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Functional Status of Men with the Fragile X Premutation, with and without the Tremor/Ataxia Syndrome (FXTAS)

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Abstract

Background—Fragile X-associated tremor/ataxia syndrome (FXTAS), which occurs in some premutation carriers of the fragile X mental retardation 1 (*FMRI*) gene, is a neurodegenerative disorder characterized by action tremor, gait ataxia, and impaired executive cognitive functioning.

Objective—To evaluate the nature and severity of functional limitations among male carriers of the fragile X premutation, both with and without FXTAS.

Methods—Forty-two subjects with FXTAS and 24 asymptomatic premutation carriers were compared to 32 control subjects on measures of physical functioning, activities of daily living (e.g., eating, bathing), and instrumental activities of daily living (e.g., shopping, managing medications). Ordinary least squares regression, controlling for age, education, medical comorbidity, and pain, was used to examine group differences in physical and functional performance.

Results—Men with FXTAS performed significantly worse than control subjects on all dependent measures, showing greater limitations in physical functioning, as well as ADL and IADL performance ($p < 0.05$). Subsequent analyses suggested that physical and functional impairments among men with FXTAS result largely from deficits in motor and executive functioning and that CGG repeat length is associated with functional impairment. Asymptomatic carriers of the fragile X premutation performed similarly to control subjects on all measures.

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Conflict of Interest
None known.

Conclusions—This study provides the first comprehensive evaluation of functional status among male premutation carriers. Although carriers without FXTAS performed similarly to control subjects, men with FXTAS showed evidence of significant physical and functional impairment, which appears to result largely from motor deficits characteristic of the syndrome.

Keywords

Fragile X; Fragile X-Associated Tremor/Ataxia Syndrome; FXTAS; functional status; activities of daily living; instrumental activities of daily living

INTRODUCTION

Fragile X-associated tremor/ataxia syndrome (FXTAS; Hagerman *et al.*, 2001) affects a subset of individuals with the fragile X premutation. The premutation is characterized by 55–200 CGG repeats in the 5' untranslated region of the fragile X mental retardation 1 (*FMR1*) gene. Symptoms of FXTAS include action tremor and gait ataxia, and often are accompanied by parkinsonism, dysautonomia, peripheral neuropathy, weakness, and other neurologic signs (Jacquemont *et al.*, 2003; Leehey *et al.*, 2007). FXTAS involves substantial impairment of the executive cognitive functions (ECF; Berry-Kravis *et al.*, 2007a,b; Brega *et al.*, 2008; Grigsby *et al.*, 2006, 2007, 2008; Leehey *et al.*, 2007), including deficits in behavioral self-regulation, attention, and working memory. A majority of males with the premutation are likely to develop FXTAS (Jacquemont *et al.*, 2004).

We studied physical limitations, and deficits in activities of daily living (ADLs) and instrumental ADLs (IADLs), among male carriers of the premutation. Whereas ADLs (e.g., eating, bathing) represent simple aspects of self-care, IADLs (e.g., meal preparation) are cognitively more complex. We expected that men with FXTAS would suffer impairment of functional status as a result of the motor and ECF deficits characteristic of the disorder.

METHODS

Subjects

Participants provided written informed consent and HIPAA authorization. The research was approved by IRBs at the University of Colorado Denver and the University of California Davis. The authors have no financial or personal interests to disclose.

Participants were 98 men aged 53 to 89, each of whom was assigned to one of three study groups. The FXTAS group included 42 subjects with definite or probable FXTAS (Jacquemont *et al.*, 2003). Men with the *FMR1* premutation without signs of FXTAS (n=24) were classified as asymptomatic premutation carriers (APC). The control group included 32 men with normal *FMR1* alleles. Participants were native English speakers with no history of any neurologic disorder other than FXTAS. Each subject had a family member or friend who was knowledgeable and willing to answer questions about the individual's functional status. Premutation carriers were identified through earlier studies, fragile X meetings or support groups, and the clinical practices of study co-investigators; control subjects were recruited from the families of carriers, medical clinics, and advertisements.

Of the 124 men enrolled in the study, 14 were excluded from these analyses because of missing functional status data. One man, a mosaic having a “smear” CGG repeat pattern ranging from the normal to the full mutation range, also was excluded. In the remaining sample of 109 participants, men with FXTAS were older than controls (mean age 68.6 versus 64.2 years; $p < 0.05$). Although asymptomatic carriers were three years younger than controls (mean age 60.9 versus 64.2 years), this difference was not significant ($p > 0.10$). To eliminate confounding by age, all men under the age of 53—the age of the youngest FXTAS participant—were excluded. Omitting these subjects (four APCs and seven controls) eliminated the significant age difference between FXTAS and controls.

Assessment of Functional Status

ECF deficits have been reported among premutation carriers (e.g., Brega *et al.*, 2008; Grigsby *et al.*, 2006, 2007, 2008), and because such individuals may have limited insight and be unable to evaluate their functional status accurately, we report data collected from informants. For 91% of cases, the informant was a spouse or significant other who lived with the subject. An additional 4% of informants were siblings or adult children of participants.

Physical limitations were measured using the Nagi and Rosow/Breslau physical disability items (Nagi, 1976), which assess ability to walk 1/4 mile; climb 10 steps without resting; stoop, crouch, or kneel; reach overhead; use fingers to grasp objects; and carry up to 10 pounds. Informants indicated whether the subject had difficulty completing each activity by himself, without special equipment. The mean of yes/no (1/0) responses across the six items, reflecting the proportion of the physical activities for which difficulty was reported, was used as a measure of physical limitations.

Measures from the Longitudinal Study on Aging (Katz *et al.*, 1963; Duke University, 1988) were used to assess ADL/IADL independence. Informants indicated whether the subject had difficulty completing seven ADLs by himself, without special equipment: bathing/showering; dressing; eating; using the toilet; transferring in and out of bed or chair; walking across a small room; getting outside. The ADL limitations score, the mean of these seven dichotomous yes/no (1/0) variables, represents the proportion of ADLs performed with difficulty.

The IADL limitations score provides a measure of subjects' difficulty engaging in eight IADLs independently (without special equipment): meal preparation; driving; shopping; using the phone; managing medications; managing money; strenuous housework; light housework. As with ADLs, the score reflects that proportion of IADLs performed with difficulty. IADL items included an additional response option indicating that a subject does not perform a task for reasons other than disability (e.g., wife always does the cooking). Such responses were coded as missing.

To examine subtle deficits in functional status, informants were asked to indicate whether subjects had changed either: (a) the frequency of performing an individual ADL/IADL, or (b) the manner of performance (Fried *et al.*, 2000; Guralnik *et al.*, 1999). There three frequency response options were *no*; *yes, less frequently*; and *yes, doesn't do it anymore*.

The two “yes” responses were collapsed to yield dichotomous (yes/no) variables and the average value for ADL and IADL variables, respectively, were computed. The degree to which a subject had changed the way he completed ADL/IADLs was computed as the mean of the yes/no (1/0) method change variables. The ADL/IADL frequency change variables and the ADL/IADL method change variables represent the proportion of ADLs or IADLs, respectively, for which a subject had changed frequency or method.

Motor and Executive Impairments

We hypothesized that tremor and ataxia would contribute to group difference in physical limitations and ADL/IADL performance. Although not all functional tasks depend on fine motor skills, several are likely to be impaired as a result of tremor (e.g., dressing, eating). The Purdue Pegboard Test (PPT; Tiffin and Asher, 1948) was used to quantify motor impairment. The PPT is a test of motor function in which subjects rapidly insert small metal pegs into holes on a pegboard. The number of pegs inserted during a 30-second trial using the dominant hand was used to quantify fine motor deficits.

Men with FXTAS have impaired ECF (Brega *et al.*, 2008; Grigsby *et al.*, 2006, 2007, 2008; Leehey *et al.*, 2007). ECF impairment limits an individual’s ability to regulate his/her behavior through planning, initiating appropriate activity, and inhibiting inappropriate behaviors. We hypothesized that ECF deficits would contribute to functional impairment. IADLs, which require planning and step-by-step execution of goal-directed activity, were expected to be particularly affected by ECF deficits. As ADLs are less complex activities, for which behavioral self-regulation over time is less crucial, we expected ADLs as well as physical limitations to be less severely affected by ECF deficits.

The measure of ECF used in this study was the Behavioral Dyscontrol Scale (BDS), a measure of the capacity for behavioral self-regulation (Diesfeldt *et al.*, 2004; Ecklund-Johnson *et al.*, 2004; Grigsby *et al.*, 1992). The BDS has consistently demonstrated deficits among persons with both the fragile X full mutation and FXTAS (Brega *et al.*, 2008; Grigsby *et al.*, 2006, 2007, 2008; Hagerman *et al.*, 2001; Loesch *et al.*, 2005). Higher scores (out of a total of 27) reflect better functioning.

Data Analysis

Regression models compared functional performance across groups. For each dependent variable, separate models examined the impact of two group-comparison variables: a) APC [1] versus control [0], and b) FXTAS [1] versus control [0].

Covariates—We adjusted for age and years of education in all analyses. To evaluate the contribution of motor and ECF deficits to differences in functional performance, regression models comparing FXTAS to control subjects were repeated using PPT dominant hand score as a covariate, and again using BDS as a covariate. Further, because performance of functional tasks can be influenced by comorbidity and pain (Bryant *et al.*, 2007), we controlled for these variables in all analyses as well.

For co-existent medical illness, we used the Charlson Comorbidity Index (CCI), a weighted measure of medical comorbidity (Charlson *et al.*, 1987), based on a set of 17 differently

weighted ICD-9 diagnoses. The degree to which pain interfered with subjects' regular activities (e.g., moving around, work, sleeping), using items from the San Luis Valley Health and Aging Study (SLVHAS; Hamman *et al.*, 1999), controlled for the influence of pain on functional status. The mean of these dichotomous responses, reflecting the proportion of activities negatively affected by pain, was used as a covariate in all analyses.

RESULTS

Sample Descriptives

Table 1 provides descriptive information about the sample. Although truncation of the sample ensured that the two carrier groups did not differ significantly from the control group with regard to age, men with FXTAS were older on average than APCs ($p < 0.01$). This age difference likely reflects the fact that the prevalence of FXTAS increases with age (Jacquemont *et al.*, 2004). Note that no premutation carrier over the age of 73 was classified as asymptomatic. Because of the marked age difference between APCs and men with FXTAS, we did not compare functional status between the carrier groups, but instead compared each premutation group separately to controls.

Participants were relatively highly educated. In each study group, subjects had 15 or more years of education on average. Controls had significantly more years of education than did men with FXTAS ($p < 0.01$) and marginally more than APCs ($p < 0.10$). Whereas the majority of APCs (71%) and controls (75%) in this sample had 16 or more years of education, only 43% of men with FXTAS had attained a similar degree of education. Analyses therefore controlled for education.

The premutation carrier groups differed with regard to CGG repeat length (Table 1). Men with FXTAS had significantly more repeats than did APCs ($p < 0.0001$). Although both carrier groups had members with CGG repeats in the 60s, large expansions were more common among men with FXTAS. Whereas only one asymptomatic carrier had a CGG repeat length greater than 94, 22 men with FXTAS (52%) had 95 repeats or more.

Among men with FXTAS, most had both tremor and ataxia (79%). An additional 12% had ataxia only, whereas 10% had tremor only. Age of onset of the two key neurologic signs of FXTAS ranged widely and was not correlated with CGG repeat length ($p > 0.10$). Although some subjects developed tremor/ataxia as early as their late 40s (minimum age of onset was 47 for ataxia and 48 for tremor), for some subjects, these symptoms first appeared in the late 70s (maximum age of onset was 78 for ataxia and 79 for tremor). Mean age of onset of tremor and ataxia was 61. Men in this sample developed FXTAS symptoms 9.1 years prior to assessment, on average, although duration of disease ranged from 0 to 22 years.

The two defining neurologic signs of FXTAS developed at similar ages for most subjects. Sixty percent of subjects with tremor and ataxia experienced onset of both symptoms within a three year period. Typically, however, tremor predated ataxia. Whereas 40% of FXTAS subjects developed tremor prior to ataxia, 37% developed ataxia first. For 23%, the onset of tremor and ataxia occurred at the same age.

Group Differences in Functional Performance

Regression analyses provided evidence of functional impairment among men with FXTAS (Table 2). In comparison with controls, men with FXTAS showed more physical limitations ($p < 0.01$). Whereas FXTAS subjects had difficulty with 42% of the six physical limitation items, on average, controls experienced difficulty with only 11%.

ADL performance also was impaired among men with FXTAS. These subjects experienced limitations in a larger proportion of ADLs ($p < 0.05$) than did controls (19% vs. 3%, respectively). In addition, men with FXTAS were more likely than controls to have changed the frequency of ADL performance ($p < 0.05$) as well as their method for performing these tasks ($p < 0.01$). FXTAS subjects had changed the frequency with which they performed 20% of ADLs and had changed the method for completing 25%. In contrast, controls had changed the frequency for completing 5% of ADLs and the method for completing 2% of these activities.

Compared with controls, FXTAS subjects scored significantly worse on IADLs ($p < 0.01$). Whereas controls had difficulty with 3% of the eight IADLs, on average, men with FXTAS had difficulty with 26% of IADLs. FXTAS subjects also were more likely than controls to have changed the frequency ($p = 0.01$) and method with which IADLs were performed ($p < 0.01$). Whereas men with FXTAS had changed the frequency with which they conducted 25% of IADLs and the method with which they completed 15%, controls had changed frequency or method for only a small percentage of tasks (4% and 2%, respectively).

Regression analyses examining group differences in functional status controlled for age, education, comorbidities, and pain. The degree to which pain interfered with daily activities was a significant predictor of physical limitations ($p < 0.001$, $r^2 = 0.23$), ADL limitations ($p < 0.01$, $r^2 = 0.20$), ADL frequency change ($p < 0.01$, $r^2 = 0.21$), ADL method change ($p < 0.05$, $r^2 = 0.14$), and IADL method change ($p < 0.05$, $r^2 = 0.16$). Age was a significant predictor of ADL method change ($p < 0.05$, $r^2 = 0.08$) and was marginally related to ADL limitations ($p < 0.10$). Comorbidity predicted ADL frequency change ($p < 0.05$, $r^2 = 0.07$) and was marginally associated with IADL limitations and IADL method change ($p < 0.10$). Education was marginally associated with IADL method change.

Among men with FXTAS, CGG repeat length predicted functional status. Post-hoc analyses regressing functional measures on CGG repeat length found that men with larger repeat expansions scored significantly worse on ADL frequency change ($p < 0.05$), IADL limitations ($p < 0.01$), and IADL frequency change ($p < 0.001$), and marginally worse on physical and ADL limitations ($p < 0.10$).

APCs showed little evidence of the functional limitations experienced by FXTAS subjects. Although there was a trend for APCs to experience greater physical limitations than controls ($p < 0.10$), this difference was not significant. APCs performed similarly to controls on all other measures of functional status.

Table 3 provides information about impairment of specific ADLs and IADLs by group. Among ADLs, men with FXTAS were particularly likely to experience difficulty

transferring to or from a bed or chair (36%). Further, about one-fifth of FXTAS subjects were reported to have difficulty with ambulation (i.e., crossing a room, getting outdoors) and dressing. Changes in the frequency for completing the transferring, ambulation, and bathing ADLs were common among men with FXTAS (19.0% – 40%). A substantial proportion of men with FXTAS had changed their method for bathing, dressing, eating, transferring, and crossing a room (21% – 36%).

With respect to IADLs, strenuous housework was particularly problematic for men with FXTAS, with difficulty reported for over one-half. Approximately one-fifth to one-third experienced difficulty with driving, shopping, managing medications, managing money, and light housework. A substantial proportion of FXTAS subjects had changed the frequency for activities related to driving, shopping, managing money, and housework. Changing the method for driving, shopping, and completing strenuous housework was common.

Table 4 shows the number of functional items with which members of each group had difficulty. Whereas 50% of men with FXTAS experienced no difficulty with ADLs, 87% and 84% of APCs and controls, respectively, had no ADL limitations. Difficulty with multiple ADLs was more common among men with FXTAS. Whereas 24% of individuals with FXTAS had difficulty with three or more ADLs, this was true for only 4.4% of APCs and none of the controls.

A similar pattern of results was found related to IADLs. The percentage of men with no IADL limitations was lower in the FXTAS group (38%) than the APC (74%) and control (81%) groups. One-third of men with FXTAS experienced limitations with three or more IADLs, but no APCs or controls did so.

Motor and Executive Impairment

In secondary sets of analyses, we explored the degree to which motor and ECF impairment contribute to functional limitations among men with FXTAS (Table 5). We recomputed regression models reported previously, controlling for motor performance in one set of models and BDS score in a second set of models. When motor functioning was controlled, group differences became nonsignificant for all dependent measures except ADL and IADL method change variables, for which the group effect was reduced but not eliminated. Similarly, inclusion of BDS score eliminated group differences for all dependent measures except the physical limitations score and the ADL and IADL method change variables.

Motor and ECF scores were not always independent predictors of the dependent measures. Motor score was a significant predictor of ADL and IADL limitations scores, and was marginally related to physical limitations and IADL frequency change. As expected, ECF was more closely related to IADL than ADL functioning, serving as a significant predictor of all three IADL scores. Even when not significantly related to dependent measures, however, the addition of these mediating variables had a strong effect on the relationship between group and functional performance. These results suggest that functional limitations among men with FXTAS result largely from impairment in motor and executive functioning.

DISCUSSION

The results provide a comprehensive picture of the nature and severity of functional impairment in FXTAS. Men with FXTAS had significantly more physical and functional limitations than did control subjects. Both ADL and IADL performance was affected, although men with FXTAS showed impairment of a greater proportion of IADLs than ADLs. Among men with FXTAS, larger CGG repeat expansions were associated with greater functional impairment.

It is possible that IADL impairment was more common than ADL deficits because the former category of functional activities relies somewhat more on complex motor skills. Bivariate correlations showed a slightly stronger relationship between motor score and IADL limitations ($r = -0.51, p < 0.0001$) than between motor score and ADL limitations ($r = -0.46, p < 0.0001$). Further, perhaps IADLs are cognitively more demanding than ADLs. Previous research has demonstrated that ECF, is consistently a stronger predictor of IADLs than ADLs (Suchy *et al.*, 1997; Grigsby *et al.*, 1998, 2000, 2002; Kaye *et al.*, 1990).

Functional impairment among men with FXTAS was heavily influenced by deficits in motor and executive functioning. As expected, motor functioning, but not ECF, accounted for some of the physical limitations experienced by men with FXTAS. Both motor ability and ECF accounted for group differences in ADL and IADL limitations as well as ADL and IADL frequency change. Impairment of fine motor skills and of the capacity for behavioral self-regulation each contributed to these functional impairments among men with FXTAS. Although controlling for motor and executive functioning did reduce group differences in the ADL and IADL method change variables, FXTAS subjects still performed significantly worse than their healthy counterparts. These results suggest that functional impairment among men with FXTAS is largely a result of the motor symptoms and executive dysfunction that accompany the syndrome.

This finding of a contribution by both ECF and motor impairment is reasonable given that fine motor control is necessary for performance of most ADL/IADLs. Importantly, ECF fundamentally represents the capacity to plan, initiate, monitor, adjust, and complete purposeful activity. Hence, significant ECF deficits may affect functional status even when one has the motor capacity to perform ADLs and IADLs (Grigsby *et al.*, 1998).

APCs demonstrated no significant functional impairment. Although they had marginally higher physical limitations scores, average performance on the ADL and IADL dependent measures in this group was similar to that of control subjects. Given that motor functioning—which is normal in this group—is a key contributor to physical and functional deficits, it is reasonable that APCs would show no ADL/IADL deficits.

Our data are consistent with those of Mioshi *et al.* (2007), who studied ADLs in persons with frontotemporal dementia (FTD) and Alzheimer disease. In particular, they noted significant problems in functional status among individuals with the behavioral variant (bv-FTD) of FTD. Interestingly, they noted that bv-FTD subjects scored well on the Mini Mental State Exam (MMSE; Folstein *et al.*, 1975), a finding similar to what we have reported in FXTAS (Brega *et al.*, 2008; Grigsby *et al.*, 2007).

Individuals with FXTAS may have significant needs for assistance with ADLs and IADLs as the syndrome progresses, although both the present study and that of Mioshi and associates, were limited to cross-sectional data. Longitudinal studies will provide more useful and compelling data on the nature and progression of FXTAS. This study complements the work of Leehey *et al.* (2007), who found that in FXTAS, tremor creates considerable disability within approximately 13 years from onset of motor symptoms. By 16 years post-onset, half of patients with FXTAS show significant ADL difficulty.

CONCLUSION

This study provides the first detailed description of the nature and severity of functional impairment among male carriers of the fragile X premutation. Although men with FXTAS experience significant functional deficits, asymptomatic carriers show no significant sign of physical or functional limitations. Impaired motor and ECF appear to be key contributors to functional impairment among men with FXTAS.

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Key Points

1. Men with FXTAS demonstrate significant impairment of physical and functional abilities.
2. Asymptomatic carriers of the fragile X premutation perform similarly to control subjects with regard to physical and functional status.
3. Motor and executive impairment are key contributors to physical and functional impairment among men with FXTAS.

Table 1Participant Characteristics by Group: Mean (Range)^a

	FXTAS (<u>n</u> = 42)	Asymptomatic Premutation (<u>n</u> = 24)	Control (<u>n</u> = 32)
Age ^b	68.6 (53 – 89)	63.7 (55 – 73)	67.2 (54 – 89)
Years of Education ^b	15.3 ^{**} (8 – 21)	16.0 [†] (12 – 19)	17.3 (10 – 21)
CGG Repeat ^c	95.9 (67 – 142)	79.2 (60 – 112)	30.5 (18 – 45)

^a Table 1 presents unadjusted means (and ranges) for participants in the three study groups.

^b When appropriate, significant differences between each premutation group and the control group are indicated:

[†] $p < 0.10$,

^{**} $p = 0.01$.

^c Men with FXTAS had significantly higher CGG repeat expansions than did their asymptomatic counterparts ($p < 0.0001$).

Table 2Functional Status: Premutation Groups Vs. Controls^a

	FXTAS (Mean) (n = 42)	Asymptomatic Carrier (Mean) (n = 24)	Control (Mean) (n = 32)
Physical Limitations Score	0.42**	0.18 [^]	0.11
ADL Limitations Score	0.19*	0.03	0.03
ADL Frequency Change Score	0.20*	0.01	0.05
ADL Method Change Score	0.25**	0.02	0.02
IADL Limitations Score	0.26**	0.04	0.03
IADL Frequency Change Score	0.25**	0.02	0.04
IADL Method Change Score	0.15**	0.00	0.02

^aTable 2 presents mean scores by group as well as the results of separate regression analyses comparing control subjects to subjects in the two premutation groups

[^]
p < 0.10,

*
p = 0.05;

**
p = 0.01.

Table 3

Impairment of Specific ADLs and IADLs

	Limitations Reported (%)		Frequency Has Changed (%)		Method Has Changed (%)	
	FXTAS	Asymptomatic Carrier	FXTAS	Asymptomatic Carrier	FXTAS	Asymptomatic Carrier
ADLs						
Bathing	14.3%	0.0%	19.0%	0.0%	28.6%	0.0%
Dressing	19.0%	8.7%	9.5%	0.0%	33.3%	4.4%
Eating	11.9%	0.0%	7.3%	0.0%	21.4%	0.0%
Toileting	9.5%	4.4%	10.0%	0.0%	14.3%	0.0%
Transferring	35.7%	8.7%	21.4%	0.0%	35.7%	8.7%
Crossing a Room	21.4%	0.0%	26.2%	4.4%	24.4%	4.4%
Getting Outside	21.4%	0.0%	40.5%	0.0%	14.6%	0.0%
IADLs						
Meal Preparation	15.2%	4.6%	11.9%	0.0%	2.6%	0.0%
Driving	31.0%	0.0%	33.3%	0.0%	18.0%	0.0%
Shopping	27.5%	4.6%	21.4%	4.6%	22.5%	0.0%
Telephone	4.8%	0.0%	9.5%	0.0%	5.0%	0.0%
Managing Medication	19.0%	0.0%	7.1%	0.0%	9.8%	0.0%
Managing Money	23.5%	4.8%	19.0%	4.4%	15.0%	0.0%
Strenuous Housework	62.2%	17.4%	59.5%	4.4%	37.5%	12.9%
Light Housework	18.9%	0.0%	34.2%	0.0%	14.6%	0.0%

Table 4Number of Impaired ADLs and IADLs: Percentages by Group^a

	FXTAS (<i>n</i> = 42)	Asymptomatic Carrier (<i>n</i> = 24)	Control (<i>n</i> = 32)
ADLs			
0	50.0%	87.0%	83.9%
1	11.9%	8.7%	9.7%
2	14.3%	0.0%	6.4%
3	14.3%	4.4%	0.0%
4 or more	9.5%	0.0%	0.0%
IADLs			
0	38.1%	73.9%	80.6%
1	23.8%	21.7%	16.1%
2	4.8%	4.4%	3.2%
3	14.3%	0.0%	0.0%
4 or more	19.0%	0.0%	0.0%

^aNot all totals equal 100% due to rounding.

Table 5Mediating Role of Motor and Executive Functioning: FXTAS Vs. Control Subjects^a

	Effect of Group (t)			Independent Effect of Mediator (t, r ²)		
	No Mediators Controlled	Motor Score Controlled	BDS Score Controlled	Motor Score	BDS Score	
Physical Limitations	3.01**	1.91 [^]	3.17**	-1.75 [^] (0.10)	1.08 (0.00)	
ADL Limitations	2.18*	0.87	1.47	-2.27* (0.11)	-0.98 (0.04)	
ADL Frequency Change	2.12*	1.08	1.52	-1.51 (0.07)	-0.76 (0.03)	
ADL Method Change	3.04**	2.06*	2.47*	-1.22 (0.08)	-0.44 (0.03)	
IADL Limitations	2.82**	1.26	1.44	-2.42* (0.14)	-2.47* (0.14)	
IADL Frequency Change	2.59**	1.29	1.15	-1.72 [^] (0.10)	-2.69** (0.15)	
IADL Method Change	2.91**	2.35*	2.07*	0.02 (0.02)	-1.08* (0.06)	

^aTable 5 presents the results of regression analyses comparing the impact of the group comparison variable (FXTAS vs. control) when motor functioning and executive functioning are controlled and are not controlled. T values and significance for the group variable as well as t values, significance, and effect sizes for the motor and executive functioning variables are reported:

[^] $p < 0.10$,
 * $p < 0.05$,
 ** $p < 0.01$.