

A Quantitative Assessment of Tremor and Ataxia in *FMR1* Premutation Carriers Using CATSYS

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While an established protocol exists for diagnosing individuals with the fragile X-associated tremor/ataxia syndrome (FXTAS), a quantitative measure of tremor and ataxia is needed. Using the CATSYS system to quantify movement abnormalities, we were able to record tremor, postural sway, manual (hand and finger) coordination, and reaction time in males with the *FMR1* premutation, both with and without FXTAS, and compare them to controls. We evaluated 16 males diagnosed with FXTAS, 16 males with the premutation without FXTAS (non-FXTAS), and 14 age-matched controls. The CATSYS system detected, in the dominant hand, a difference in intention tremor between the FXTAS group and controls ($P = 0.0008$). The 30-sec postural sway tasks revealed differences between the FXTAS group and controls, both with

eyes open and closed ($P = 0.0004$ and $P = 0.0031$, respectively). There was also a difference between FXTAS and non-FXTAS 30-sec postural sway performances with eyes open ($P = 0.0008$). The 10-sec postural sway tasks (with eyes closed) served to confirm the differences between the FXTAS group and both the controls ($P = 0.0017$) and non-FXTAS premutation carriers ($P = 0.0016$). These results demonstrate that the quantitative measures of the CATSYS system can document significant differences in intention tremor and postural sway in patients with FXTAS compared to controls.

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INTRODUCTION

Fragile X-associated tremor and ataxia syndrome (FXTAS) affects approximately 40% of males with

premutation alleles (55–200 CGG repeats) of the fragile X mental retardation 1 (*FMR1*) gene who are older than 50 years [Jacquemont et al., 2004]. The expanded (premutation) CGG-repeat leads to elevated

CATSYS Manufacturing Information: For manufacturing supplies and details, please refer to the Danish Product Development Ltd. website at <<http://www.catsys.dk/purchase.htm>>. Budgeting for the complete system used in this investigation should be maximized at 10,000 Euros, or under 15,000 US dollars, based on current exchange rates.

This project was conducted without any relationship between investigators and the CATSYS manufacturers and distributors. There was no discount or prior agreement to using the CATSYS for this investigation, nor are we, the investigators, shareholders, or consultants to the company.

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FMRI mRNA levels, resulting in a gain-of-function toxicity and subsequently causing progressive neurodegenerative features [Jacquemont et al., 2003]. Standardized measures to diagnose these symptoms include the Unified Parkinson Disease Rating Scale (UPDRS) for Parkinsonism [Fahn et al., 1987], the Clinical Rating Scale for Tremor (CRST) for tremor [Fahn et al., 1998], the International Cooperative Ataxia Rating Scale (ICARS) for ataxia [Trouillas et al., 1997], the FXTAS rating scale [Leehey et al., 2007b], and the FXTAS clinical staging scale [Adams et al., 2007]. These measures are available for research and clinical practices, but are time consuming and may not be well-known to clinicians who are not movement disorder specialists [Berry-Kravis et al., 2007; Leehey et al., 2007b].

Recent MRI studies have demonstrated subtle brainstem atrophy, particularly in the pons, of older male carriers who do not have FXTAS [Cohen et al., 2006; Loesch et al., 2007]. These neuroanatomical changes are likely to be accompanied by subtle disturbances of movement that precede the clinical diagnosis of FXTAS. To assess the extent to which movement is disturbed in older premutation carriers in both FXTAS and non-FXTAS carriers, we utilized the CATSYS system, a set of computer-assisted diagnostic instruments useful for quantitative measurement of tremor, postural sway, manual coordination, and reaction time [Despres et al., 2000]. During the course of these studies we also wanted to evaluate which performance tasks in the CATSYS system's battery of tests best assess the movement abnormalities of patients with FXTAS compared to age-matched controls.

MATERIALS AND METHODS

Subjects

Participants were recruited through the Fragile X Research and Treatment Center at the M.I.N.D. Institute of the University of California, Davis Medical Center (UCDMC). Following informed consent approved by the Institutional Review Board, participants underwent a detailed medical history and

neurological examination, including an MRI when possible, to document their diagnosis of FXTAS. All FXTAS patients and non-FXTAS carriers had family members with fragile X syndrome. A total of 46 male participants included 16 premutation carriers with FXTAS (mean age 64.6 years), 16 non-FXTAS premutation carriers (mean age 62.6 years), and 14 healthy controls (mean age 60.4 years). Although the observed mean ages for controls and non-FXTAS premutation carriers were lower than the FXTAS patients, age differences among groups were not significant ($P=0.25$). Of the 46 participants, 91% were Caucasian. The average amount of education was about 17 years, with no significant differences among the groups ($P=0.53$). Further details on the demographic variables for the study subjects are described in Table I.

Methods

The published CATSYS protocol was followed as closely as possible. The various tasks performed were grouped into one of four categories: postural tremor, postural sway, manual coordination, and reaction time. Because of the unique dyskinetic profile observed in the FXTAS population [Hagerman et al., 2001], an intention tremor performance task was appended to the standard CATSYS protocol and analyzed as a parameter of a fifth category [Juncos et al., 2006].

Postural tremor was measured in the standard manner, per the CATSYS protocol. For both hands, the patient was asked to grasp a pen-like instrument (Tremor Pen[®]) like one would grasp any writing utensil, and steadily hold it at abdomen level (approximately 4 inches in front of the navel). The pen contains a biaxial micro-accelerometer which measures movement in the plane perpendicular to the axis of the pen. Movement of the pen was recorded for 16.4 sec, with additional run-in and -out times (periods of time at the beginning and end of the test where movement is not recorded) of 2.0 sec each.

During the intention tremor performance task, the patient was asked to grip the pen in the same manner

TABLE I. Demographic Characteristics

Characteristics	Mean (SD) or percent			P-value
	FXTAS	Non-FXTAS	Controls	
Age	64.56 (6.60)	62.56 (6.29)	60.36 (7.62)	0.253 ^a
Education	16.69 (2.85)	16.21 (1.97)	17.57 (2.99)	0.529 ^a
Ethnicity (%)				
Caucasian	34.88	34.88	20.93	—
Hispanic	0	2.33	0	—
Others	2.33	0	4.65	—
CGG repeat	93.67 (15.70)	75.77 (16.59)	32.0 (6.87)	0.007 ^b
<i>FMRI</i> mRNA	3.75 (0.95)	2.93 (1.50)	1.66 (0.44)	0.134 ^b

^aOverall ANOVA P-value.

^bComparison between FXTAS and Non-FXTAS.

as was done in the postural tremor tasks. Instead of holding the pen steady in a certain position, however, the patient was asked to use the pen to alternately tap the centers of two points located on either side of the computer screen, designated as points A and B. The patients were uniformly instructed to sit in front of the computer monitor and begin the task with the right hand, moving at a moderate speed and continuing the tapping through the duration of the task without pausing or breaking their motion. Point A was a fixed point on the left inferiolateral corner of the computer's monitor border, about 10 inches above the table top. Point B was approximately 13 inches to the right of point A, on the opposite side of the monitor. As with the postural tremor task, the tapping motion was recorded for 16.4 sec, with additional run-in and -out times of 2.0 sec. The patient was not allowed to rest his elbows on the table while carrying out the task.

In order to quantify postural sway, we had to slightly modify the standard protocol for the CATSYS force plate so that we could fully illuminate the dysfunctional balance observed in patients with FXTAS. Because the CATSYS program only records data for what it deems a "completed" task, patients unable to stand on the force plate for the entire duration of the performance task had their data automatically voided. Our modification allowed the patients with balance problems to steady themselves briefly with one hand if they were on the verge of falling over. This modification was necessary to quantify sway patterns among the populations. Perhaps a better approach would have been to change the current CATSYS measurement parameters, allowing the recording of incomplete data. This would allow us to normalize the sway area by the duration of time spent on the force plate, but would have required access to, and modification of, the source code of the CATSYS program. Aside from allowing the use of a steadying hand by the patient, the CATSYS postural sway protocol was followed. Patients were asked to stand on the force plate for 32.8 sec (with an additional run-in time of 10.0 sec and a run-out time of 5.0 sec) while the area of their stance fluctuations were recorded. This was done once with the eyes open and once with the eyes closed. This process was repeated for a shorter recording duration of 10.0 sec (run-in time of 10.0 sec, and a run-out time of 5.0 sec) with the eyes closed. Participants were then asked to balance on each foot for a recording time of 16.4 sec (run-in time of 10.0 sec and run-out time of 5.0 sec), while the sway area was recorded. Some patients were unable to complete this task because they were wheelchair bound or were unable to stand on the force plate long enough for the CATSYS to record their performances (Table II, footnote c).

Manual hand coordination was measured by the CATSYS system per the standard protocol, as

previously described [Despres et al., 2000]. With this task, patients were asked to rhythmically tap the drum in time with sounds generated by the CATSYS program. The two initial trials involved tapping on the CATSYS drum with a repetitive pronation-supination motion of the hands. The manual coordination category was completed with the testing of finger coordination. We included two trials involving the rhythmic tapping of the index fingers (left and right). For all manual coordination trials, movement was recorded for 12.0 sec during which the sound probes gradually increased from a starting frequency of 1.6 Hz to a final frequency of 8.1 Hz.

Finally, the reaction time for response to an auditory stimulus was recorded using the reaction handle of the CATSYS system. Both hands were tested for 40.0 sec, with auditory stimuli triggered at random intervals (the average inter-probe interval period was 4.0 sec).

Molecular Analysis

DNA was isolated from peripheral blood leukocytes, where 5 ml of whole blood was processed using standard methods (Puregene and Purescripts Kits, Gentra Inc., Minneapolis, MN; Tempus Tubes, Applied Biosystems, Foster City, CA) [Saluto et al., 2005]. For Southern blot analysis, 5–10 g of isolated DNA was digested with *Eco*R1 and *Nru*1. The probe used in the hybridization was the StB12.3 [Saluto et al., 2005]. Details were previously described [Saluto et al., 2005]. Analysis and calculation of the repeat size were carried out using an Alpha Innotech FluorChem 8800 Image Detection System.

Statistical Analysis

Group comparisons (FXTAS, non-FXTAS carriers, and controls) were based on an analysis of covariance (ANCOVA), which adjusts for age. Hypothesis testing was based on a significance level of 0.05. Comparisons of the performances between groups, adjusted for age, were based on contrasts constructed within the ANCOVA model. For CATSYS variables measured on both the left and right hands (positional and intention tremor tests, hand pronation-supination, finger-tapping tests, and reaction time tests), outcome variables were defined for dominant and non-dominant hands. Thirty-six subjects were right hand dominant, while eight were left hand dominant. For the two ambidextrous subjects, dominant and non-dominant hand values were assigned the average of the left and right hand measurements. A few FXTAS patients had measurements that were extremely outlying (more than three times the interquartile range), especially on sway tests. For these variables, analysis of covariance was performed with and without the outliers. With the exception of right foot sway, the conclusions

TABLE II. The Comparison of the Parameters

CATSYS group	CATSYS performance task	Mean (SD) or median (MAD) ^a			P-value*		
		Control	Non-FXTAS	FXTAS	FXTAS vs. control	Non-FXTAS vs. control	FXTAS vs. non-FXTAS
Postural tremor, tremor intensity (m/sec ²)	Hand						
	Dominant	0.11 (0.05)	0.12 (0.03)	0.12 (0.04) ^a	0.0742	0.8600	0.0861
	Non-dominant	0.12 (0.05)	0.11 (0.03)	0.11 (0.04) ^a	0.1009	0.9913	0.0807
Intention tremor, tremor intensity (m/sec ²)	Hand						
	Dominant	2.22 (1.23)	2.45 (0.80)	2.89 (0.88)	0.0008**	0.0285	0.1118
	Non-dominant	2.11 (0.90)	2.19 (0.61)	2.94 (1.20)	0.0264	0.8294	0.0322
Postural sway area (mm ²)	30 sec ^a						
	Eyes closed ^b	12.00 (8.15)	17.00 (5.93)	37.50 (29.65)	0.0031**	0.6269	0.0083
	Eyes open	5.00 (2.22)	8.00 (5.83)	22.00 (11.86)	0.0004**	0.6067	0.0008**
	10 sec ^a						
	Eyes closed ^b	6.00 (6.67)	11.00 (5.93)	30.00 (29.65)	0.0017**	0.8998	0.0016**
	Single foot ^a						
	Right foot ^b	12.00 (8.90)	13.00 (7.41)	21.00 (26.69)	0.0790	0.4611	0.0111 ^c
	Left foot ^b	13.50 (11.12)	13.00 (16.31)	9.50 (12.60)	0.7022	0.4885	0.7757
Manual coordination, maximum frequency (Hz)	Hand						
	Pronation-supination						
	Dominant	6.85 (0.87)	6.73 (1.15)	6.35 (1.25)	0.3646	0.8987	0.4085
	Non-dominant	6.86 (0.87)	6.54 (0.81)	6.38 (1.08)	0.4091	0.5373	0.8227
	Finger tapping						
	Dominant	7.52 (1.45)	7.90 (0.41)	7.74 (0.55)	0.6928	0.3360	0.5466
	Non-dominant	7.95 (0.36)	7.32 (1.51)	7.19 (1.27)	0.1072	0.1802	0.7636
Reaction time (sec)	Hand						
	Dominant	0.23 (0.04)	0.21 (0.05)	0.25 (0.05)	0.7532	0.2654	0.1412
	Non-dominant	0.23 (0.04)	0.21 (0.04)	0.23 (0.05) ^a	0.6299	0.0962	0.2562

*Significance level 0.05.

**Significant after adjustment for multiple comparisons using Sidak stepdown procedure.

^aValues reported are median and median absolute deviation, which are robust estimates in place of mean and SD Due to a few outlying observations.

^bA number of FXTAS subjects excluded due to incompleteness of task (six for 30 sec. eyes closed, one for 10 sec. eyes closed, five for right foot, four for left foot).

^cNot significant with four extreme outliers included.

based on the two sets of statistical analyses were consistent. The summary measures of mean and standard deviation (SD) for some of the subjects with extreme observations (Table II) were replaced with median and median absolute deviation (MAD), respectively. These measurements tend to be more robust estimates, and are less sensitive to extreme observations than mean and S.D. All reported *P* values are raw *P* values. Significant results after *P*-value adjustment for multiple comparisons are marked with an asterisk. The Sidak stepdown method was used to adjust *P* values.

RESULTS

In order to obtain a more complete spectrum of data that encompasses symptoms often seen in patients with FXTAS, the performance tasks were categorized into five groups, consisting of positional and intention tremor evaluations, postural sway, manual coordination, and reaction time. The postural tremor measure showed no significant differences between any groups. Within the intention tremor measure, the FXTAS group exhibited significant differences in the non-dominant hand compared to both controls ($P=0.0264$) and the non-FXTAS

group ($P=0.0322$). In the dominant hand, there was a distinct difference in intention tremor between the FXTAS group and controls ($P=0.0008^*$), as well as a more subtle difference between the non-FXTAS population and controls ($P=0.0285$; Fig. 1). However, only intention tremor between the FXTAS group and controls was significant after the *P*-value adjustment.

The postural sway results consistently showed a significant difference in sway area. The 30 sec postural sway test with eyes open revealed differences between those with FXTAS and both controls ($P=0.0004^*$) and premutation carriers without FXTAS ($P=0.0008^*$), but not between non-FXTAS carriers and controls ($P=0.6067$). Similar differences were seen with the closed-eyed trials (Fig. 2), particularly the 10 sec trial, which more patients were able to complete (Table II). There were no differences between groups on the single foot postural sway test. This was likely related to the fact that subjects were allowed to steady themselves with a hand on the wall if they were about to fall. Even with this assistance, between one and six FXTAS subjects could not complete the various sway tasks (Table II, footnote c). We note that this testing procedure likely resulted in positively biased esti-

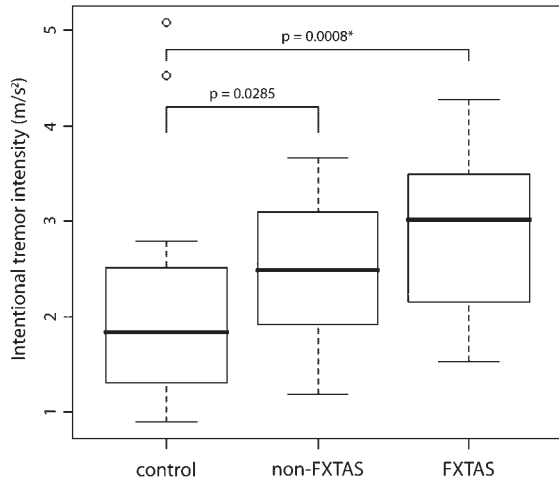


FIG. 1. Comparison of the box plots of intention tremor intensity in the dominant hand of male controls, premutation carriers without FXTAS (non-FXTAS), and premutation carriers with FXTAS. Circles represent outlier subjects. There was a significant difference between the control group and the FXTAS group in intention tremor intensity ($P = 0.0008^*$), as well as a more subtle difference between the control group and the non-FXTAS group ($P = 0.0285$). The difference between the FXTAS group and the non-FXTAS group was not significant. * Indicates significance after adjustment for multiple comparisons.

mates of sway for FXTAS subjects, making them seem more similar to controls and non-FXTAS carriers than they actually are. However, we also note that for the 30 sec, eyes-open sway test, all 16 FXTAS subjects completed the task, and performed substantially worse than controls and non-FXTAS premutation carriers. For the 30 sec, eyes-closed test, the results were the same, even with six (out of 16, 37.5%) subjects being excluded due to an incomplete task.

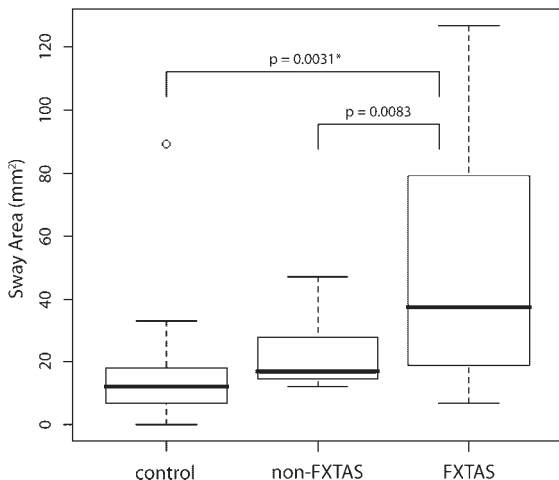


FIG. 2. Comparison of the box plots of sway area for the 30-sec postural sway test with eyes closed of male controls, premutation carriers without FXTAS (non-FXTAS), and premutation carriers with FXTAS. Circles represent outlier subjects. There was a significant difference between controls and premutation carriers with FXTAS ($P = 0.0031^*$) and between the FXTAS group and the non-FXTAS group ($P = 0.0083$). There was no difference between the controls and the non-FXTAS group. * Indicates significance after adjustment for multiple comparisons.

Because of the positive nature of the bias, the conclusion would still be valid; the mean/median sway area estimates would be underestimated for the FXTAS patients. This similarly applies to the 10 sec, eyes-closed sway test results, although there was only one FXTAS patient excluded. The validity issue is more of a concern for tests of sway area performed on the right and left feet (with eyes open), where FXTAS patients appeared to have gained a substantial advantage through the allowed balance assistance. For this reason, we caution that the non-significant difference between FXTAS patients compared to controls (and possibly to non-FXTAS carriers as well) is likely due to the limitation of our current postural sway data.

The manual coordination measures (pronation-supination hand tapping and index finger tapping) and the reaction time measure did not expose any quantitative differences between the groups (Table II).

DISCUSSION

The diagnosis of FXTAS is based on clinical (observational) criteria that include the presence of tremor or ataxia, executive function and memory deficits, and the presence of white matter disease on MRI, which often involves the middle cerebellar peduncles, in a patient with the fragile X premutation (55–200 CGG repeats) [Jacquemont et al., 2003]. FXTAS is a progressive condition, but there are only a few tools available for documenting this progression. A video rating scale has been reported, which utilizes standardized measures such as the UPDRS [Leehey et al., 2007b]. However, these measures require substantial training, and therefore may not be practical for the general physician. By contrast, the CATSYS system allows for quantitative documentation of neuromotor deficits with minimal operator training. This study assessed the utility of the CATSYS system for use in patients with the *FMRI* premutation, both with and without FXTAS.

A number of the measures collected with the CATSYS protocol were not helpful in differentiating patients with FXTAS from controls. These non-informative measures included the hand coordination variables and reaction time. Nevertheless, the CATSYS system was quite useful in documenting differences between the groups in several other measures, especially the variables involving the core features of FXTAS (tremor and ataxia). For example, we found disparities in postural sway (a component of ataxia) and intention tremor. Thus the CATSYS system should be amenable to studies that chart the course and progression of the symptoms of patients with FXTAS.

According to previous studies, there appears to be a slight bias toward tremor, over ataxia, as the presenting feature of FXTAS [Leehey et al., 2007a].

We have now corroborated this clinical observation with the quantitative measures from the CATSYS system. In particular, we observe a subclinical tremor only in the dominant hand of non-FXTAS patients compared to controls, which corresponds with the clinical observation that tremor often begins in the dominant hand and progresses to the non-dominant hand over the following year or two [Hagerman et al., 2001; Jacquemont et al., 2003; Leehey et al., 2007a]. In patients with FXTAS, ataxia develops at a mean age of 62 years, whereas the mean age of tremor development is approximately 60 years [Leehey et al., 2007a]. The lack of a difference in sway variables between the non-FXTAS group and the controls is not surprising in view of the clinical observation that ataxia generally develops a year or two after the onset of tremor.

The differences between the non-FXTAS group and controls should help to better define the subclinical changes in motor function of premutation carriers that presumably precede the onset of clinically apparent FXTAS, and which are likely to represent the earliest clinical signs of *FMR1* mRNA toxicity [Hagerman and Hagerman 2004]. Another example of subclinical changes preceding the diagnosis of FXTAS includes, in males, decreases in gray and white matter density in multiple areas of the brain, including the cerebellum [Moore et al., 2004b]. In addition, brainstem size (mainly the pons) has been found to be smaller in male premutation carriers than in controls [Cohen et al., 2006], and white matter changes in the brain have been found to occur before the diagnosis of FXTAS [Loesch et al., 2007]. Asymptomatic male carriers also demonstrate decreases in executive function and memory [Loesch et al., 2003; Moore et al., 2004a; Cornish et al., 2005]. Young boys with the premutation have a higher rate of ADHD, shyness, and social deficits compared to controls [Farzin et al., 2006], while adult males with the premutation, but without FXTAS, also demonstrate social deficits [Cornish et al., 2005]. It has also recently been demonstrated by functional MRI that there is a lack of activation of the amygdala to fearful faces in adult male carriers without FXTAS compared to controls [Hessl et al., 2007]. These studies all suggest that subclinical brain changes may be occurring in adult males with the premutation before the clinical onset of FXTAS. Some of these changes may be developmental, such as ADHD deficits and shyness or social deficits [Farzin et al., 2006; Hessl et al., 2007]. Other changes, such as the movement problems reported here, are also likely to be subclinical in some patients. How often this subclinical movement change progresses to FXTAS is a topic for further research.

Beyond its ability to detect subclinical changes, the CATSYS system will be a valuable adjunct in tracking the progression of FXTAS and in evaluating the efficacy of treatment. In addition, the progression of

tremor and balance problems of those patients at high risk for FXTAS could be monitored as the patients begin preventative treatments with neuroprotective agents.

We have described a small pilot study exploring the usefulness of the CATSYS protocol for assessment of people with, or at risk for, FXTAS. The results should be interpreted with the limits of the size of the study in mind. Nonetheless, the results indicate there is a potentially valuable role for the CATSYS system in the study of FXTAS, as well as in treatment programs. We encourage the use of this instrument in further studies, so that its value can be fully assessed.

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