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Tremorography in fragile X-associated tremor/ataxia syndrome, Parkinson's disease and essential tremor

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ABSTRACT

Background: Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disease affecting carriers of a 55–200 CGG repeat in the *fragile X mental retardation 1* gene, may receive an initial diagnosis of Parkinson's disease (PD) or essential tremor (ET) due to overlapping motor symptoms. Therefore, tremor and bradykinesia were compared in these disorders using quantitative tremorography.

Methods: The inertial sensor based Kinesia ™ system was used to quantify upper extremity tremor and bradykinesia in participants with FXTAS (n = 25), PD (n = 23), ET (n = 18) and controls (n = 20) and regression analysis was performed to determine whether tremorography measures distinguished between the groups. The FXTAS Rating scale (FXTAS-RS) was administered to determine whether sub-score items on the clinician rated scale correlated with tremorography variables.

Results: FXTAS participants had reduced finger tap speed compared to those with ET, and ET had increased kinetic tremor compared to PD. Higher kinetic tremor distinguished FXTAS from PD (p = .02), and lower finger tap speed distinguished FXTAS from ET (p = .004). FXTAS-RS tremor and bradykinesia items correlated with tremorography measures (p = .005 to <0.0001).

Conclusions: This is the first quantitative study to compare tremor and bradykinesia in FXTAS, PD and ET. Kinetic tremor and bradykinesia measures using a quantitative inertial sensor system distinguished FXTAS from PD and ET, respectively. Such technologies may be useful for detecting precise tremor and bradykinesia abnormalities and distinguishing the tremor and bradykinesia profiles in each of these disorders.

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disease that occurs in some carriers of a 'premutation' size (55–200) CGG repeat expansion in the *fragile X mental retardation 1 (FMR1)* gene, typically after age 50 [1]. In addition to the characteristic tremor and/or cerebellar ataxia, patients with FXTAS may have parkinsonism, peripheral neuropathy, cognitive decline and psychiatric symptoms [1–5]. FXTAS patients are frequently given an initial diagnosis of Parkinson's disease (PD) or essential tremor (ET) due to their similarities, especially when patients are seen by a primary care physician, general neurologist, or at a non-fragile X clinic where FXTAS may not be readily recognized [6]. Inaccurate diagnosis delays the initiation of targeted treatments and the provision of critical genetic counseling, which can have serious consequences for family members who may also be carriers and at risk of passing on a full mutation in the next generation. Distinguishing the tremor and bradykinesia profiles of FXTAS from those of PD and ET may facilitate better medical management.

The most common tremor type in FXTAS is an "essential tremor-like" action tremor, seen in 35% of patients [7,8]. The tremor in both FXTAS and ET is typically characterized by postural and kinetic tremor of the upper extremities [8–10], and may improve with alcohol in both disorders [11–15]. Upper limb rest tremor resembling that seen in PD has been reported in 12% of individuals with FXTAS [7,8] and may show a good response to levodopa, making it difficult to recognize as atypical [16–18]. Furthermore, 29–32% of FXTAS patients exhibit bradykinesia that is milder

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but indistinguishable from that seen in PD [19–21]. No studies have directly compared tremor or bradykinesia in FXTAS to that of PD or ET. Therefore, the objective of this study was to characterize the distinct tremor and bradykinesia profiles in FXTAS, PD, and ET using quantitative tremorography, and to determine whether these measures may be sensitive for distinguishing FXTAS from PD and ET.

Methods

Participants

FXTAS, PD, and ET participants were recruited through the Movement Disorders Clinic at Rush University Medical Center (RUMC). Inclusion criteria for participants with movement disorders were: [1] A diagnosis of only one of these disorders made by a movement disorders neurologist at RUMC, [2] a *FMR1* gene test showing one allele with CGG repeats between 55200 for FXTAS participants and $<$ 55 repeats on both alleles for PD and ET participants, [3] symptom onset at $\geq$age 50, [4] mild to severe tremor, and [5] mild parkinsonism for PD participants with Hoehn & Yahr staging of PD score $\leq$ 3 [22]. Diagnoses of movement disorders were made based on previously established criteria for FXTAS [23], PD [24] and ET [25]. FXTAS participants could have a diagnosis of possible, probable or definite FXTAS [7,23,26]. A diagnosis of PD was made based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [24]. ET participants could have a diagnosis of definite or probable ET [25]. A diagnosis of definite ET was made if postural tremor of moderate amplitude was present in at least one arm, tremor of moderate amplitude was present in at least one arm during four or more upper extremity tasks, tremor interfered with at least one activity of daily living and medications, hyperthyroidism, alcohol and other neurological conditions were not the cause of the tremor. A diagnosis of probable ET was made if tremor was present during at least four tasks or head tremor was present, and medications, hyperthyroidism, alcohol and other neurological conditions were not the cause of the tremor. Exclusion criteria were: [1] A prior history of stroke with focal neurological deficit or any other neurological or muscular disease, [2] seizure disorder or past head trauma resulting in structural brain damage, [3] deep brain stimulation surgery, [4] presence of dyskinesia on neurological exam and [5] clinical diagnosis of dementia as determined by the neurologist and/or neuropsychologist. Twenty healthy control participants were recruited from RUMC or from the community. Inclusion criteria were: [1] a normal neurological examination, and [2] a *FMR1* gene test showing both alleles with CGG repeats $<$55. Exclusion criteria were the same as for the FXTAS, PD and ET participants, but also included a significant history of tremor, balance problems, falls, or dizziness. All participants were required to be between >50 years of age; this was chosen because FXTAS typically develops after age 50. This study was approved by the RUMC Institutional Review Board and all participants gave written informed consent.

Tremorography

The *ETSense*™ inertial sensor tremorography device along with *Kinesia Home View*™, which has been validated for the quantitative measurement of upper extremity (UE) tremor and bradykinesia in PD and ET patients [27,28], was used to assess tremor and bradykinesia in both UE. Prior studies have demonstrated the ability of this system to accurately quantify kinetic, postural, and rest tremor [27,29] and UE bradykinesia [30], with high correlations to clinician rating scales including the Unified Parkinson's Disease Rating Scale (UPDRS) [31] and the modified bradykinesia rating scale [32]. Quantitative measures of tremor and bradykinesia were obtained in both UE during a series of motor tasks including arms resting, arms extended, finger to nose and finger taps while participants wore an inertial sensor on the index finger. Motion was captured within six degrees of freedom using three accelerometers and three gyroscopes located in the sensor unit. Motor data was processed into quantitative variables using an algorithm derived to output tremor and bradykinesia scores shown previously to highly correlate with clinician-rated UPDRS scores [27]. Tremor outcome measures included kinetic tremor (finger to nose task), rest tremor (arms resting task) and postural tremor (arms extended task). Two bradykinesia outcome measures were selected for analysis, finger tap speed and amplitude, as these have been used in previous studies in PD [27,29]. Severity scores of 0–4 with 0.1 resolution were generated for each measure by algorithms developed and validated by the manufacturer [27] with 0 indicating no symptoms and 4 indicating high symptom severity. The severity scores for rest, postural and kinetic tremor represent tremor amplitude and not frequency. All participants, if medicated, were tested in their optimal medicated state and had been on stable medication doses for at least six months. A summary of all medications participants were taking during the study for their motor symptoms is presented in Supplementary Table 1.

FXTAS rating scale

Participants were videotaped performing the FXTAS Rating Scale (FXTAS-RS), a 44-item scale that rates tremor, postural sway, gait, parkinsonism, coordination, dystonia, speech, and oculomotor deficits in order to assess the presence and severity of FXTAS symptoms [33,34]. The scale was created using items from the UPDRS [31], the Clinical Rating Scale for Tremor [35], the International Cooperative Ataxia Rating Scale [36], and a tandem item from the Unified Huntington's Disease Rating Scale [37]. Two items (leg agility and pouring) were not collected for all participants. Therefore, forty-two items were included in the final modified scale. Videotapes were acquired for 16 control participants, 16 FXTAS participants, 14 PD participants and 10 ET participants and were rated by a movement disorders neurologist who was blinded to genotype. The three UE tremor items and the finger tap bradykinesia item from the FXTAS-RS were correlated with the same measures obtained from the inertial sensor system. Because the finger tap measure on the FXTAS-RS includes assessment of both speed and amplitude in a single item, these two values from tremorography were averaged for each participant prior to analysis.

Molecular analysis

Blood samples and buccal swabs were sent to the RUMC Molecular Diagnostic Laboratory (EBK) for genotyping testing. DNA was isolated using QIAGEN Blood and Tissue DNA isolation kits. Allele-specific CGG repeat length was determined by PCR using the Asuragen Amplidex *FMR1* kit, and normal activation ratio (AR) was determined using the Asuragen Amplidex *FMR1* mPCR kit (Asuragen Inc. Austin, Texas) as previously described [38].

Statistical analysis

All measures were first compared between the four participants groups with one-way ANOVA followed by post hoc pairwise comparisons with Bonferroni correction. Right and left hand tremorography measures were compared within groups using paired *t*-tests. Within-group sex differences on tremorography measures were also analyzed using unpaired *t*-tests. Next, significant measures from the above analyses were included in stepwise multinomial logistic regressions to determine which measures were best able to distinguish between the groups. Age was controlled for in the regression model, as the control group was significantly younger than the three movement disorder groups. Receiver operating characteristics (ROC) curve analysis was performed to evaluate the discriminatory ability of any significant measures from the regression analysis to distinguish the movement disorder groups. Area under the curve (AUC) with 95% confidence interval was computed for each tremorography measure. Sensitivity and specificity were calculated for the optimal cut-off value using the maximum Youden index. Spearman's rank correlation coefficient (*rho*) was used to assess the relationship between the molecular measures, tremor and bradykinesia measures, and total FXTAS-RS scores. Correlations were also assessed between the quantitative tremor and bradykinesia measures and the same tremor and bradykinesia items on the FXTAS-RS. A $p < .05$ was

considered significant. Statistical analyses were performed with SAS (SAS Institute Inc., Cary NC, USA). For the FXTAS-RS, missing values were imputed using the Hot Deck technique.

Results

Participant characteristics

Demographic and clinical characteristics are summarized in Table 1. The study included 23 participants with FXTAS, 23 with PD, 18 with ET, and 20 controls. In the FXTAS group, six had a diagnosis of possible FXTAS, nine had probable FXTAS, and eight had definite FXTAS. The three movement disorder groups did not differ in age, although the control group was younger than the PD group ($p = .006$). All movement disorder groups had significantly worse total FXTAS-RS scores compared to controls, but were not different from each other ($p < .0001$). There were no significant differences in BMI, education, WAIS-III Full IQ and WAIS-III VIQ or PIQ between any of the groups. Roughly 48%, 87% and 50% of FXTAS, PD and ET participants, respectively, were on medications for their motor symptoms at the time of testing (Supplementary Table 1).

Tremorography

In control participants, finger tap speed differed significantly between right and left hands ($p = .04$), and in FXTAS participants, postural tremor differed significantly between right and left hands ($p = .002$). Therefore, separate right and left hand values for these measures are reported in addition to the mean values for the right and left hands in the analysis of between-group differences (Table 2). The movement disorder groups scored worse than controls on many measures; however, this report focuses on differences between FXTAS, PD and ET participants. ET participants had worse combined right and left kinetic tremor than PD (Fig. 1A; $p = .007$), and FXTAS and ET participants were not different from each other. FXTAS participants had significantly slower combined finger tap speed compared to ET ($p = .01$), but this measure was similar to PD (Fig. 1B). Separate left and right hand finger tap speed was significantly different between FXTAS and ET ($p = .006$ and 0.02, respectively). Men had significantly greater postural and kinetic tremor and slower finger tap speed compared to women in the FXTAS group only ($p = .01$ to 0.001).

In FXTAS participants, no significant correlations were found between CGG repeat size and AR (women) and tremor measures. FXTAS-RS total scores did not correlate with any tremorography measures in the three movement disorder groups or controls. However, significant correlations were found between tremor and bradykinesia measures and these same items on the FXTAS-RS ($p = .005$ to < 0.0001; Table 4).

In the regression analysis (Table 3) the following tremor measures were able to distinguish between groups. Combined right and left kinetic tremor was able to distinguish between FXTAS and PD and FXTAS and controls, such that participants with greater kinetic tremor were more likely to have a diagnosis of FXTAS ($p = .02$ and 0.002, respectively). Combined right and left finger tap speed was able to distinguish between FXTAS and ET and FXTAS and controls, such that participants with slower finger tap speed were more likely to have a diagnosis of FXTAS ($p = .004$ and 0.01, respectively).

ROC curves for combined kinetic tremor distinguishing FXTAS from PD had an AUC of 0.67 (95% CI: 0.51, 0.83) (Supplementary Fig. 1A). At a cut off value of 1.26, the sensitivity is 0.56 and the specificity is 0.74, with positive/negative predictive values of 0.74 and 0.62, respectively. When combined kinetic tremor was analyzed with FXTAS and ET as the disease positive group and controls and PD as the disease negative group, the AUC increased to 0.75 (95% CI: 0.65, 0.86), indicating the test had fair accuracy for distinguishing the groups (Supplementary Fig. 1B). At a cut off value of 1.25, the sensitivity is 0.63 and the specificity is 0.81, with positive/negative predictive values of 0.77 and 0.69, respectively. ROC curves for finger tap speed distinguishing FXTAS from ET had an AUC of 0.79 (95% CI: 0.65–0.92), indicating that this is a fair test for accuracy (Supplementary Fig. 1C). At a cut off value of 0.69, the sensitivity is 0.84 and specificity is 0.56 with positive/negative predictive values of 0.72 and 0.71, respectively. When right finger tap speed was analyzed with FXTAS and PD as the disease positive group and controls and ET as the disease negative group, the AUC was 0.76 (95% CI: 0.66, 0.87); at a cut off value of 0.69, the sensitivity is 0.79 and specificity is 0.66 with positive/negative predictive values of 0.75 and 0.71, respectively (Supplementary Fig. 1D).

Discussion

Our study is the first to compare tremor and bradykinesia in FXTAS, PD, ET and controls using quantitative inertial sensor based tremorography and

Table 1
Demographic and clinical characteristics.

Variable	Control ($n = 20$)	FXTAS ($n = 25$)	PD ($n = 23$)	ET ($n = 18$)
Age	62.7 ± 8.5 (50–83) **c****	69.0 ± 8.0 (55–86)	71.3 ± 7.9 (56–87) **a****	69.3 ± 9.2 (53–85)
Men, *n* (%)	11 (55)	15 (65)	15 (65)	9 (50)
Education	17.5 ± 2.6	15.8 ± 3.1	16.6 ± 2.7	16.1 ± 2.3
Ethnicity, *n*	19 White/Non-Hispanic, 1 White/Hispanic	23 White/Non-Hispanic	20 White/Non-Hispanic, 1 White/Hispanic, 1 African-American, 1 Asian	17 White/Non-Hispanic, 1 African-American
Disease duration (years)	N/A	7.1 ± 4.5 (1–16)	5.7 ± 3.7 (1–15)	12.5 ± 10.2 (2 − 33)
Dominant right hand, *n* (%)	18 (90)	21 (84)	19 (83)	15 (83)
CGG repeat	31.4 ± 5.4 **b****	85.8 ± 12.2 **a****, **c****, **d****	29.6 ± 5.0 **b****	28.9 ± 6.5 **b****
FXTAS-RS	13.6 ± 7.9 (3–26) **b****, **c****, **d****	46.4 ± 17.6 (24–78) **a****	41.7 ± 13.1 (21–65) **a****	46.1 ± 19.6 (24–73) **a****
H&Y Stage	N/A	N/A	2.09 ± 0.28 (2–3)	N/A
BMI	27.1 ± 3.4	24.9 ± 4.0	25.9 ± 3.6	26.2 ± 5.2 (19.6–42.0)
WAIS-III Full IQ	127.1 ± 10.2	116.8 ± 13.3	117.7 ± 15.2	118.5 ± 14.4
WAIS-III VIQ	124.5 ± 8.6	117.8 ± 11.2	120.2 ± 13.5	119.3 ± 11.8
WAIS-III PIQ	124.0 ± 11.5	112.0 ± 15.3	111.6 ± 16.7	112.7 ± 16.1

All data (except sex, ethnicity and dominant hand) reported as mean ± SD (range). Age, disease duration, CGG repeat, modified FXTAS Rating Scale score (FXTAS-RS), Body Mass Index (BMI), Education, and Wechsler Abbreviated Scale of Intelligence (WAIS-III) Full Intelligence Quotient (IQ), Verbal IQ (VIQ) and Performance IQ (PIQ) were compared between controls, FXTAS, PD and ET. Disease duration is reported from the onset of symptoms. The WAIS-III Full, VIQ and PIQ were scaled to age and years of education. **a**, significantly different from controls; **b**, significantly different from FXTAS. * $p \leq .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$.

Table 2
Tremorography comparisons between controls, FXTAS, PD and ET participants.

Variable	Control (n = 20)	FXTAS (n = 25)	PD (n = 23)	ET (n = 18)
Combined rest tremor, mean (SD)	0.06 (0.06) **c***	0.16 (0.28)	0.64 (1.13) **a***	0.31 (0.43)
Left postural tremor, mean (SD)	0.04 (0.07) **b*, d*****	0.61 (0.72) **a***	0.49 (0.82)	0.91 (0.71) **a*****
Right postural tremor, mean (SD)	0.03 (0.07) **c*, d***	0.25 (0.34)	0.6 (1) **a***	0.71 (0.74) **a***
Combined kinetic tremor, mean (SD)	0.98 (0.26) **b****	1.35 (0.39) **a****	1.11 (0.34) **d****	1.49 (0.43) **c****
Combined finger tap speed, mean (SD)	0.72 (0.47) **b***	1.3 (0.75) **a*, d***	1.15 (0.66)	0.71 (0.33) **b***
Left finger tap speed, mean (SD)	0.84 (0.59) **b***	1.46 (0.91) **a*, d****	1.11 (0.72)	0.72 (0.36) **b****
Right finger tap speed, mean (SD)	0.61 (0.48) **c***	1.25 (0.59) **d***	1.18 (0.75) **a***	0.7 (0.38) **b***
Combined finger tap amplitude, mean (SD)	1.12 (0.75) **c****	1.7 (1.1)	2.11 (0.72) **a****	1.5 (0.76)

Mean (SD) tremorography severity scores were compared between controls, FXTAS, PD and ET. **a**, significantly different from controls; **b**, significantly different from FXTAS; **c**, significantly different from PD; **d**, significantly different from ET. * $p \leq .05$, ** $p < .01$, *** $p < .001$.

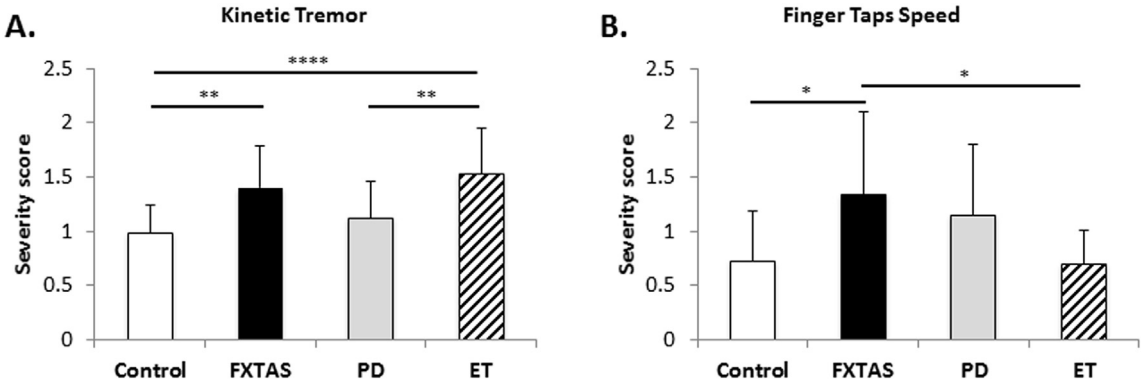

Fig. 1. A. Kinetic tremor. **B.** Finger taps speed. Between-groups comparison of controls, FXTAS, PD and ET using one-way ANOVA or the Kruskal-Wallis test.

we found the technology was able to distinguish differences in these measures between the three movement disorders. ET participants had significantly greater kinetic tremor than PD participants, a finding that is not surprising given that the tremor of ET is characterized by kinetic tremor of the upper extremities (25–98% prevalence) [39,40]. Additionally, the kinetic tremor in ET has been shown to be more severe than postural tremor using clinical rating scales [41]. The classic tremor in PD is a rest tremor [42] and although we would expect significantly more rest tremor in PD, we did not see a difference between the groups. This is likely due to the fact that all PD subjects were in their ON state for medication. FXTAS participants had significantly slower finger tap speed compared to ET participants, but were similar to that of PD participants on this measure. This finding is consistent with studies reporting that signs of parkinsonism including bradykinesia are common in FXTAS [4] and are seen in approximately 30% of patients [19,20]. Similarly, in the regression analysis, kinetic tremor and finger tap speed were the best measures for distinguishing between the three movement disorders. This was confirmed by the ROC analyses with AUC values indicating that these tremorography variables were fair for distinguishing between the three movement disorders and controls.

Tremor and bradykinesia sub-score items from the FXTAS-RS were significantly correlated with the same measures on tremorography, demonstrating the validity of using Kinesia-derived tremorography in FXTAS studies. The lack of correlations between tremorography scores and total FXTAS-RS scores is not surprising given that the scale also includes items related to gait ataxia, balance, rigidity, dystonia, and speech and oculomotor function.

Our findings suggest that individuals with FXTAS have a mixed clinical picture of kinetic tremor and bradykinesia. Therefore, in addition to ET and PD, other conditions that can display similar clinical features to FXTAS are benign tremulous parkinsonism, patients with coexistent ET and PD, and functional tremor and bradykinesia disorders. Future research comparing these disorders to FXTAS is warranted.

Limitations of this pilot study include a relatively small sample size. This is particularly problematic for the FXTAS group given that FXTAS is a rare and heterogeneous disease and can vary in severity between affected men and women as shown in previous studies [7] and the current study. Increasing the sample size in future studies will help to strengthen these findings. The control group was also significantly younger than the FXTAS, PD and ET groups, although this was not a relevant problem as the focus of the study was on comparing the movement disorders to each other. Another potential limitation was that all medicated study participants were on

Table 3
Stepwise multinomial logistic regression for determining ability of tremor measures to distinguish between groups.

	OR (95% CI)	p-value
Combined kinetic tremor		
PD vs FXTAS	0.1 (0.02, 0.65)	0.02*
Control vs FXTAS	0.02 (0.002, 0.26)	0.002**
Combined finger taps speed		
ET vs FXTAS	0.1 (0.02, 0.47)	0.004**
Control vs FXTAS	0.16 (0.04, 0.69)	0.01*

Key: OR, odds ratio; CI, confidence interval.
* $p \leq .05$, ** $p < .01$.

Table 4
Spearman's correlations between tremorography tremor measures and FXTAS-RS tremor and bradykinesia sub-score items.

FXTAS-RS Item	Spearman r	p-value
Upper extremity tremor at rest R (UPDRS)	0.3832	0.0046**
Upper extremity tremor at rest L (UPDRS)	0.1779	0.2026
Action or postural tremor of hands R (UPDRS)	0.4667	0.0004***
Action or postural tremor of hands L (UPDRS)	0.6813	<0.0001****
Finger-to-nose test: intention tremor of the finger L (ICARS)	0.4217	0.0017**
Finger-to-nose test: intention tremor of the finger R (ICARS)	0.4369	0.0011**
Finger Taps L speed and amplitude (UPDRS)	0.6317	<0.0001****
Finger Taps R speed and amplitude (UPDRS)	0.4881	0.0002***

* $p \leq .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$.

medications at time of testing due to logistical and feasibility issues; therefore, their tremor was not tested in its most severe and natural state. However, these results demonstrate that significant tremor and bradykinesia differences between FXTAS, PD and ET are present even when participants are in their optimal medicated state. In future studies, participants should be tested both on and off their medication to obtain a more accurate measurement of tremor and bradykinesia in these disorders. Lastly, it is possible that there was some overlap between the groups, as autopsy cases have been published of individuals with both FXTAS and PD [43], which could limit interpretation of the results.

This study had several strengths including objective tremor measurement using highly sensitive quantitative analysis that has been validated in PD and ET in previous studies. These findings demonstrate that FXTAS, PD and ET may exhibit distinct tremor profiles. Tremorography was able to distinguish differences between FXTAS and PD, FXTAS and ET, and PD and ET. These quantitative measures may also improve characterization of cohorts for future studies and serve as outcome measures to evaluate treatment responses in future clinical trials.

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