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The Primary Cognitive Deficit among Males with Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) is a Dysexecutive Syndrome

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Abstract

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder associated with a premutation trinucleotide repeat expansion in the fragile X mental retardation 1 gene (*FMRI*). Symptoms include gait ataxia, action tremor, and cognitive impairment. The objectives of the study were to clarify the nature of the dysexecutive syndrome observed in FXTAS and to assess the contribution of executive impairment to deficits in nonexecutive cognitive functions. Compared to controls, men with FXTAS demonstrated significant executive impairment, which was found to mediate group differences in most other cognitive abilities. Asymptomatic premutation carriers performed similarly to controls on all but two measures of executive functioning. These findings suggest that the impairment of non-executive cognitive skills in FXTAS is in large part secondary to executive dysfunction.

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Keywords

fragile X; premutation; cognition disorders; trinucleotide repeats; executive cognitive function; spinocerebellar degeneration; fragile x-associated tremor/ataxia syndrome

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder associated with a trinucleotide (CGG) repeat expansion in the fragile X mental retardation 1 (*FMRI*) gene (Hagerman et al., 2001; Jacquemont et al., 2003). Normal *FMRI* alleles have between six and 44 CGG repeats, with a mode of 29 or 30. Individuals who have between 55 and 200 repeats (*premutation* alleles) may show subtle neurodevelopmental anomalies, including mild executive cognitive deficits, psychiatric problems, and premature ovarian failure (Cornish et al., 2005; Hessler et al., 2005; Loesch et al., 2003; Loesch, Hay, & Mulley, 1994; Loesch, Churchyard, Brotchie, Marot, & Tassone, 2005; Moore et al., 2004a; Moore et al., 2004b; Sherman, 2000; Sherman et al., 2002). In addition, it appears likely that a majority of male premutation carriers develop FXTAS, with the onset of symptoms typically in the mid-60s (Berry-Kravis et al., 2003; Brussino et al., 2005; Hagerman & Hagerman, 2004; Jacquemont et al., 2004; Loesch et al., 2005; Rogers, Partington, & Turner, 2003).

Clinically, FXTAS is characterized by gait ataxia, action tremor, Parkinsonism, peripheral neuropathy, autonomic disorders, and cognitive impairment (Bacalman et al., 2006; Grigsby et al., 2006a,b, 2007a,b; Hagerman et al., 2001; Jacquemont et al., 2003; Leehey et al., 2003). Intranuclear eosinophilic astrocytic and neuronal inclusion bodies are found throughout the cortex and in many subcortical areas, and are especially prevalent in the hippocampus (Arocena et al., 2005; Greco et al., 2002; Greco et al., 2006; Iwahashi et al., 2006; Louis, Moskowitz, Friez, Amaya, & Vonsattel, 2006). Inclusions are rare in the cerebellum, which nevertheless shows considerable atrophy associated with large-scale dropout of Purkinje cells. It is noteworthy that Purkinje cells (the sole efferent neuronal population of the cerebellum) inhibit the activity of neurons in the deep cerebellar nuclei, which have been shown to play a role in cognition (Fiez & Raichle, 1997; Hallett & Grafman, 1997; Leiner, Leiner, & Dow, 1993; Schmahmann, 2000).

T2-weighted magnetic resonance imaging (especially fluid-attenuated inversion recovery, or FLAIR sequences) shows white matter hyperintensities in the middle cerebellar peduncles (MCPs) bilaterally in a majority of FXTAS patients (Brunberg et al., 2002; Jacquemont et al., 2003). The MCPs project from the pontine nuclei to widely distributed regions of the vermis and cerebellar hemispheres. Pathologic examination has shown this anomalous signal to be associated with spongiform changes (Greco et al., 2002; Greco et al., 2006).

The ataxia and action tremor observed in FXTAS are probably a consequence of the loss of Purkinje cells and degeneration of the MCPs. Although cerebellar degeneration also may cause cognitive impairment (e.g., Schmahmann, 2000), the anatomic substrate of most FXTAS-specific cognitive deficits cannot be localized readily, as the brains of persons with FXTAS typically demonstrate generalized atrophy of cerebrum, brainstem, and cerebellum.

Moreover, a large percentage of hippocampal cells (both neurons and astrocytes) contain intranuclear inclusions, and volumetric MRI analysis of the hippocampus shows considerable volume loss (Adams et al., 2007; Brunberg et al., 2002; Cohen et al., 2006; Greco et al., 2002; Greco et al., 2006).

In previous papers, we reported preliminary findings regarding the pattern of cognitive impairment characteristic of FXTAS. Our initial work (Bacalman et al., 2006; Bourgeois et al., 2006; Grigsby et al., 2006a,b, 2007b) was limited primarily to the assessment of IQ and key indicators of executive cognitive functioning (ECF). A more comprehensive study (Grigsby et al., 2007a) demonstrated that FXTAS involves substantial executive cognitive impairment as well as diffuse deficits on a range of neuropsychological measures. The dysexecutive syndrome seen in FXTAS includes deficits in behavioral self-regulation, control of attention, working memory, and verbal fluency. Speech and language remain generally intact (Grigsby et al., 2007a), apart from a mild cerebellar dysarthria as the disorder progresses (Grigsby et al., 2006b). Basic verbal reasoning and visuospatial perception also appear to be preserved. Although average scores were at about the mean for the general population, mental status as well as verbal and performance (nonverbal) IQ were impaired in men with FXTAS compared to healthy controls. Declarative memory and information processing speed and capacity also were substantially impaired among participants with FXTAS (Grigsby et al., 2007a).

Executive Cognitive Functioning

In this study, we approached the assessment of ECF from the theoretical-empirical perspective of Fuster (Deco, Ledberg, Almeida, & Fuster, 2005; Fuster, 1997; Fuster, 2000; Quintana & Fuster, 1999), who defined the executive abilities as “a set of cognitive operations that mediate *cross-temporal contingencies*” (pg. 67, emphasis in original). The ECFs mediate the integration of working memory and the intentions held therein, mental representations of the environment and the goal state, and a prospective “motor short-term memory” that supports planning for action. These functions allow intentions formulated in the past to be maintained across time until appropriate behavior (cognitive, motor, or perceptual) can be initiated and carried out to completion. Fuster refers to this process as the “perception-action” cycle (1997). An important component of Fuster's model is the capacity for inhibition (1997). Thus, according to Fuster's theory, cross-temporal contingencies must be mediated by “a temporally retrospective function of short-term memory, a temporally prospective function of anticipatory set or preparation, and a protective function of inhibitory control of interference” (1997, pg. 230).

The executive abilities are mediated by a complex network that includes the dorsolateral prefrontal cortex (DLPFC), medial frontal cortex (cingulate gyrus and supplementary motor area), cerebellum (especially the dentate nuclei), portions of the basal ganglia, mediodorsal thalamus, and other areas (Alexander & Crutcher, 1990; Fuster, 1997; Luria, 1966; Luria, 1980; Middleton & Strick, 1997; Scarnati & Florio, 1997; Schmahmann, 2000; Stuss & Benson, 1986). Hence, ECF is an emergent property of widely distributed, overlapping, modular functional systems. Given the generalized atrophy observed in FXTAS, localization of ECF deficits to any particular node(s) in this network is not possible.

Purpose of the Study

The objectives of this study were twofold. First, we sought to clarify the precise nature of the executive deficits seen in FXTAS. Performance on multiple measures of ECF was compared across three groups (premutation carriers with FXTAS, premutation carriers without signs of FXTAS, and controls with a normal allele). Second, we evaluated the contribution of ECF impairment to performance on measures of other cognitive abilities that are not primarily executive in nature. Although executive functioning has been shown to be at least somewhat dissociable from performance on measures of intelligence (Hebb, 1939; Stuss & Benson, 1986), a number of cognitive abilities, including certain aspects of learning and memory, may be affected by dysexecutive disorders (Duncan, Burgess, & Emslie, 1995; Duncan, Emslie, Williams, Johnson, & Freer, 1996; Shimamura, Janowsky, & Squire, 1990; Shimamura, Janowsky, & Squire, 1991). Using our previous comprehensive study of cognition in FXTAS as a foundation (Grigsby et al., 2007a), we assessed the degree to which ECF mediates the deficits identified in general mental status, verbal and nonverbal intelligence, remote memory, declarative (semantic) memory, information processing speed, visuospatial functioning, and temporal sequencing. Our intent was to determine whether the non-executive impairments identified in our previous work represent primary deficits or impairments mediated by deficient ECF.

Methods

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

Participants

Participant Recruitment—We have previously described the recruitment process for this study in detail (Grigsby et al., 2007a). Each study participant was categorized in one of the following groups: 1) premutation carriers without signs of FXTAS (“asymptomatic carriers”), 2) FXTAS, or 3) control (i.e., normal allele). All premutation carriers were identified as a result of their involvement in pedigree studies conducted at the participating institutions, through their participation in the National Fragile X Foundation or fragile X-related support groups, or through the clinical practices of study co-investigators. Controls were recruited from the families of participants with the premutation and from the community through recruitment advertisements. Although a small number of participants had been involved in prior studies and included in earlier journal articles (Grigsby et al., 2006a, 2007b), for only five participants (two men with FXTAS and three controls) were the data reported in this paper included in analyses underlying prior papers. (Most of the participants included in the investigation of general cognitive functioning reported by Grigsby et al. (2007a) were included in the sample used for this paper.

Participants were English-speaking males over the age of 40. Women were not included in the study because, at the time the study began, it was unclear whether female premutation

carriers could develop FXTAS. Evidence has now accumulated that some females with the premutation develop FXTAS, although at a lower rate and with a somewhat different phenotype than males (Berry-Kravis, Potanos, Weinberg, Zhou, & Goetz, 2005; Hagerman & Hagerman, 2004; Hagerman et al., 2004; Jacquemont, Leehey, Hagerman, Beckett, & Hagerman, 2006). Exclusion criteria included the following: sensory/language deficit or medical condition making participation impossible; medical condition or medical treatment with the potential to affect cognitive or emotional functioning adversely; moderate to severe head injury; epilepsy; definitively diagnosed movement disorders other than FXTAS; history of psychosis, toxic encephalopathy, encephalitis, or bacterial meningitis.

Description of Sample—One hundred and twenty-eight men were enrolled in the study. Five participants were excluded from the analyses reported in this paper as a result of medical conditions that had the potential to confound the relationships under investigation (three men had experienced head injury significant enough to potentially affect cognition; one control was found to have advanced dementia; one participant was a mosaic with a “smear” of CGG repeat values ranging from the normal range into the full mutation range [44 to 270 repeats]).

Within the remaining sample of 123 participants, men with FXTAS were found to be significantly older than control participants (mean age 68.2 versus 63.9 years; $t(89) = 2.02$, $p < 0.05$). Asymptomatic carriers differed marginally in age from controls (mean age 59.4 versus 63.9 years; $t(76) = -1.85$, $p < 0.10$). To ensure that the study findings would not be confounded by age differences between the premutation carrier groups and the control group, the sample was truncated to reduce age differences across groups. Specifically, the three men in the sample who were under the age of 42 (two asymptomatic carriers and one control) were removed from the analysis file. Excluding these three participants raised the average age among controls (64.5) and asymptomatic carriers (60.6), resulting in age differences of less than four years between each of the two premutation carrier groups and the control group. In this truncated sample, the average age of premutation carriers with and without FXTAS did not differ significantly from that of the control group ($p > 0.05$).

The final, age-matched sample included 120 men. Of the 79 premutation carriers included in the sample, 47 (59.5%) met diagnostic criteria for definite or probable FXTAS (Jacquemont et al., 2003). Thirty-two carriers (40.5%) did not meet FXTAS diagnostic criteria and thus were classified as asymptomatic carriers. Because FXTAS is diagnosed based on an expansion of *FMRI* and clinical signs, it is possible that some members of the asymptomatic group were preclinical and may yet develop symptoms. At this time, however, there is no way to determine which asymptomatic carriers will develop the syndrome. Two premutation carriers—one member of the FXTAS group and one asymptomatic carrier—were mosaics with two distinct CGG repeat values. In both cases, the two values were quite similar (i.e., within 18 points of each other). For these participants, the mean of the two CGG values was used in analyses. The control group included 41 men with normal alleles at *FMRI*.

Table 1 presents descriptive information for the men included in the analysis sample. As previously reported, asymptomatic premutation carriers and men with FXTAS did not differ from the control group in age. There was a significant age difference between the two

groups of carriers ($t(79) = -4.01, p = 0.0001$). However, as the cognitive performance of these two groups is not contrasted in this report, this age difference was not considered meaningful. Significant group differences in education were not detected ($p > 0.05$; note that for four participants with missing education information, the sample mean was substituted). The majority of study participants were non-Hispanic White. Participants in the three study groups did not differ significantly by race or ethnicity ($p > 0.05$).

Procedures

All participants underwent a thorough battery of cognitive and neuropsychological tests in addition to a neurological evaluation and a blood draw for the determination of *fMRI* status. The neurological exam and blood work, which are described in detail elsewhere (Grigsby et al., 2007a), were used to categorize premutation carriers into the FXTAS group or the asymptomatic carrier group. Previously, we used a composite score to examine ECF. In this paper, performance on individual measures of executive cognitive functioning was examined across study groups. In addition, we assessed the degree to which impairment in executive functioning explains deficits in performance on non-ECF measures reported in our prior, comprehensive study of cognitive functioning in male premutation carriers (Grigsby et al., 2007a). The measures of ECF, as well as those that reflect functioning in other cognitive areas, are described below. In this paper, we do not address those functional systems (e.g., language) for which we found no significant group differences in our prior study.

Executive Cognitive Functioning—The measures of ECF used in this study assessed behavioral self-regulation, working memory, and verbal fluency. We also considered other cognitive abilities that are related to dysexecutive syndrome, as discussed below.

a. Behavioral Self-Regulation: The primary measure of ECF used in the study was the Behavioral Dyscontrol Scale (BDS; Grigsby, Kaye, & Robbins, 1992; Kaye, Grigsby, Robbins, & Korzun, 1990), an extensively-validated measure of the capacity for behavioral self-regulation involving intentional control of simple voluntary motor behavior (Diesfeldt, 2004; Ecklund-Johnson, Miller, & Sweet, 2004; Grigsby et al., 2002b; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Grigsby, Kaye, Eilertsen, & Kramer, 2000; Grigsby et al., 1992; Kaye et al., 1990). Based on the work of Luria (1966, 1980) and Fuster (1997, 2000), the BDS was developed to measure the capacity to use intentions to guide the performance of goal-directed, purposeful activity. The BDS has been used to assess ECF in a number of different populations (e.g., Belanger et al., 2004; Grigsby et al., 2000, 2002a,b,c; Suchy, Blint, & Osmon, 1997; Suchy, Leahy, Sweet, & Lam, 2003), and the instrument has consistently demonstrated deficits among persons who carry the fragile X premutation and full mutation (e.g., Grigsby et al., 2006a,b, 2007a,b; Hagerman et al., 2001; Loesch et al., 2003; Loesch et al., 2005). In this study, the 27-point version of the BDS was used.

The nine items included in the BDS assess different aspects of ECF as conceptualized by Fuster (1997, 2000). For this reason, we examined between-group differences both using the total BDS score and the scores of individual BDS items, or clusters of items, which are described in detail below and in Table 2. By examining individual item differences, as well

as differences on the total score, we obtained a somewhat more fine-grained understanding of the nature of ECF impairment in FXTAS.

Items 1 and 2 involve rapid, repetitive tapping of the hands. These two tasks typically are learned quickly and require little contribution from working memory (correlations between these items and working memory tasks such as the Letter-Number Sequencing [LNS] subtest of the Wechsler Adult Intelligence Scale-Third Edition [WAIS-III] are generally ~ 0.30). Such simple motor programs are likely to be handled downstream in the motor hierarchy (Fuster, 1997), in a functionally more efficient network than that involved in the early stages of learning, or the learning of complex motor routines (Doyon & Benali, 2005; Haslinger et al., 2004; Seitz & Roland, 1992). Because items 1 and 2 are very similar to and were highly correlated with one another in this sample ($r = 0.74$), we analyzed the mean of the raw score for these items rather than each item score individually.

Item 3 is a go-no go task, during the performance of which the participant must maintain in working memory the intention to squeeze on one verbal stimulus (“red”) and to refrain from squeezing on a second stimulus (“green”). Such tasks involving response inhibition typically involve the DLPFC bilaterally (as would be expected when working memory is required), as well as dorsal anterior cingulate gyrus (e.g., Menon, Adelman, White, Glover, & Reiss, 2001). Accurate performance on this task presumably involves both ends of Fuster's perception-action cycle. Item 4 is similar in this regard, as the individual is required to inhibit an echopraxic response and must give a response that is the opposite of that of the examiner. Items 3 and 4 showed a moderately strong correlation with one another in this sample ($r = 0.42$), and have been found to load on the same factor (Ecklund-Johnson et al., 2004; Grigsby et al., 1992), but are different enough that we analyzed each item's raw score separately.

Items 5 and 6 involve motor procedural learning. Given that scores for these items are based on learning of motor sequences, the emphasis presumably shifts from working memory, to motor memory or motor programming (Suchy et al., 1997), and hence to more downstream processing (e.g., basal ganglia) as the program is acquired (Seitz & Roland, 1992; Shadmehr & Holcomb, 1997). Failure to learn the task well enough that it becomes relatively automatic could be a result of problems with working memory, prospective motor memory, or such cognitive processes as error detection. Because item 5 involves a sequence of finger taps that is simple and logical, it typically is more easily learned than item 6, which involves learning Luria's fist-edge-palm sequence (1966, 1980). We therefore analyzed the raw score for each of these items individually.

Item 7 is an adaptation of Head's test (Head, 1920), in which the examiner and participant sit facing one another. As the examiner places his or her hand in different positions near the head, the participant is required to imitate these gestures, using the same (e.g., right-right) hand. This task involves little motor activity, and is largely cognitive in nature, demanding that the participant actively think about which hand to use and avoid echopraxic (mirroring) errors in his/her performance.

For item 8, alphanumeric sequencing (Grigsby, Kaye, & Busenbark, 1994), the participant must alternate counting with saying the alphabet (essentially a mental version of Trail Making part B, beginning with the number 1 and ending with the letter L). This item involves no motor performance, but a verbal response is required in the perception-action cycle. Although this item relies on working memory, it is primarily a measure of attentional control, which is closely related to behavioral control, as in attention deficit hyperactivity disorder (Barkley, 1997). We analyzed the raw score for item 8, which is based on both the time required to complete the task and the number of errors.

Finally, BDS item 9 is a rating by the examiner of the individual's capacity for critical and accurate monitoring of his/her performance throughout the exam (i.e., insight). In this sample, the raw score for this item is strongly correlated with the total BDS score ($r = 0.79$). The item is cognitive in nature, and in all likelihood relies heavily on a network involved in error detection, including the anterior cingulate gyrus and supplementary motor area (e.g., Gehring, Goss, Coles, Meyer, & Donchin, 1993).

The Stroop Test (Spreen & Strauss, 1998; Stroop, 1935) provided two additional measures of behavioral self-regulation. The total number of colors correctly identified on the color-word component of the test, and the total number of errors committed during that 45-second trial provide measures of the capacity for cognitive inhibition.

b. 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; Friedman, Janas, & Goldman-Rakic, 1990; Fuster, 1997; Fuster, 2000). Previous studies have suggested that men with FXTAS may experience impaired working memory (Grigsby et al., 2006a,b, 2007a,b). The Letter-Number Sequencing (LNS), Digits Forward, and Digits Backward subtests of the WAISIII were used as measures of working memory capacity (Wechsler, 1997a). We also used trial 1 of the Rey Auditory Verbal Learning Test (RAVLT; Spreen & Strauss, 1998) (discussed below) as a measure of working memory. We used raw scores for Digits Forward and Digits Backward, whereas the LNS score was The WAIS-III age-adjusted scaled score.

c. Verbal Fluency: The Controlled Oral Word Association Test (COWAT) is a subtest of the Neurosensory Center Comprehensive Exam for Aphasia (Spreen & Benton, 1977). The COWAT is a reliable measure of verbal fluency (desRosiers & Kavanaugh, 1987), and presumably a component of ECF insofar as it involves the ability to generate information actively. During three 60-second trials, each participant was asked to say as many words as possible starting with a given letter (F, A, and S). The raw total number of words provided was used as a measure of verbal fluency.

d. Declarative Verbal Learning and Memory: The RAVLT (Spreen & Strauss, 1998) also was used to measure declarative verbal learning and memory, which is associated with ECF dysfunction. The RAVLT consists of a list of 15 unrelated concrete nouns repeated five times (the learning trials). Recall is requested after each presentation of the word list. After the fifth trial, a different (interference) list is presented and recall for the interference list is

tested. The participant is then asked to recall the words from the first word list (Post-Interference Recall Trial). Three measures of declarative verbal learning and memory were computed from the RAVLT: (1) the raw total number of words recalled on the interference list trial; (2) the raw score on RAVLT trial 6 (i.e., the post-interference recall trial); and (3) the raw number of intrusions across all learning.

Contribution of ECF to Other Cognitive Functions—Grigsby et al. (2007a) identified deficits on several non-executive neuropsychological measures among males with FXTAS, and circumscribed impairment in asymptomatic carriers of the fragile X premutation. Men with FXTAS performed significantly worse than controls on measures of mental status, general intellectual functioning, remote semantic memory, declarative verbal learning and memory, speed and capacity of information processing, visuospatial functioning, and temporal sequencing. In comparison with controls, asymptomatic premutation carriers showed significant deficits in declarative verbal learning and memory. Although group differences were highly significant, the mean scores of persons with FXTAS were nevertheless in the average range on many measures (e.g., WAIS verbal and performance IQ). This suggested that the impairment observed in FXTAS might be primarily executive in nature, with performance on other “non-executive” tasks affected secondarily. Therefore, in the current paper we examine the role that ECF plays in mediating the group differences reported by Grigsby et al. (2007a). The tests used to measure these different aspects of cognition are described below.

a. Mental Status and General Intellectual Functioning: The raw total score on the Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975) provides a measure of general mental status. The WAIS-III (Wechsler, 1997a) is the most widely used test of intelligence. The Verbal IQ (VIQ) and Performance IQ (PIQ) scores, which are adjusted for age, were utilized as measures of general intellectual functioning. In our earlier work (Grigsby et al., 2007a), men diagnosed with FXTAS were found to score significantly worse than control participants on MMSE total score as well as the VIQ and PIQ indices, although it is important to note that the FXTAS group's performance on both measures was at approximately the mean for the general population. Scores were unusually low, however, for this highly educated group.

b. Remote Semantic Memory: The Information subtest of the WAIS-III (Wechsler, 1997a) examines an individual's general knowledge, and thus reflects the capacity for long-term semantic memory. In our prior study (Grigsby et al., 2007a), age-adjusted scores on this subtest were significantly lower among participants with FXTAS than among controls.

c. Declarative Verbal Learning and Memory: The Logical Memory Test (LMT) of the Revised Wechsler Memory Scale (WMS-III; Wechsler, 1997b) measures verbal declarative memory based on the participant's ability to recall the details of a short story read aloud by the examiner. Participants were asked to recall the story immediately and after a 30-minute delay. In our previous comprehensive examination of cognitive functioning in male premutation carriers (Grigsby et al., 2007a), FXTAS participants and asymptomatic carriers of the fragile X premutation recalled significantly fewer story elements than did controls,

both immediately and after the delay. The RAVLT (Spreen & Strauss, 1998) also was used by Grigsby et al. (2007a) to measure aspects of declarative learning and memory that are not directly related to ECF. Men with definite or probable FXTAS remembered significantly fewer words across the five learning trials and fewer words on the final learning trial (trial 5) than did their healthy counterparts. LMT scores were age-adjusted, whereas RAVLT scores were not.

d. Speed and Capacity of Information Processing: In comparison with control participants, men with FXTAS in our earlier comprehensive study of cognition were found to have significant deficits on the following four measures of information processing speed and capacity (Grigsby et al., 2007a): unadjusted total score on the Symbol Digit Modalities Test (SDMT; (Smith A., 1968); age-adjusted score on the Symbol Search Subtest of the WAIS-III (Wechsler, 1997a); and participants' raw scores on the word-reading and color-naming components of the Stroop Test (Spreen & Strauss, 1998; Stroop, 1935).

e. Visuospatial Functioning and Temporal Sequencing: We previously found group differences on the age-adjusted (scaled) score for the Block Design subtest of the WAIS-III, a measure of visuospatial functioning (Grigsby et al., 2007a). Participants with FXTAS showed significant impairment on this measure in comparison to controls. Men with FXTAS also scored significantly worse than controls on the scaled score for the Picture Arrangement subtest of the WAIS-III (Wechsler 1997a), a measure of the capacity for temporal sequencing. Given Fuster's emphasis on cross-temporal organization of perception and behavior as the primary function of ECF (1997, 2000), we were interested in the role played by executive functioning in performance on this measure.

Motor Functioning—The Purdue Pegboard Test (PPT; Tiffin & Asher, 1948) is a measure of motor functioning in which participants rapidly insert small metal pegs into holes on a pegboard, first using the dominant hand, then the nondominant hand, then both hands simultaneously. The total number of pegs inserted during the 30-second trial using the participant's dominant hand was used as a measure of fine motor functioning. Because FXTAS participants perform poorly on this measure due to action tremor (Grigsby et al., 2007a), the PPT was used to control for motor deficits in analyses involving cognitive tests that require the manual manipulation of stimulus materials (i.e., WAIS-III Block Design and Picture Arrangement subtests).

Data Analysis

Two primary sets of analyses are reported in this paper. The first set examined group differences in executive functioning between the carrier groups and the control group. The second set of analyses assessed the degree to which ECF mediates performance on neuropsychological tests not typically considered to measure ECF, but in the performance of which executive cognitive functioning plays some role. These were reported in our earlier work (Grigsby et al., 2007a).

Analyses designed to examine group differences in ECF were conducted using ordinary least squares (OLS) regression with nonparametric bootstrapping for estimation of

confidence intervals. For each ECF measure, two separate OLS models were conducted. One compared the performance of FXTAS to control participants, whereas the other compared asymptomatic carriers to control participants. Although age and educational level did not differ significantly between the carrier groups and the control group, we controlled for these variables in all models (with one exception), as is customary in analysis of cognitive performance. Because we used the LNS scaled score, only education (and not age) was controlled in models examining performance on this test.

The OLS models provided the test statistics that are reported in the Results section (e.g., t , R^2). However, because the distributions of the dependent variables were nonnormal in most cases, nonparametric bootstrapping with accelerated bias correction was used to determine whether the group differences examined in the OLS models were significant (Efron & Tibshirani, 1993). (The SAS programming code [“jackboot.sas”] used to conduct these analyses was obtained from the SAS Website, <http://support.sas.com/ctx/samples/index.jsp?sid=479&tab=downloads>.)

In nonparametric bootstrapping, a sampling distribution is created by randomly resampling (with substitution) the original data repeatedly and computing the test statistic of interest for each resample (in this case, the regression coefficient for the group variable). This distribution is then used to estimate the 95% confidence interval (CI) for the regression coefficient. Accelerated bias correction adjusts the CI to account for median bias. If zero is in the 95% CI, the group variable included in the model is not a significant predictor of executive functioning. If the 95% CI does not contain zero, the group difference examined in a given model is considered to be significant. (Because bootstrapping provides more accurate estimates of a 95% CI than a 99% CI, an alpha level of 0.05 was used to identify significant results.)

Typically, bootstrapping for statistical inference requires at least 2,000 random samples (Efron & Tibshirani, 1993). However, the larger the number of bootstrap replications, the greater the accuracy of the bootstrap CIs due to the decrease in error resulting from resampling. Therefore, for all dependent variables, we began by computing CIs for sampling distributions including 2,000 and 5,000 samples. To ensure that the estimates produced were stable, we compared the relative change in the lower CI, upper CI, and variance for the two sampling distributions. If the relative change for each statistic was less than 5%, we used the CI from the distribution of 5,000 samples for the purposes of statistical inference. If the relative change was greater than 5% for any of these statistics, we created larger sampling distributions until the relative change between the largest and the next smallest distributions (e.g., 10,000 samples versus 5,000 samples) was less than 5% for the three statistics.

For two models examining differences between the asymptomatic carriers and controls, (i.e., BDS item 9, the RAVLT first learning trial), we were unable to reduce the relative error in the CI or variance to less than 5%. For these comparisons, we report the models with the largest number of resamples. In all cases, the group variable was not a significant predictor of test performance.

The second set of analyses reported in this paper was conducted to assess the contribution of ECF to the cognitive deficits reported in our previous work (Grigsby et al., 2007a). We examined the degree to which ECF impairment accounts for—or *mediates*—group differences in these other cognitive functions, hypothesizing that the reported group differences on tests that do not explicitly assess ECF may result from or be influenced by group differences in executive functioning.

Because the sample included in the current report differs slightly from that examined by Grigsby et al. (2007a), we repeated the OLS regression models described in detail in that prior study to ensure that significant group differences in cognitive functioning were reproducible using this very similar, but not identical, sample. The results of these analyses replicated the findings reported by Grigsby et al. (2007a), laying the foundation for our examination of the contribution of ECF to deficits in these non-executive cognitive functions. Specifically, FXTAS participants were found to score significantly worse than control participants on measures of mental status, general intelligence, remote recall of information, declarative verbal learning and memory, information processing speed, one measure of visuospatial functioning (WAIS-III Block Design subtest), and temporal sequencing ($p < 0.01$ for all models). Asymptomatic carriers were found to differ from the control group only for the LMT immediate and delayed recall scores, which reflect verbal learning and memory. Note that group difference identified for the former variable attained a lower threshold for significance than it had in our prior work ($p < 0.05$ vs. $p < 0.01$; Grigsby et al., 2007a). For all other variables, group differences met the same or more stringent thresholds than reported by Grigsby et al., 2007a (e.g., $p < 0.0001$ vs. $p < 0.01$).

After repeating the OLS models reported by Grigsby et al. (2007a), the Sobel test (Sobel, 1982) and nonparametric bootstrapping with accelerated bias correction were used to test the mediating role of ECF (SAS code for estimating the indirect effect of ECF was obtained from Preacher and Hayes, 2004). In these analyses, bootstrapping was used to create a sampling distribution of the indirect or mediating effect of ECF on a given test of non-executive cognitive function (e.g., VIQ). The indirect effect can be thought of as the difference between the regression coefficient for the group variable when ECF is not controlled and the regression coefficient for the group variable in a model containing ECF as a covariate. If ECF mediates the relationship between the group variable and cognitive test performance, the parameter estimate associated with group should change significantly as a result of the inclusion of a measure of ECF. In addition to providing a direct test of the mediating effect of ECF on general cognitive functioning, this method has the advantage of making no assumptions about the shape of the sampling distribution (Preacher & Hayes, 2004).

Following the same procedure described previously, we created sampling distributions of increasing size until the upper and lower bounds of the CI and the variance were stable. When the 95% CI for the indirect effect does not contain zero, ECF is shown to significantly change the relationship between group and cognitive test score, and thus is considered to mediate the relationship between the two variables.

Analyses examining the role of ECF as a mediator of cognitive impairment among male premutation carriers examined four measures of ECF: BDS total score, COWAT total score, LNS scaled score, and number of colors correctly identified on the color-word component of the Stroop Test. Because these analyses focused on group differences reported by Grigsby et al. (2007a), we included the same covariates that were used in that earlier work. All analyses controlled for years of education. Further, models examining variables that were not already age-adjusted controlled for age at the time of assessment. (Age was not controlled in analyses related to the WAIS-III measures, which are already age-adjusted; analyses of all other dependent measures included age as a covariate.) Finally, because the WAIS-III Block Design 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 measures to ensure that findings would not be confounded by action tremor.

Results

Group Differences in Executive Cognitive Functioning

Descriptive information about the performance of study participants on the various measures of executive functioning is provided in Table 3. The table presents unadjusted mean scores and standard deviations by group for each measure. In addition, 95% CIs and significance for differences between (1) FXTAS and control participants and (2) asymptomatic carriers and controls are reported.

Adjusted OLS and bootstrapping analyses indicated significant impairment in multiple components of executive functioning among men diagnosed with FXTAS. Group differences were present for all measures of behavioral self-regulation. Participants with FXTAS scored significantly worse than controls on the nine measures derived from the BDS ($p < 0.05$ for all): total score ($t(84) = -4.91$, partial $R^2 = 0.18$); the mean of items 1 and 2 (repetitive tapping; $t(82) = -2.86$, partial $R^2 = 0.09$); item 3 (go-no go; $t(82) = -2.44$, partial $R^2 = 0.06$); item 4 (disinhibition; $t(82) = -3.19$, partial $R^2 = 0.10$); item 5 (learning finger sequence; $t(82) = -2.77$, partial $R^2 = 0.08$); item 6 (motor learning; $t(82) = -4.92$, partial $R^2 = 0.19$); item 7 (Head's test; $t(82) = -2.30$, partial $R^2 = 0.06$); item 8 (alphanumeric sequencing; $t(82) = -2.78$, partial $R^2 = 0.08$); and item 9 (insight; $t(82) = -4.24$, partial $R^2 = 0.15$).

FXTAS participants also showed substantial impairment on both Stroop measures ($p < 0.05$ for both models). The number of words for which the ink color was correctly named in the color-word component of the Stroop test was significantly lower for men with FXTAS than for control participants ($t(76) = -5.12$, partial $R^2 = 0.20$). Men with FXTAS also made more errors than did their counterparts in the control group ($t = 1.60$, partial $R^2 = 0.04$).

Asymptomatic premutation carriers performed similarly to controls on both Stroop measures and all but one of the measures derived from the BDS ($p > 0.05$). Carriers not diagnosed with definite or probable FXTAS performed significantly worse than controls on BDS item 6 ($t(66) = -2.19$, partial $R^2 = 0.06$, $p < 0.05$).

Whereas premutation carriers without FXTAS did not differ significantly from controls on any of the working memory measures ($p > 0.05$), working memory was affected among men

with FXTAS. Participants in the FXTAS group scored significantly worse than control participants on each of the four measures of working memory ($p < 0.05$): (LNS: $t_{(77)} = -3.48$, partial $R^2 = 0.14$); (Digits Forward: $t_{(79)} = -2.19$, partial $R^2 = 0.05$); (Digits Backward: $t_{(79)} = -2.29$, partial $R^2 = 0.05$); RAVLT Trial 1: $t_{(81)} = -3.78$, partial $R^2 = 0.14$).

Note that FXTAS participants scored at the normative mean on the age-adjusted LNS score. Although this suggests that these participants are not “impaired” in comparison with the general population, their performance is low given their educational attainment. Data from the U.S. Census Bureau (1997) indicate that approximately 26% of men 25 years of age or older in the United States have a college or advanced degree. In our highly-educated sample, 49% of FXTAS participants had received Bachelor's or advanced degrees. Asymptomatic carriers and control participants in the sample, who had similar levels of educational attainment as FXTAS participants, scored approximately 2/3 of a standard deviation above the mean.

Verbal fluency was strongly affected for men with FXTAS, but not for asymptomatic carriers of the fragile X premutation. Men with FXTAS performed significantly worse on the COWAT than did controls ($t_{(83)} = -4.39$, partial $R^2 = 0.17$, $p < 0.05$). Asymptomatic carriers performed similarly to controls on this measure ($p > 0.05$).

Declarative verbal learning appeared to be somewhat impaired among men diagnosed with FXTAS. Although FXTAS participants performed similarly to controls on the RAVLT interference trial and the RAVLT total intrusions measure ($p > 0.05$), FXTAS participants remembered significantly fewer words than did controls on the post-interference recall trial ($t_{(81)} = -2.89$, partial $R^2 = 0.08$, $p < 0.05$). Premutation carriers without FXTAS performed similarly to controls on the post-interference trial and the total intrusions measure ($p > 0.05$), but scored significantly worse than controls on the interference trial ($t_{(68)} = -2.41$, partial $R^2 = 0.07$, $p < 0.05$).

ECF Contribution to Performance on Other Neuropsychological Measures

Grigsby et al. (2007a) found that participants with FXTAS scored significantly worse than controls on measures of mental status, verbal and nonverbal intelligence, remote semantic memory, declarative verbal learning and memory, information processing speed, visuospatial functioning, and temporal sequencing. Asymptomatic premutation carriers performed similarly to controls on all but two measures (the LMT immediate and delayed recall scores), on which they performed significantly worse. Prior to examining the mediating role of ECF in these group differences, we repeated the analyses reported by Grigsby et al. (2007a), confirming that the group differences previously identified were replicated.

ECF as a Mediator of Cognitive Impairment Among FXTAS Participants—

Accelerated bias-corrected bootstrap analyses were conducted to examine the degree to which deficits in ECF account for weaknesses in other cognitive functions identified among FXTAS participants. Table 4 presents the 95% CI intervals and statistical significance for each model examining ECF as a mediator of differences between the FXTAS and control groups.

The analyses reported in Table 4 provide strong evidence that deficits in executive functioning contribute to impairments on neuropsychological tests that are not considered primarily executive in nature. In the majority of models, the ECF variable included was found to be a significant mediator of group differences in test performance. That is, inclusion of ECF as a covariate in models examining group differences on non-executive measures significantly reduced the effect of the group variable. BDS total score was a significant mediator in all models. COWAT total score, LNS age-adjusted score, and Stroop color-word score were found to be significant mediators of group differences in non-executive functioning for 12 of the 14 tests of cognitive performance. For most cognitive tests, mediation was demonstrated for each of the four measures of ECF that were used as mediators. For the LMT immediate and delayed recall scores, however, only BDS total score and LNS were significant mediators. For the Block Design and Picture Arrangement subtests, LNS score did not account for differences between FXTAS and control participants.

As discussed previously, Grigsby et al. (2007a) found that asymptomatic premutation carriers performed worse than controls on the LMT immediate and delayed recall scores. As part of the current analyses, we intended to examine the possibility that deficits in executive functioning may have contributed to these impairments in declarative verbal learning and memory. However, as reported in Table 3, asymptomatic carriers did not differ from controls on any of the four measures used to examine the contribution of ECF to impairment in non-executive functioning (i.e., BDS total score, COWAT, LNS, Stroop color-word score). As mediation analyses are intended to determine whether group differences in one variable account for group differences in a second variable, it was not appropriate to examine the impact of ECF on the LMT immediate and delayed recall scores (Baron & Kenny, 1986). Differences in executive functioning, which did not exist for the key ECF variables, cannot explain impairment of declarative learning and memory among asymptomatic premutation carriers.

Discussion

Group Differences in Executive Functioning

Risk-adjusted analyses indicated that participants with FXTAS had significantly worse executive cognitive functioning than did healthy controls. Men diagnosed with definite or probable FXTAS performed significantly worse than controls on 17 of the 19 measures of ECF employed in the study ($p < 0.05$ for all comparisons). The only measures for which FXTAS participants scored similarly to controls were the RAVLT interference trial and total intrusions scores. Although group differences on these measures were not significant, the average score of control participants was better than that of FXTAS participants.

Executive impairment was very limited among premutation carriers without FXTAS. Although test scores were lower for asymptomatic premutation carriers than controls on most measures of ECF, carriers without FXTAS performed significantly worse than controls only on BDS Item 6 (motor procedural learning) and the RAVLT interference trial.

In the context of Fuster's model of executive cognitive functioning, these findings suggest that FXTAS leads to impairment across the entire perception-action cycle. In addition to problems with working memory, participants with FXTAS had difficulty with short-term motor memory (as seen especially in tasks of motor learning). They also made errors on relatively simple motor tasks that, in theory, should involve the transition from DLPFC to basal ganglia (the finger tapping tasks in items 1 and 2). The third aspect of Fuster's ECF model—inhibition—was likewise impaired, both on the BDS and the Stroop. Finally, limitations of insight suggest a deficit in error detection, as participants with FXTAS tended to be unaware of their errors on BDS items. Hence, they may have difficulty retaining intentions, inhibiting incorrect or inappropriate responses, initiating the correct motor response, and monitoring the accuracy of their performance.

Contrary to our expectations, FXTAS participants did not show more intrusions or perform worse on the RAVLT interference trial than did controls, as might be expected in association with a dysexecutive syndrome. However, on this measure, men with FXTAS did show significant difficulty with recall following the presentation of an interference word list.

Overall, the findings of a dysexecutive syndrome are consistent with the behavior frequently reported by spouses and caregivers of males with FXTAS, which is characterized both by disinhibition and failure of initiation. A daughter of one of our FXTAS participants, for example, recounted how at a family holiday dinner her father had become extremely critical of one of his adult children as a result of a trivial incident, a type of behavior formerly atypical of him. Two spouses described incidents of physical abuse by husbands who had never behaved in this way prior to the onset of FXTAS. Yet another of the participants with FXTAS described himself as “going to work” every day, yet according to his wife, his time at work is spent aimlessly and he accomplishes little. She stated that when she asks about what he does at work, he becomes irritable and verbally abusive. These types of behavior are consistent with a dysexecutive syndrome, as reflected in impaired performance on the BDS.

Contribution of ECF Deficits to Impairment in Non-executive Cognitive Functions

Our earlier comprehensive examination of cognitive functioning among premutation carriers (Grigsby et al., 2007a) showed that men with FXTAS performed significantly worse than healthy controls on several non-executive measures, including general mental status, verbal and nonverbal intelligence, remote memory, declarative (semantic) memory, information processing speed, visuospatial functioning, and temporal sequencing. Asymptomatic carriers performed similarly to controls on all but two tests of declarative verbal learning and memory, for which their scores were significantly lower than controls.

In the current study, we sought to determine whether deficits in ECF might account for the group differences on non-executive measures reported by Grigsby et al. (2007a), as ECF could be expected to contribute at least in part to performance on these tests. Mediation analyses performed using nonparametric bootstrapping provided substantial evidence that problems with executive functioning lead to poor performance on a range of neuropsychological tests that are not explicitly measures of executive functioning *per se*. Regardless of the ECF measure included as a mediator (BDS total score, COWAT, LNS, or Stroop color-word score), we found that ECF accounted for differences in performance

between the FXTAS and control groups on the MMSE, VIQ, PIQ, Information subtest, RAVLT total score and the RAVLT final learning trial, SDMT, Symbol Search, and the Stroop word-reading and color-naming scores. For four other measures (LMT immediate and delayed recall, Block Design, Picture Arrangement), ECF was found to mediate the effect of group on cognitive performance for two or three of the ECF measures. ECF accounted for group differences on the two LMT measures when the BDS score or LNS score was included as a covariate, but not when the COWAT or Stroop color-word scores were controlled. LNS score was not a significant mediator of differences between the FXTAS and control groups on the Block Design and Picture Arrangement subtests of the WAIS-III. BDS total score was found to mediate differences between these groups on all non-executive measures examined. In contrast, group differences between asymptomatic carriers and controls on the LMT immediate and delayed recall scores were not mediated by deficits in executive functioning.

The results of this study confirm and extend previous findings regarding the cognitive disorder observed among males with FXTAS (Bacalman et al., 2006; Hagerman et al., 2001; Jacquemont et al., 2003; Loesch et al., 2005). Previously, we reported impairment in executive functioning in a case study (Grigsby et al., 2006b), a case series (Grigsby et al., 2006a), a small case control study (Grigsby et al., 2007b), and a more comprehensive study using age- and education-matched control participants (Grigsby et al., 2007a). In the present study we have confirmed that the primary cognitive deficit among males with FXTAS is a dysexecutive syndrome, and that ECF impairment significantly influences performance on a range of neuropsychological tests which depend to some extent on executive cognitive functioning.

In this regard, the cognitive phenotype of FXTAS is similar to that of several of the spinocerebellar ataxias, the frontal variant of frontotemporal dementia, Parkinson disease, multiple system atrophy, and other subcortical dementias (e.g., Bak, Crawford, Hearn, Mathuranath, & Hodges, 2005; Burk et al., 2003; Dubois & Pillon, 2002; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; Liu et al., 2004; McKhann et al., 2001; O'Hearn, Holmes, Calvert, Ross, & Margolis, 2001; Robbins et al., 1992; Schelhaas & van de Warrenburg, 2005). Viewed from the perspective of Fuster's model of executive functioning, FXTAS is marked especially by deficits in behavioral self-regulation (including disinhibition), working memory, and control of attention.

The present study was cross-sectional, and therefore it is not yet possible to draw inferences regarding the trajectory of cognition over time. The individual histories of participants in the FXTAS group suggest that the cognitive disorder is progressive, but the rate and nature of decline remain to be determined. Moreover, as some participants with FXTAS obtained scores suggestive of minimal or no impairment, it is not clear that all males affected by FXTAS will experience significant cognitive problems. When cognition is affected, the pattern of deficits may vary somewhat across individuals. Two brothers with FXTAS, for example, demonstrated moderate declines in behavioral self-regulation, but appeared to have insight into the quality of their performance. Other participants appeared to be unable to assess deficiencies in their test performance accurately. Given that we are following this cohort over a period of three years, we may be able in the near future to draw conclusions

regarding the short-term course of cognition in FXTAS. Further research will enhance our understanding of this disorder, of the relationships between neurologic and neuropsychological findings, and of other genetic and epigenetic variables that determine the development, course, and severity of FXTAS.

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Table 1Participant Characteristics by Group ^a

	FXTAS (<u>n</u> = 47)	Asymptomatic Premutation (<u>n</u> = 32)	Control (<u>n</u> = 41)
Age	68.2	60.6	64.5
Years of Education	15.4	15.9	16.7
White (%)	97.8%	100%	94.9%
Non-Hispanic (%)	93.6%	100%	97.4%

^aTable 1 presents unadjusted means/rates for participants in the three study groups.

Table 2

Items of the Behavioral Dyscontrol Scale

Item		Primarily a measure of:
1	Rapidly tap twice with dominant hand and once with nondominant	Simple motor control
2	Rapidly tap twice with nondominant hand and once with dominant	Simple motor control
3	Go-no go: squeeze when the stimulus is "red," do nothing on "green"	Inhibition
4	Tap once in response to two taps and tap twice in response to one tap	Inhibition
5	Learning of a finger sequence	Motor learning
6	Learning of a hand sequence (fist-edge-palm)	Motor learning
7	Head's test (imitation of gestures, directly across from examiner)	Cognition & error detection
8	Alphanumeric sequencing	Control of attention
9	Examiner's rating of patient's insight into performance	Insight

Table 3

ECF Test Performance by Group ^a

	Control Mean (SD) (Min - Max) ($\bar{n}$ = 41)	FXTAS Mean (SD) (Min - Max) ($\bar{n}$ = 47) ^b	FXTAS vs. Control (95% CI)	Asymptomatic Premutation Mean (SD) (Min - Max) ($\bar{n}$ = 32) ^c	Asymptomatic Carrier vs. Control (95% CI)
Behavioral Self-Regulation					
BDS Total Score	21.5 (3.4) (11 - 27)	16.0 (5.2) (3 - 25)	-6.58 - -2.86*	20.4 (3.8) (12 - 26)	-2.74 - 0.75
BDS Items 1 & 2 (Mean)	2.6 (0.6) (1 - 3)	2.1 (0.8) (0 - 3)	-0.74 - -0.17*	2.5 (0.6) (1.5 - 3)	-0.28 - 0.26
BDS Item 3	2.1 (0.9) (0 - 3)	1.5 (0.9) (0 - 3)	-0.88 - -0.07*	1.8 (0.8) (1 - 3)	-0.74 - 0.08
BDS Item 4	2.6 (0.7) (0 - 3)	1.9 (1.0) (0 - 3)	-1.01 - -0.25*	2.7 (0.6) (1 - 3)	-0.26 - 0.40
BDS Item 5	2.2 (0.7) (1 - 3)	1.6 (0.9) (0 - 3)	-0.82 - -0.12*	2.1 (0.9) (1 - 3)	-0.41 - 0.32
BDS Item 6	2.3 (0.5) (1 - 3)	1.4 (0.8) (0 - 3)	-1.03 - -0.44*	2.0 (0.7) (1 - 3)	-0.61 - -0.03*
BDS Item 7	2.5 (0.6) (1 - 3)	2.0 (0.9) (0 - 3)	-0.75 - -0.09*	2.3 (0.7) (1 - 3)	-0.47 - 0.17
BDS Item 8	2.1 (1.0) (0 - 3)	1.3 (0.9) (0 - 3)	-0.99 - -0.14*	2.0 (1.0) (0 - 3)	-0.51 - 0.40
BDS Item 9	2.8 (0.5) (1 - 3)	2.0 (0.8) (0 - 3)	-0.93 - -0.35*	2.5 (0.6) (1 - 3)	-0.52 - 0.00
Stroop Test - Number Correct in Color-Word Condition	40.2 (10.9) (23 - 70)	26.2 (10.6) (5 - 45)	-16.83 - -7.66*	40.7 (10.4) (29 - 81)	-5.99 - 3.20
Stroop Test - Number of Errors in Color-Word Condition	0.2 (0.6) (0 - 3)	1.1 (3.1) (0 - 15)	0.18 - 2.47*	0.2 (0.6) (0 - 3)	-0.36 - 0.37
Working Memory					
WAIS-III Letter-Number Sequencing (Age-Adjusted Score)	12.3 (2.5) (7 - 19)	10.1 (3.0) (3 - 16)	-3.47 - -0.99*	11.7 (2.5) (6 - 19)	-1.80 - 0.71
WAIS-III Digits Forward	10.6 (2.5) (6 - 15)	9.4 (2.1) (6 - 14)	-2.13 - -0.09*	10.3 (2.1) (6 - 16)	-1.47 - 0.74
WAIS-III Digits Backward	7.6 (2.9) (2 - 13)	6.0 (1.6) (4 - 10)	-2.06 - -0.19*	7.1 (2.4) (3 - 14)	-1.92 - 0.51
RAVLT First Learning Trial	5.7 (2.0) (2 - 12)	3.9 (1.8) (0 - 10)	-2.64 - -0.77*	4.9 (1.9) (0 - 8)	-1.70 - 0.00
Verbal Fluency					
COWAT Total Score	46.4 (13.5) (23 - 85)	32.4 (12.2) (11 - 65)	-17.71 - -7.32*	42.3 (12.1) (18 - 70)	-11.01 - 1.38
Declarative Verbal Learning and Memory					
RAVLT Interference Trial	5.0 (1.9) (1 - 10)	4.1 (1.9) (1 - 11)	-1.36 - 0.26	4.1 (1.9) (1 - 9)	-1.93 - -0.17*
RAVLT Trial 6 (Post-Interference Recall Trial)	8.8 (4.0) (1 - 15)	6.1 (3.3) (0 - 12)	-3.84 - -0.76*	8.6 (3.1) (2 - 13)	-2.32 - 0.75

	Control Mean (SD) (Min - Max) (n = 41)	FXTAS Mean (SD) (Min - Max) (n = 47) ^b	FXTAS vs. Control (95% CI)	Asymptomatic Prenutation Mean (SD) (Min - Max) (n = 32) ^c	Asymptomatic Carrier vs. Control (95% CI)
Behavioral Self-Regulation					
RAVLT Total Intrusions	2.6 (3.0) (0 - 14)	3.3 (3.3) (0 - 14)	-1.06 - 1.84	3.2 (3.8) (0 - 15)	-0.91 - 2.56

^aTable 3 presents the raw mean scores and standard deviations, as well as minimum and maximum scores, by group for each measure of ECF. The 95% CIs for comparisons of FXTAS participants versus controls and asymptomatic carriers versus controls are presented. The difference between two groups was considered significant if zero was not included within the 95% CI

* $p < 0.05$.

Table 4

Indirect Effect of ECF on Cognition: FXTAS vs. Control *

	BDS Total Score (95% CI)	COWAT Total Score (95% CI)	Letter-Number Sequencing (95% CI)	Stroop Color-Word Condition (95% CI)
Mental State				
MMSE Total Score	-2.14 - -0.29 ^a	-1.27 - -0.13 ^a	-1.82 - -0.25 ^a	-1.46 - -0.28 ^a
General Intelligence				
Verbal IQ	-12.42 - -4.64 ^a	-9.63 - -2.98 ^a	-10.43 - -2.41 ^a	-12.40 - -4.26 ^a
Performance IQ	-12.52 - -4.15 ^a	-9.89 - -3.44 ^a	-8.88 - -1.87 ^a	-12.82 - -4.22 ^a
Remote Memory				
Information Subtest	-1.73 - -0.42 ^a	-1.75 - -0.41 ^a	-1.61 - -0.29 ^a	-1.80 - -0.26 ^a
Declarative Memory				
LMT – Immediate Recall	-2.52 - -0.36 ^a	-1.39 - 0.21	-1.57 - -0.12 ^a	-1.62 - 0.38
LMT – Delayed Recall	-3.02 - -0.79 ^a	-1.73 - 0.07	-1.56 - -0.05 ^a	-2.17 - 0.16
RAVLT Total Score	-8.01 - -1.83 ^a	-4.96 - -0.50 ^a	-4.93 - -0.32 ^a	-9.24 - -3.01 ^a
RAVLT Final Learning Trial	-2.28 - -0.53 ^a	-1.59 - -0.30 ^a	-1.55 - -0.15 ^a	-2.64 - -0.78 ^a
Processing Speed				
SDMT Total Score	-11.87 - -2.44 ^a	-7.49 - -0.72 ^a	-8.65 - -0.67 ^a	-10.45 - -1.44 ^a
Symbol Search Subtest	-2.14 - -0.53 ^a	-1.50 - -0.35 ^a	-1.84 - -0.33 ^a	-2.36 - -0.61 ^a
Stroop Word-Reading	-16.45 - -4.27 ^a	-16.06 - -4.56 ^a	-12.39 - -2.21 ^a	-22.65 - -9.14 ^a
Stroop Color-Naming	-13.01 - -2.81 ^a	-12.12 - -3.39 ^a	-10.40 - -1.70 ^a	-17.31 - -6.86 ^a
Visuospatial Functioning				
Block Design Subtest	-1.49 - -0.08 ^a	-0.95 - -0.03 ^a	-1.09 - 0.05	-1.63 - -0.14 ^a
Temporal Sequencing				
Picture Arrangement	-1.83 - -0.14 ^a	-1.41 - -0.07 ^a	-1.17 - 0.07	-1.85 - -0.16 ^a

^aTable 4 presents the indirect effect of each of the four ECF mediator variables on cognitive test performance, controlling for group (FXTAS versus control) and covariates described in the Methods section. Lower and upper bounds for the 95% CI are reported. An ECF variable is considered to be a mediator of group differences in cognitive performance if zero is not in the CI

* $p < 0.05$.