significantly lower mean MMSE scores than did controls ($t = -2.75$, $p < .01$). Although this finding suggests mildly impaired mental status among FXTAS men, the mean score in the FXTAS group (27.6) did not meet the criteria for the classification of cognitive impairment (<24) or dementia (<20). However, whereas 100% of men in the asymptomatic carrier and control groups scored 27 or higher on the MMSE, 25% of FXTAS men scored less than 27, including 1 who would be classified as demented on the basis of his score of 16.

#### *General Intellectual Functioning*

We measured general intelligence using the WAIS–III VIQ and PIQ scores. Adjusted analyses provided evidence of intellectual impairment among the subjects with FXTAS, who had significantly lower VIQ ($t = -3.62$, $p < .001$) and PIQ ($t = -5.31$, $p < .0001$) scores than did control subjects. Asymptomatic carriers scored significantly better than FXTAS subjects on PIQ ($t = 3.95$, $p < .001$, partial $R^2 = .21$) and marginally better on VIQ ($p < .05$). Asymptomatic carriers did not differ from controls on either measure of IQ.

#### *ECF*

Regression analyses showed differences in executive functioning across groups. Men in the FXTAS group ($t = -5.16$, $p < .0001$) and in the asymptomatic carrier group ($t = -3.13$, $p < .01$) scored significantly worse than controls on the ECF composite score. FXTAS subjects did not differ significantly from asymptomatic premutation carriers on this measure.

#### *Working Memory*

The Working Memory Index of the WAIS–III was used to examine differences in short-term memory capacity across groups. Subjects with FXTAS scored significantly worse on the Working Memory Index than did men in the control group ($t = -3.70$, $p < .001$). Asymptomatic premutation carriers did not differ from FXTAS or control subjects on working memory capacity.

#### *Remote Recall of Information*

Remote declarative memory (measured by the Information subtest of the WAIS–III) was impaired in men with FXTAS. These subjects performed significantly worse than did men in the control group ($t = -3.38$, $p = .001$). The scores of asymptomatic premutation carriers did not differ significantly from the scores of men in either the FXTAS group or the control group.

#### *Declarative Verbal Learning and Memory*

Two tests—the LMT and the RAVLT—measured declarative verbal learning and memory. Subjects with FXTAS scored significantly worse than controls on the immediate ($t = -3.54$, $p < .001$) and delayed recall ($t = -3.37$, $p = .001$) components of the LMT. Subjects in the asymptomatic carrier group also had significantly worse immediate ($t = -2.62$, $p = .01$) and delayed recall ($t = -3.37$, $p = .001$) scores in comparison with control subjects. The two premutation groups did not differ significantly from one another.

Although immediate and delayed recall were decreased among premutation carriers, these groups did not differ significantly from the control group or each other in the percentage of story elements recalled after the delay. This finding suggests that memory decay was similar across groups, although immediate recall was poorer among men with the fragile X premutation.

The RAVLT results provide additional evidence of impairment of declarative verbal learning and memory among men with FXTAS. Controlling for age and education, subjects diagnosed with FXTAS recalled fewer total words across the five learning

Table 2
*Cognitive Test Performance: Premutation Groups Versus Controls*

| Variable | FXTAS *M* (Partial $R^2$) ($n$ = 42)[a] | Asymptomatic premutation *M* (Partial $R^2$) ($n$ = 28)[b] | Control *M* ($n$ = 39) |
|---|---|---|---|
| Mental status | | | |
| Mini Mental State Exam | 27.6* (0.08) | 29.2 (0.00) | 29.4 |
| General intellectual functioning | | | |
| Verbal IQ | 106.6** (0.13) | 113.6 (0.01) | 120.7 |
| Performance IQ | 97.7*** (0.25) | 111.8 (0.01) | 116.4 |
| Executive cognitive functioning | | | |
| Composite ECF Score | −0.57*** (0.22) | 0.08* (0.13) | 0.58 |
| Working memory | | | |
| WAIS–III Working Memory Index | 101.9** (0.17) | 106.6 (0.04) | 115.8 |
| Remote recall of information | | | |
| WAIS–III Information Subtest | 11.6** (0.10) | 12.9 (0.01) | 14.2 |
| Declarative verbal learning and memory | | | |
| WMS–III LMT—Immediate Recall | 10.2** (0.12) | 12.0* (0.10) | 14.0 |
| WMS–III LMT—Delayed Recall | 8.6** (0.10) | 10.1** (0.15) | 12.8 |
| WMS–III LMT—Percent Recall | 79.0 (0.03) | 81.3 (0.08) | 92.1 |
| RAVLT—Total Correct | 32.0*** (0.16) | 41.6 (0.06) | 45.1 |
| RAVLT—Final Learning Trial | 8.4* (0.09) | 11.2 (0.01) | 11.4 |
| RAVLT—Percent Correct | 61.8 (0.01) | 67.4 (0.02) | 70.9 |
| Verbal reasoning and comprehension | | | |
| WAIS–III Similarities Subtest | 10.8 (0.06) | 12.5 (0.01) | 12.8 |
| WAIS–III Vocabulary Subtest | 11.3 (0.04) | 12.1 (0.01) | 13.2 |
| WAIS–III Comprehension Subtest | 12.0 (0.04) | 13.2 (0.00) | 13.8 |
| Language | | | |
| BDAE—Following Spoken Commands | 14.4 (0.06) | 14.8 (0.01) | 14.9 |
| BDAE—Complex Ideational Material | 11.3 (0.01) | 11.3 (0.01) | 11.6 |
| BDAE—Verbal Agility | 12.5 (0.08) | 13.3 (0.01) | 13.4 |
| BDAE—Repetition of Single Words | 9.6 (0.00) | 9.9 (0.00) | 9.9 |
| BDAE—Repetition of Nonsense Words | 4.4 (0.00) | 4.8 (0.03) | 4.7 |
| BDAE—Repetition of Sentences | 9.4 (0.03) | 9.7 (0.02) | 9.8 |
| BDAE—Responsive Naming | 19.5 (0.09) | 19.8 (0.02) | 19.9 |
| BDAE—Reading Sentences and Paragraphs | 9.3 (0.01) | 9.9 (0.04) | 9.7 |
| BDAE—Praxis: Natural Gestures | 11.5 (0.02) | 11.8 (0.03) | 11.9 |
| BDAE—Praxis: Conventional | 11.7 (0.02) | 11.9 (0.04) | 12.0 |
| BDAE—Praxis: Use of Pretend Objects | 23.8 (0.00) | 23.9 (0.00) | 23.8 |
| BDAE—Praxis: Bucco–Facial | 12.0 (0.06) | 12.0 (0.03) | 11.8 |
| Boston Naming Test—Short Form Score | 13.9 (0.05) | 14.4 (0.01) | 14.7 |
| Speed and capacity of information processing | | | |
| Symbol Digit Modalities Test (SDMT) | 45.7* (0.09) | 64.6 (0.02) | 59.6 |
| WAIS–III Symbol Search Subtest | 9.1*** (0.27) | 10.7 (0.06) | 12.3 |
| Stroop Test—Word-Reading | 81.7** (0.17) | 97.2 (0.06) | 104.0 |
| Stroop Test—Color-Naming | 55.2*** (0.17) | 69.2 (0.04) | 73.4 |
| Visuospatial functioning and visual attention | | | |
| WAIS–III Block Design Subtest | 9.7* (0.11) | 11.3 (0.07) | 12.8 |
| WAIS–III Object Assembly Subtest | 9.6 (0.08) | 11.4 (0.01) | 11.5 |
| WAIS–III Picture Completion Subtest | 10.4 (0.05) | 12.4 (0.00) | 12.1 |
| Temporal sequencing | | | |
| WAIS–III Picture Arrangement | 9.6* (0.10) | 12.0 (0.00) | 12.5 |

*Note.* Table 2 presents the results of separate regression analyses comparing control subjects with subjects in the two premutation groups. FXTAS = fragile X-associated tremor/ataxia syndrome; ECF = executive cognitive functioning; WAIS–III = Wechsler Adult Intelligence Scale—Third Edition; WMS–III = Wechsler Memory Scale—Third Edition; LMT = Logical Memory Test; RAVLT = Rey Auditory Verbal Learning Test; BDAE = Boston Diagnostic Aphasia Exam.
[a] FXTAS subjects versus controls. [b] Asymptomatic carriers versus controls.
* $p \leq .01$. ** $p \leq .001$. *** $p \leq .0001$.

trials ($t = -4.69$, $p < .0001$) and on the last learning trial ($t = -3.11$, $p < .01$) than did men in the control group. Asymptomatic carriers did not differ significantly from controls or FXTAS subjects on the total number of words recalled on the final learning trial or across the five learning trials. As in the analyses of the LMT data, the percentage of words recalled after the delay, given the number of words recalled on the final learning trial, did not differ by group.

### *Verbal Reasoning and Comprehension*

Verbal reasoning and comprehension were not significantly affected in FXTAS. Subjects with FXTAS scored slightly lower

than controls on the WAIS–III Similarities, Vocabulary, and Comprehension subtests. However, in all cases, these differences only approached significance ($p < .05$). Asymptomatic carriers scored significantly better than FXTAS subjects on the Similarities subtest ($t = 2.65$, $p = .01$, partial $R^2 = .09$). No other group differences were detected.

### *Language*

The BDAE and BNT were used as measures of impairment in circumscribed aspects of language. There were no significant differences between groups on any of the language measures.

### *Speed and Capacity of Information Processing*

Subjects with FXTAS scored significantly worse than controls on all measures of information processing speed and capacity: SDMT ($t = -2.89$, $p < .01$), Symbol Search ($t = -5.01$, $p < .0001$), Stroop word-reading ($t = -3.97$, $p < .001$), and Stroop color-naming ($t = -4.13$, $p = .0001$). Men in the asymptomatic carrier group scored significantly better than FXTAS subjects on the SDMT ($t = 2.57$, $p = .01$, partial $R^2 = .06$), Symbol Search ($t = 2.62$, $p = .01$, partial $R^2 = .11$), Stroop word-reading ($t = 2.74$, $p < .01$, partial $R^2 = .11$), and Stroop color-naming ($t = 2.89$, $p < .01$, partial $R^2 = .12$). Asymptomatic carriers and control subjects did not differ on information processing speed and capacity.

### *Visuospatial Functioning and Visual Attention*

The WAIS–III Block Design and Object Assembly subtests were used as measures of visuospatial functioning. Because these tests are timed and involve a motor component, subjects' scores on the dominant hand trial of the Purdue Pegboard Test were used as covariates in analyses related to these dependent variables to obtain a cleaner measure of visuospatial functioning independent of tremor. FXTAS subjects scored significantly worse than controls on Block Design ($t = -3.26$, $p < .01$). A similar group difference on Object Assembly approached significance ($p < .05$). Asymptomatic carriers of the fragile X premutation did not differ significantly from FXTAS or control subjects on these measures.

The Picture Completion subtest of the WAIS–III provides a measure of the capacity to attend actively to visual information. Premutation carriers did not differ from controls on this measure. However, asymptomatic carriers did score significantly better than men with FXTAS ($t = 2.62$, $p = .01$, partial $R^2 = .10$).

### *Temporal Sequencing*

Temporal sequencing was affected in men with FXTAS. After controlling for education and subjects' scores on the dominant hand trial of the Purdue Pegboard Test, subjects with FXTAS obtained significantly lower scores than controls on the WAIS–III Picture Arrangement subtest ($t = -3.13$, $p < .01$). Asymptomatic carriers of the fragile X premutation did not differ from FXTAS subjects or controls with regard to temporal sequencing.

## Discussion

This study provides the first comprehensive overview of the nature of the cognitive impairment associated with FXTAS. The findings are consistent with previously reported research on cognition among premutation carriers, both with and without the tremor/ataxia syndrome (e.g., Grigsby, Brega, et al., 2006; Grigsby et al., 2007; Grigsby, Leehey, et al., 2006; Loesch et al., 2003; Moore, Daly, Schmitz, et al., 2004), but also extend those findings to provide a more complete picture of the cognitive profile of male carriers of the fragile X premutation, both those with and without FXTAS. The discussion first addresses findings related to motor functioning among premutation carriers both with and without FXTAS. We then discuss cognition among asymptomatic carriers in comparison with the control group. Finally, we address the results as they pertain to men with FXTAS.

### *Motor Functioning Among Premutation Carriers*

Given that motor impairment is a key feature of FXTAS, it was expected that subjects diagnosed with the tremor/ataxia syndrome would show substantial impairment on tests of motor functioning, in comparison with asymptomatic carriers and controls. As expected, men with FXTAS performed significantly worse than did the control group on all five measures of motor functioning. FXTAS subjects performed significantly worse than asymptomatic carriers on four of the five measures. In comparison with the control group, asymptomatic carriers showed no deficits in motor functioning.

The prevalence of neurologic diagnoses of tremor and ataxia differed substantially across groups. Given that tremor and ataxia are key features of the FXTAS diagnosis, it was to be expected that men in the FXTAS group would have either tremor or ataxia, and that most had both. Prevalence of these signs fell within the range expected for an aging population for the control group but was slightly higher among asymptomatic carriers. Whereas 87% of men in the control group showed no sign of tremor or ataxia on neurologic evaluation, only 71% of asymptomatic carriers had neither tremor nor ataxia. This finding may suggest that some men in the asymptomatic carrier group have begun to show subclinical signs of FXTAS, but they are not yet formally diagnosable as having definite or probable FXTAS.

### *Cognitive Functioning Among Asymptomatic Carriers*

Although asymptomatic carriers scored lower than controls on most tests, with the exception of the ECF composite score as well as the immediate and delayed recall components of the LMT, these differences were not significant. Hence, cognitive impairment among asymptomatic carriers was relatively circumscribed. However, it should be noted that subjects in the asymptomatic carrier group were significantly younger than those in the FXTAS group, suggesting that premutation carriers who did not meet the criteria for diagnosis of FXTAS may not yet have begun to show a clinically significant decline in cognitive functioning. It also is possible that the smaller size of the asymptomatic carrier sample ($n = 28$) may have resulted in a reduction of statistical power to find significant differences between the control and asymptomatic carrier groups.

In a series of between-groups comparisons, the very slight advantage of controls over asymptomatic carriers on the MMSE, VIQ, and PIQ was not statistically significant. Among asymptomatic carriers, the mean scores on both VIQ and PIQ were approx-

imately one standard deviation above the normative mean for the general population. Likewise, the mean MMSE score for this group provided no indication of impairment in mental status. Consistent with these findings, asymptomatic carriers did not differ from controls on measures of working or remote memory, verbal reasoning, information processing speed, visuospatial functioning, or temporal sequencing (see Table 2). The same held true for measures of speech, language, and praxis (all subtests of the BDAE and the BNT).

The results for asymptomatic carriers of the premutation are generally in line with the findings of other studies of adult male carriers of the fragile X premutation (Cornish et al., 2005; Dorn et al., 1994; R. J. Hagerman et al., 1996; Jäkälä et al., 1997; Loesch et al., 1994, 2003, 2005; Moore, Daly, Schmitz, et al., 2004; Moore, Daly, Tassone, et al., 2004). In the largest previous study of premutation carriers, Moore, Daly, Schmitz, et al. (2004) reported deficits in ECF, along with impaired performance on certain aspects of learning and memory. The 10 subjects studied by Loesch et al. (1994) were relatively impaired on the WAIS–Revised Block Design subtest (Wechsler, 1984) and on the Peabody Picture Vocabulary Test (Dunn, 1981). In our study, asymptomatic premutation carriers had lower mean scores on the WAIS–III Block Design and Vocabulary subtests than did controls, but the differences were not statistically significant. The agreement of findings in the current study with those of Moore, Daly, Schmitz, et al. (2004), as well as those of Loesch et al. (2003), provides further support for the hypothesis that certain of the ECFs are subtly impaired in at least a subset of carriers of the fragile X premutation who are unaffected by FXTAS.

### *Cognitive Functioning Among Men With FXTAS*

The results for men with FXTAS are consistent with what is known about a class of disorders often referred to as *subcortical*, *frontal*, or *dysexecutive* in nature. Because the neuropathology of FXTAS is not localized, but instead affects many regions of the brain (Brunberg et al., 2002; Greco et al., 2002, 2006), we use the functional term dysexecutive to describe the pattern of impairment observed in FXTAS, rather than the terms frontal or subcortical, which suggest more focal or circumscribed pathology.

#### *Mental Status and General Intellectual Functioning*

Men with FXTAS obtained MMSE scores that, although significantly worse than those of controls, were nevertheless in the normal range. VIQ and PIQ scores also were significantly worse among FXTAS than control subjects. In contrast to the results related to MMSE total score, average VIQ and PIQ scores in the FXTAS group were reflective of clinically significant impairment. Although subjects in the FXTAS group obtained IQ scores in the normal range, their average scores on these measures were 0.88 and 1.23 standard deviations below the mean for control subjects, respectively. Given the relatively high level of educational attainment in the FXTAS group (15.3 years of schooling on average), these scores are quite low. Although longitudinal data are unavailable, it is possible that poor performance on these measures represents a decline in functioning among men with FXTAS. However, long-term follow-up studies are needed to answer this question precisely.

#### *ECF and Working Memory*

As expected, the cognitive impairment seen in FXTAS was consistent with a dysexecutive syndrome. One of the most marked differences between the FXTAS and control groups was on the ECF composite score, for which the group comparison variable explained 22% of the variance in subjects' scores. Also as anticipated, working memory—an important component of ECF—was significantly worse among men with FXTAS than among control subjects. As mentioned previously, the difference between groups on the two Wechsler IQ scores, which was especially marked for PIQ, suggests impairment in general cognitive functioning. However, this difference also may be interpreted as a consequence of the fact that many of the nonverbal measures are novel tasks requiring active problem solving and, hence, are more dependent upon the ECFs for successful completion. Likewise, the Picture Arrangement subtest of the WAIS–III involves temporal sequencing and, hence, is probably affected by the integrity of executive functioning (Fuster, 2000); persons with FXTAS performed worse on this test than did controls.

The dysexecutive syndrome seen in FXTAS bears some similarity to that seen in several other disorders. For example, there is a resemblance to the pattern of impairment observed in Parkinson's disease and also to the cerebellar type of multiple system atrophy. In all three of these disorders, overall intellectual functioning may not be significantly deficient, but ECF performance is problematic (Bak, Crawford, Hearn, Mathuranath, & Hodges, 2005; Dubois & Pillon, 2002; Robbins et al., 1992). In addition, Spinocerebellar Ataxias (SCAs) 1, 2, 3, 6, 7, and 19 all have been reported to be accompanied by dysexecutive disorders and impaired information processing, sometimes associated with other cognitive deficits (Bürk et al., 2003; Schelhaas & van de Warrenburg, 2005). Finally, the clinical presentation of the frontal variant of frontotemporal dementia shares a number of characteristics with FXTAS (Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; McKhann et al., 2001).

#### *Declarative Memory*

The present study is the first systematic examination of declarative memory to be conducted among persons with FXTAS. Compared with controls, men with FXTAS had more difficulty with immediate and delayed recall of narrative material. The total number of details recalled on the LMT both immediately and after a 30-min delay was worse for FXTAS subjects than for controls. When the number of story elements recalled after the delay was examined as a percentage of the number of details recalled on the first presentation, the difference between the FXTAS and control groups was not statistically significant. This finding may be related to the large standard deviations for both groups on this measure. However, this also may suggest that consolidation of information into declarative memory is not as severely deficient as in disorders, such as Alzheimer's disease (AD), in which primary memory storage (and hence later recall) is significantly impaired.

On the RAVLT, men with FXTAS recalled significantly fewer words overall and on the final learning trial than did control subjects, indicating decreased learning efficiency. Given deficient working memory among individuals with FXTAS, the amount of material presented in the first learning trial of the RAVLT (15 words) could overload the capacity of the working memory sys-

tem, leading to poor performance. Secondary to their impaired executive functioning, persons with FXTAS then may have difficulty actively working to acquire those words missed on preceding trials when the words are presented again. This deficit also may be a result of problems with error detection, the development of a strategy for recall, or appropriate direction of attention. It is interesting that subjects with FXTAS did not differ from controls in the percentage of words recalled after the delay (although both numerator and denominator were smaller than for controls). As is observed among persons with Parkinson's disease, those words that are retained may be more likely to be recalled after a delay than is the case for persons with AD (Pillon, Deweer, Agid, & Dubois, 1993).

Finally, recall of information learned many years previously, as assessed by the WAIS–III Information subtest, was impaired in the FXTAS group. Interpretation of this finding is not entirely straightforward. It may be that this result reflects some forgetting of general information of the kind typically acquired in school. However, it is possible that this kind of information was not learned as well in the first place. That carriers of the fragile X premutation who were not affected by FXTAS did not differ from control subjects on this measure suggests that cultural knowledge previously learned may be lost in FXTAS.

### *Verbal Reasoning and Comprehension*

Verbal reasoning appears to be intact among men with FXTAS. These subjects did not differ from healthy controls on any of the measures assessing comprehension of verbal material, including the Similarities, Vocabulary, and Comprehension subtests of the WAIS–III.

### *Speech, Language, and Praxis*

For most individuals with FXTAS, both speech and language are intact (although individual cases of persons with advanced FXTAS may show a cerebellar type of dysarthria; e.g., Grigsby, Leehey, et al., 2006). This distinguishes the clinical presentation of FXTAS from AD, in which there typically are significant problems with both syntax and semantics (Della Sala, Lucchelli, & Spinnler, 1987; Emery, 1996). Dysnomia and aphasic phenomena are common as AD progresses, and many individuals with AD eventually become mute. With regard to apraxia, we have observed occasional individuals with advanced FXTAS who demonstrated ideomotor and ideational apraxia on items from the BDAE, but this does not seem to be a consistent or common feature of the disorder (e.g., Grigsby, Leehey, et al., 2006), in contrast to AD.

### *Speed of Information Processing*

Compared with controls, speed of information processing was significantly impaired in the FXTAS group. This slowing contributed to deficient performances on most timed tests, such as most of the nonverbal subtests that comprise the WAIS–III PIQ index, and it was likely to contribute to difficulties with working memory. Although we did not compare FXTAS patients with persons with Parkinson's disease, the clinical presentation of individuals with FXTAS suggests the hypothesis that they experience less severely slowed processing than do persons with Parkinson's disease, especially the slowing observed when patients with Parkinson's disease are in the "off" condition associated with minimal efficacy of l-dopa. Apart from this possible difference, FXTAS and Parkinson's disease appear to be somewhat similar to one another in that they are both characterized by a significant dysexecutive syndrome. Both also differ considerably from AD in that language is minimally affected in FXTAS and Parkinson's disease (Dubois & Pillon, 2002).

### *Visuospatial Processing*

The difference between FXTAS and AD also was apparent in performance on tests involving visuospatial perception and manipulation. FXTAS subjects appeared not to have constructional dyspraxia, although this was difficult to assess because of the severity of action tremor in many cases. The FXTAS sample differed significantly from controls on only one of the two WAIS–III measures most sensitive to spatial perceptual difficulties (Block Design).

## *Conclusion*

The results of this study are of considerable interest. They are consistent with and expand upon previous research on FXTAS, which was limited primarily to the assessment of IQ and ECF (Grigsby, Brega, et al., 2006; Grigsby et al., 2007; Grigsby, Leehey, et al., 2006; R. J. Hagerman, Leehey, et al., 2001; Jacquemont et al., 2003; Loesch et al., 2005). The results, which provide a thorough overview of cognition in this disorder, confirm the preliminary impression of FXTAS as a dysexecutive syndrome, marked especially by deficits in behavioral self-regulation, control of attention, and working memory. In addition, the findings regarding asymptomatic carriers of the premutation are in line with other published literature (e.g., Cornish et al., 2005; Moore, Daly, Schmitz, et al., 2004; Moore, Daly, Tassone, et al., 2004).

The present study was cross-sectional, and although the individual histories of subjects in the FXTAS group suggest that the cognitive disorder is progressive, many questions remain unanswered. It is not clear that all men affected by FXTAS will experience significant cognitive decline, and it is possible that some may avoid it altogether. A number of genetic and epigenetic variables may affect penetrance and expression of the disorder, and these have yet to be identified. Likewise, the temporal relationship between the onset of cognitive symptoms and motor impairment is uncertain. Further study will enhance our understanding of the nature of this executive cognitive disturbance and of how ECF impairment influences other functional systems not directly affected by the neuropathological process of FXTAS.

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