Psychiatric Manifestations in Early to Middle Stages of Fragile X-Associated Tremor-Ataxia Syndrome (FXTAS)

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Objective: The purpose of the present study was to assess the psychiatric manifestations of early to middle stages of fragile X-associated tremor-ataxia syndrome (FXTAS) and their relationship with executive function and *FMR1* cytosine-guanine-guanine (CGG) repeat numbers across genders.

Methods: Cross-sectional data from 100 participants (62 men, 38 women; mean±SD age=67.11±7.90 years) with FXTAS stage 1, 2, or 3 were analyzed, including demographic information, cognitive measures, psychiatric assessments (Symptom Checklist-90–Revised and Behavioral Dyscontrol Scale–II [BDS-II]), and CGG repeat number.

Results: Participants with FXTAS stage 3 exhibited significantly worse psychiatric outcomes compared with participants with either stage 1 or 2, with distinct gender-related differences. Men showed differences in anxiety and hostility between stage 3 and combined stages 1 and 2, whereas women exhibited differences in anxiety, depression, interpersonal sensitivity, obsessive-compulsive symptoms, and somatization, as well as in the Global Severity Index, the Positive Symptom Distress Index, and the Positive Symptom Total. Among male participants, negative correlations were observed between BDS-II total scores and obsessive-compulsive symptoms, as well as between anxiety and CGG repeat number.

Conclusions: These findings suggest that even at early FXTAS stages, patients have significant cognitive and other psychiatric symptoms, with notable gender-specific differences. This study underscores the clinical and prognostic relevance of comorbid psychiatric conditions in FXTAS, highlighting the need for early intervention and targeted support for individuals with relatively mild motor deficits.

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The discovery of fragile X syndrome (FXS) and the fragile X-messenger ribonucleoprotein 1 (*FMR1*) gene at Xq27.3 has led to a series of fragile X genetic studies and their clinical psychiatric correlates in recent decades. The *FMR1* gene codes for the *FMR1* protein (FMRP), which plays an important role in synaptic neuroplasticity, neural development, and nervous system functioning (1). For those with cytosine-guanine-guanine (CGG) repeat numbers greater than 200, defined as full mutation, transcriptional gene silencing occurs and results in the absence or substantial reduction of FMRP, which manifests clinically as developmental delay, learning disorders, intellectual disability, autism, and other neuropsychiatric illness associated with FXS (2).

CGG repeat numbers between 55 and 200 fall in the premutation range. Premutation carriers have a risk of developing fragile X premutation-associated conditions, including fragile X-associated tremor-ataxia syndrome (FXTAS) and fragile X-associated primary ovarian insufficiency (2). The prevalence rate of premutation carriers in the general population is estimated to be between 1 per 400 males and 1 per 200 females (3). These fragile X premutation-associated conditions are often underdetected clinically because many premutation carriers have no awareness of premutation-associated conditions until genetic counseling and recognition of their offspring's FXS or other pedigree testing, once another family member is ascertained to have fragile X-related illness.

Among these associated disorders, FXTAS is the most severe and was first reported in 2001 (4). FXTAS is a neurodegenerative disorder characterized by intention tremor, gait ataxia, neuropathy, parkinsonism, autonomic dysfunction, cognitive impairment, sleep problems, and other comorbid psychiatric conditions, and it typically develops among individuals in their fifties and sixties (2). The penetrance of FXTAS is age-related and ranges from 17% to 75%, with an average of 40% for male premutation carriers and 16.5% for female premutation carriers (5, 6). Elevated *FMR1* mRNA levels, with consequent mRNA toxicity, CGG

protein-binding sequestration, a DNA damage response, and mitochondrial dysfunction among premutation carriers lead to the development of FXTAS (2, 7). Intranuclear inclusions in neurons and astrocytes are the neuropathological hallmark of FXTAS and contain *FMR1* mRNA and proteins (8). Brain MRI shows white matter disease involving the left and right middle cerebellar peduncles, the periventricular areas, the splenium of the corpus callosum, and the brainstem (2, 9). There is atrophy, with gray matter loss in the prefrontal cortex, anterior cingulate cortex, precuneus, amygdala, and insula. MRI findings correlate strongly to FXTAS stages and clinical manifestations of motor symptoms and psychiatric symptoms of depression, anxiety, and major neurocognitive disorder or dementia (2, 10).

There are various other psychiatric trajectories across life stages among premutation carriers. In childhood and adolescence, neurodevelopmental disorders and social deficits have been reported, although many young carriers do not have formally diagnosed psychiatric illnesses (2, 11). Various anxiety disorders, depressive disorders, obsessive-compulsive symptoms, or substance use disorders may emerge as early as adolescence in some cases (12). One study showed lifetime prevalence rates of 65% for anxiety disorders and 50% for depressive disorders among patients with FXTAS (11). Multiple psychiatric symptoms that precede the motor and cognitive symptoms of FXTAS are commonly seen among adult premutation carriers. These cases could represent a psychiatric prodrome of FXTAS, although such a prodromal state has not yet been validated by detailed longitudinal studies (11, 13). With aging, and usually after the onset of cerebellar motor signs, further neurodegeneration leads to FXTAS with major neurocognitive disorder or dementia, particularly among males (2).

The aim of the present study was to document the psychiatric presentations among premutation patients and to compare participants' cognitive performance between disease severity states—that is, between the initial (stages 1 and 2) and middle (stage 3) stages of FXTAS—to determine whether more severe motor symptoms of middle-stage FXTAS correlated with more severe psychiatric symptoms. We also explored relationships between the psychiatric symptoms and both standard measures of executive function and CGG repeat numbers. Our design did not include longitudinal observation of participants over time.

METHODS

Study Sample and Procedure

Data for this study were obtained from the established cohort of patients with FXTAS from the Genotype-Phenotype Relationships in Fragile X Families study and the Trajectories and Markers of Neurodegeneration in Fragile X Premutation Carriers study. Ethics approval for these studies was obtained from the institutional review board at the University of California, Davis. This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and all participants provided written informed consent. Clinical and molecular measures were collected from the study participants over a 2-day period. There was no control group because the study examined correlations within the FXTAS group. Data analysis was completed for participants with FXTAS stages 1 and 2 (combined as early-stage FXTAS) and stage 3 (middle-stage FXTAS). The following data were collected: demographic variables (age and gender); clinical variables (FXTAS stage and scores on the Mini-Mental State Examination [MMSE], the Wechsler Adult Intelligence Scale–Fourth Edition [WAIS-IV], the Symptom Checklist-90–Revised [SCL-90-R], and the Behavioral Dyscontrol Scale–II [BDS-II]); and molecular variables (CGG repeat numbers).

Study Measures

Diagnosis of FXTAS and the assignment of FXTAS stages were done by an experienced physician (R.J.H.) with extensive experience in fragile X-associated conditions. The FXTAS stages were defined on the basis of published criteria that stratify physical manifestations on the basis of motor deficits and functional impairment as follows: stage 1, subtle or equivocal tremor or balance problems; stage 2, minor tremor or balance problems and minimal interference in activities of daily living; stage 3, moderate tremor or balance problems and significant interference in activities of daily living; stage 4, severe tremor or balance problems and reliance on a cane or walker; stage 5, daily use of a wheelchair; and stage 6, the patient is bedridden (14).

The WAIS-IV and MMSE were used to measure intelligence and cognitive status of the participants. The SCL-90-R and BDS-II were standardized measures used to assess other psychiatric symptoms and executive function.

The SCL-90-R is a 90-item self-administered multidimensional psychological instrument assessing psychological symptoms and distress within the previous week. The SCL-90-R also includes three global indices: the global severity index (GSI) for overall psychological distress, the positive symptom distress index (PSDI) for intensity of symptoms, and the positive symptom total (PST). It has adequate reliability and validity and has been used widely in previous premutation studies (15).

The BDS-II is a 9-item instrument designed to evaluate executive function with a focus on the capacity of behavioral regulation and attention among geriatric patients; it yields scores ranging from 0 to 27, with higher scores indicating better performance. The BDS-II has been used in multiple studies of premutation carriers (16).

Molecular measures included the CGG repeat number and methylation status. Both specific polymerase chain reaction assays and Southern blot analyses were carried out for all participants as previously described (17).

Statistical Analysis

Statistical analyses of data were performed with the open-source software R, version 4.2.3. Results were expressed as

TABLE 1. Demographic, clinical, and molecular characteristics of participants in early and middle stages of fragile X-associated tremor-ataxia syndrome (FXTAS)[a]

Characteristic	All participants			FXTAS stages 1 and 2			FXTAS stage 3			p
	Total N	N	%	Total N	N	%	Total N	N	%	
Male	100	62	62	41	24	59	59	38	64	0.552[b]
	Total N	Mean	SD	Total N	Mean	SD	Total N	Mean	SD	
Age (years)	100	67.11	7.90	41	66.13	8.25	59	67.80	7.65	0.300
MMSE	86	28.36	2.26	31	28.90	1.76	55	28.05	2.46	0.046[c]
FSIQ	84	108.37	15.12	34	114.85	15.21	50	103.96	13.51	<0.001
CGG repeats	99	88.03	17.40	41	87.34	18.30	58	88.52	16.88	0.479[c]
BDS-II (total)	90	21.29	3.65	35	22.63	2.38	55	20.44	4.01	0.010[c]

[a] BDS-II scores range from 0 to 27, with higher scores indicating better performance; FSIQ scores range from 40 to 160, with a mean score of approximately 100; MMSE scores have a maximum of 30, with higher scores indicating better performance. BDS-II=Behavioral Dyscontrol Scale–II; CGG=cytosine-guanine-guanine; FSIQ=full-scale intelligence quotient; MMSE=Mini-Mental State Examination.
[b] The p value was obtained with a Pearson's chi-square test for the group comparison between FXTAS stages 1 and 2 and FXTAS stage 3.
[c] The p value was obtained with a Kruskal-Wallis rank sum test for the group comparison between FXTAS stages 1 and 2 and FXTAS stage 3.

the mean±standard deviation or standard error of the mean or the median (25th percentile, 75th percentile) for continuous variables and as frequency (%) for categorical variables. For quantitative variables, normality of the data was assessed by using the Shapiro-Wilk test prior to statistical analysis. Group differences in means or medians were determined with t tests, analyses of variance (ANOVAs), Kruskal-Wallis tests, or aligned rank transform ANOVAs as appropriate. For categorical variables, Pearson's chi-square tests were performed for comparisons of proportions across groups.

Linear regression analyses were performed to assess the main effects of the BDS-II total score, CGG repeats, and gender, as well as their interactions (i.e., to test effect modification by gender) on all psychiatric symptoms, with age and full-scale intelligence quotient (FSIQ) as covariates in covariate-adjusted analyses. Gender-specific analyses were also performed. Results from the regression models are presented as the coefficient estimate of the parameter (beta) with the standard error. The Benjamini-Hochberg false discovery rate (FDR) was applied to control for multiple testing of several outcome measures. Two-tailed p values <0.05 or FDR-corrected p values <0.05 were considered statistically significant as appropriate.

RESULTS

Data from a total of 100 (62 men and 38 women) premutation carriers with FXTAS stages 1, 2, and 3 were obtained from the established cohort. We focused on early-stage FXTAS (stage 1 or 2) and middle-stage FXTAS (stage 3), because late-stage FXTAS can be clouded by significant cognitive decline or major neurocognitive disorder or dementia, which dramatically affects other psychiatric symptoms. We were interested in the earlier manifestations of psychiatric symptoms in FXTAS and how such problems relate to executive function deficits. Almost all participants, except for four, identified as White non-Hispanic. Three participants identified as Hispanic/Latino, and one identified as Native Hawaiian/Pacific Islander. Comparisons of the demographic, clinical, and molecular characteristics of the study participants with early-stage FXTAS (N=41) and middle-stage FXTAS (N=59) are summarized in Table 1.

The comparisons between these two FXTAS groups did not show significant differences in age, gender, or CGG repeat numbers. Significant differences were noted in the MMSE, FSIQ, and BDS-II total scores, with worse neurocognitive test scores among participants in the FXTAS stage 3 group. We examined and compared scores for individual items of the BDS-II between the two groups. BDS-II items 5 and 6, which represent the capacity of motor procedural learning, showed significant differences between the two groups (item 5: $p<0.001$; item 6: $p=0.001$). In the experience of the authors, the BDS-II is the most robust measure for the cognitive changes in FXTAS, and it assesses motor procedural learning well.

Comparisons of psychiatric symptom severity, assessed with the SCL-90-R, between the early-stage FXTAS group and middle-stage FXTAS group are presented in Table 2. The middle-stage FXTAS group had significantly higher scores in all nine dimensional subscales and three global indices compared with the early-stage FXTAS group. We subsequently stratified the participants into groups of men and women for gender-specific analyses. Significantly higher anxiety scores were found between groups for both male (FDR-corrected $p=0.029$) and female (FDR-corrected $p=0.033$) participants. Hostility (FDR-corrected $p=0.030$) was found to be higher only among male participants, and depression (FDR-corrected $p=0.028$), interpersonal sensitivity (FDR-corrected $p=0.049$), obsessive-compulsive symptoms (FDR-corrected $p=0.033$), somatization (FDR-corrected $p=0.021$), GSI (FDR-corrected $p=0.011$), PSDI (FDR-corrected $p=0.011$), and PST (FDR-corrected $p=0.028$) were higher only among female participants in the middle-stage FXTAS group compared with those in the early-stage FXTAS group (Figure 1). It is also worth noting that the average T scores for anxiety, depression, obsessive-compulsive symptoms, and somatization were above the cutoff point of 60 among female participants

TABLE 2. Group comparisons of Symptom Checklist-90–Revised (SCL-90-R) subscale scores between fragile X-associated tremor-ataxia syndrome (FXTAS) stages 1 and 2 and FXTAS stage 3 in male and female groups[a]

	Male group					Female group					Combined	
	FXTAS stages 1 and 2 (N=20)		FXTAS stage 3 (N=32)			FXTAS stages 1 and 2 (N=15)		FXTAS stage 3 (N=21)			Stage difference	Sex×stage interaction
SCL-90-R subscale	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p	p	p
Anxiety	46.8	8.69	55.25	9.7	0.002[b,d]	53	8.63	61	11.28	0.019[b,d]	<0.001[c,d]	0.967[c]
Depression	51.2	8.96	56.09	11.77	0.118	53.4	10.16	61.38	7.83	0.012[d]	0.021[d]	0.489
GSI	50.7	8.18	57.31	11.89	0.034	51.6	11.81	63.24	8.87	0.002[d]	0.001[d]	0.28
Hostility	46.1	6.63	53.53	9.6	0.005[b,d]	48.6	8.75	56.14	11.22	0.046[b]	0.01[c,d]	0.939[c]
Interpersonal sensitivity	50.05	8.46	57.03	11.25	0.044[b]	49.33	10.29	58.57	12.95	0.032[b,d]	0.001[c,d]	0.505[c]
OC symptoms	53.1	9.41	60.03	12.21	0.035	55.73	10.35	65	11.51	0.018[d]	0.016[d]	0.637
Paranoid ideation	46.75	7.96	52	11.36	0.101[b]	44.93	7.27	52.76	13.16	0.06[b]	0.029[c,d]	0.821[c]
Phobia	50	7.44	54.25	9.24	0.067[b]	49.53	10.37	56.67	10.81	0.043[b]	<0.001[c,d]	0.226[c]
PSDI	51.65	9.01	54.75	9.64	0.236[b]	52.8	7.12	62.33	8.81	0.001[b,d]	0.004[c,d]	0.084[c]
PST	49.95	7.72	55.81	10.3	0.033	51.4	11.98	60.48	8.39	0.011[d]	0.007[d]	0.454
Psychoticism	49	7.55	53.66	9.87	0.095[b]	52	10.89	58.19	10.68	0.055[b]	0.003[c,d]	0.495[c]
Somatization	51.75	12.74	56.03	11.2	0.14[b]	51	12.88	63.14	8.57	0.005[b,d]	0.002[c,d]	0.131[c]

[a] Subscale and overall scores are presented as T scores, with higher scores indicating greater severity. GSI=Global Severity Index; OC=obsessive-compulsive; PSDI=Positive Symptom Distress Index; PST=Positive Symptom Total score.
[b] The sex-specific p value was obtained by using Kruskal-Wallis rank sum test for group comparison between FXTAS stages 1 and 2 and FXTAS stage 3 within sex; otherwise, the p value was obtained by using one-way parametric analysis of variance (ANOVA).
[c] The p value was obtained by using two-way aligned rank transform ANOVA for main effects of FXTAS stage (i.e., stage difference collapsed across sex), sex (collapsed across stage), and their interaction (i.e., sex difference in the effect of FXTAS stage); otherwise, the p value was obtained by using two-way parametric ANOVA.
[d] $p<0.05$ (remained significant at a false discovery rate <0.05 after correction for multiple comparisons).

with FXTAS stage 3, indicating that these symptoms were clinically significant.

The gender-specific associations between SCL-90-R scores and BDS-II total scores are summarized in Table 3. For men, there were negative associations between the BDS-II total score and subscale scores of depression, GSI, interpersonal sensitivity, obsessive-compulsive symptoms, and PSDI; however, the associations were no longer significant after adjustments for age and intelligence, except for the negative association between BDS-II total scores and obsessive-compulsive symptoms (FDR-corrected $p=0.048$). Higher severity of obsessive-compulsive symptoms correlated with poorer executive function.

Gender-specific associations between SCL-90-R scores and CGG repeats are summarized in Table 4. For men, there was a significant negative association between anxiety and CGG repeats after adjustments for age and intelligence (FDR-corrected $p=0.036$).

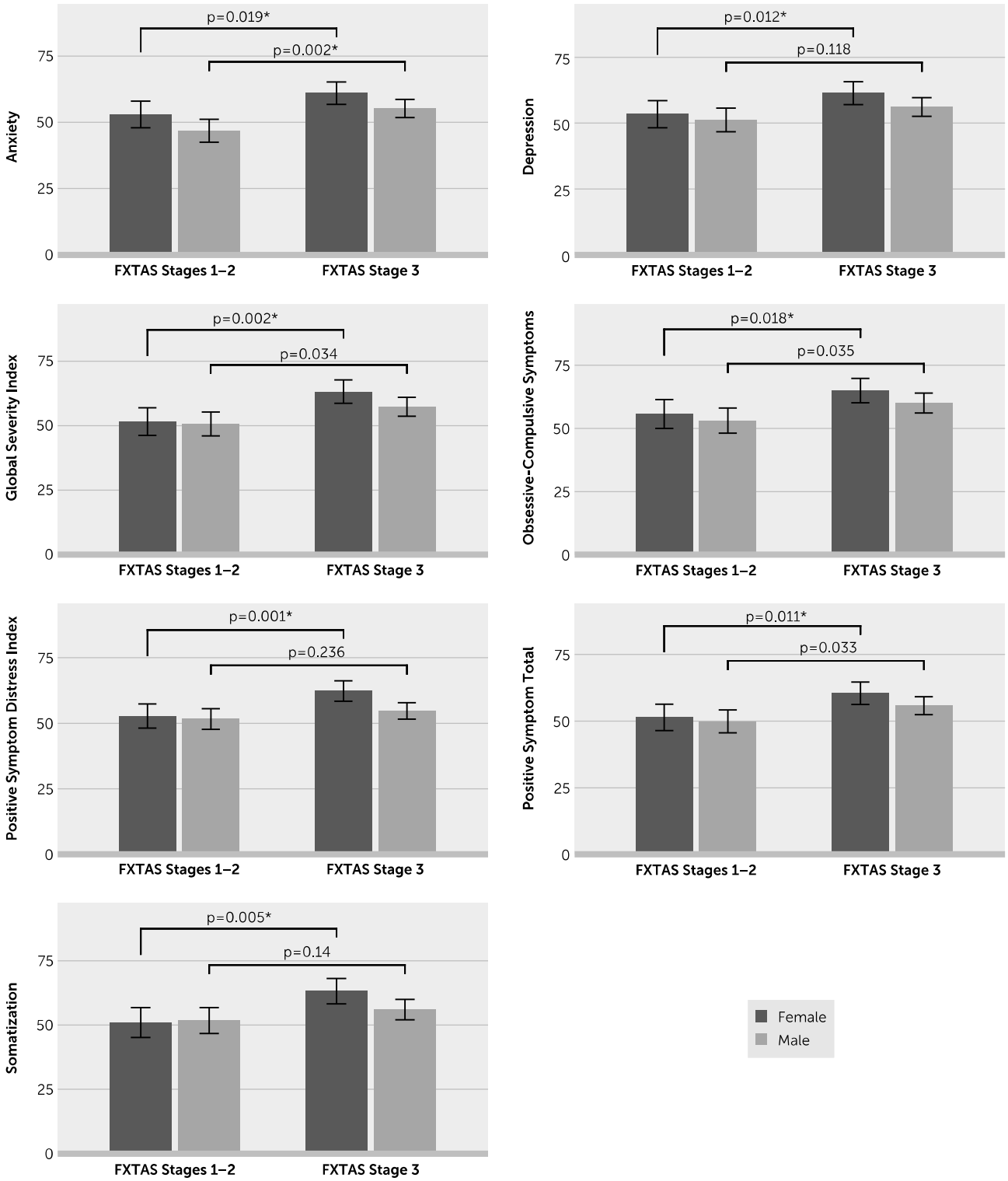
DISCUSSION

The results of our study demonstrated differences in psychiatric (including cognitive) symptoms between the early and middle stages of FXTAS. Various assessments of psychiatric symptoms all revealed worse scores at the higher FXTAS stage. Marked worsening in specific aspects was noted when the groups were stratified by gender; specifically, anxiety and hostility increased among men, and anxiety, depression, interpersonal sensitivity, obsessive-compulsive symptoms, somatization, and global indices increased among women. These findings are similar to those of previous studies that showed (for individuals developing FXTAS) that men had higher levels of agitation-aggression, apathy, disinhibition, and irritability, clustered as the phenotypes commonly seen in fronto-subcortical dementia (14), whereas women had elevated rates of depressive and anxiety disorders (18).

Our results suggest that once the neurodegeneration among premutation carriers correlates with the emergence of significant motor symptoms, all clusters of psychiatric symptoms worsen as FXTAS progresses, irrespective of gender. There are other studies that have discussed the higher rates of psychiatric symptoms with the progression of FXTAS across stages. One study showed a greater prevalence in anxiety and obsessive-compulsive symptoms among female premutation carriers with FXTAS compared with males premutation carriers with FXTAS (19). Other studies have reported that male FXTAS patients have more major neurocognitive disorder or dementia-related symptoms and more impairing motor symptoms compared with female patients with FXTAS, who present with more depression-anxiety spectrum symptoms and chronic pain (19, 20).

An important point to consider is whether FXTAS patients develop more psychiatric symptoms because they are emotionally distressed about having a progressive neurodegenerative disease or whether the comorbid psychiatric symptoms are an intrinsic component of the FXTAS illness itself. Indeed, both may be true. To address this will require a detailed longitudinal design examining carriers and ascertaining whether meaningful psychiatric symptoms clearly precede the onset of any motor FXTAS signs or are

FIGURE 1. Group comparisons of Symptom Checklist-90–Revised subscale scores between fragile X-associated tremor-ataxia syndrome (FXTAS) stages 1 and 2 and FXTAS stage 3 among male and female participants[a]



[a] The asterisks indicate p values that remained significant at a false discovery rate <0.05 after correction for multiple comparisons.

exacerbated by impairments in motor or cognitive function that are clearly associated with the progression of FXTAS.

It is likely that many female premutation carriers are or have been caretakers both for FXS-affected offspring and for their own FXTAS-affected fathers or mothers; the chronic distress associated with these caring roles may represent an additional source of stress that is reflected in psychiatric symptoms. In a study by Hall et al. (21) on neurological and endocrine phenotypes of women with fragile X premutation, in addition to finding a high rate of

TABLE 3. Gender-specific associations between Symptom Checklist-90–Revised (SCL-90-R) subscale scores and Behavioral Dyscontrol Scale–II (BDS-II) total scores, unadjusted and adjusted for age and full-scale intelligence quotient, among male and female participants[a]

	Male group (N=39)						Female group (N=28)					
	Unadjusted BDS-II total score			Adjusted BDS-II total score			Unadjusted BDS-II total score			Adjusted BDS-II total score		
SCL-90-R subscale	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Anxiety	−0.58	0.46	0.211	−0.68	0.6	0.262	−0.55	0.65	0.41	0.16	0.78	0.835
Depression	−1.44	0.46	0.003[b]	−1.31	0.6	0.037	−0.48	0.54	0.379	0.01	0.58	0.982
GSI	−1.3	0.45	0.007[b]	−1.14	0.6	0.066	−0.79	0.66	0.242	0.03	0.7	0.967
Hostility	−0.42	0.4	0.294	−0.2	0.52	0.701	−0.58	0.62	0.351	0.11	0.64	0.863
Interpersonal sensitivity	−1.07	0.43	0.017[b]	−1.12	0.56	0.054	−0.32	0.72	0.659	0.28	0.77	0.714
OC symptoms	−1.79	0.48	0.001[b]	−1.93	0.63	0.004[b]	−0.62	0.65	0.343	0.14	0.71	0.847
Paranoid ideation	−0.95	0.44	0.039	−0.78	0.59	0.192	0.34	0.67	0.62	1.36	0.74	0.078
Phobia	−0.72	0.32	0.031	−0.68	0.42	0.118	−1.19	0.57	0.049	−0.46	0.61	0.461
PSDI	−1.09	0.4	0.009[b]	−1.01	0.52	0.06	−0.61	0.49	0.218	−0.31	0.62	0.626
PST	−0.99	0.41	0.02[b]	−0.83	0.54	0.135	−0.56	0.63	0.38	0.16	0.63	0.797
Psychoticism	−0.67	0.43	0.134	−0.34	0.57	0.554	−0.11	0.59	0.856	0.45	0.62	0.475
Somatization	−1.02	0.54	0.065	−0.33	0.69	0.636	−1.34	0.62	0.04	−0.7	0.7	0.329

[a] GSI=global severity index; OC=obsessive-compulsive; PSDI=positive symptom distress index; PST=positive symptom total score.
[b] $p<0.05$ (remained significant at a false discovery rate <0.05 after correction for multiple comparisons).

neurological symptoms and signs, the authors found a neuroticism profile on the Neuroticism, Extraversion, Openness Personality Inventory and high rates of anxiety. Whether these outcomes are temporally related to the social stress of caregiving for fragile X-affected family members remains unclear but plausible. Similarly, in a self-report study of women with the premutation, Allen et al. (22) found anxiety and depression in more than 30% of those analyzed, with an association between having a fragile X-affected child and higher rates of anxiety and depression.

The cognitive profiles in major neurocognitive disorder or dementia associated with FXTAS include impairment in executive function, working memory, information processing speed, inhibition control, attention, verbal fluency, behavioral monitoring, and self-regulation, with the impact on nonverbal intelligence being prominent (23). These clinical manifestations are similar among affected individuals across genders (16). Our results revealed significantly worse BDS-II total scores, specifically scores for items 5 and 6 at the middle stage of FXTAS but not for the other items on the BDS-II.

Because other commonly impaired neurocognitive components were also measured with the BDS-II but did not reveal significant differences between early and middle stages, our results suggest that deterioration of neurocognition among FXTAS patients may have started with motor procedural learning. Motor procedural learning is a form of nondeclarative

TABLE 4. Gender-specific associations between Symptom Checklist-90–Revised (SCL-90-R) subscale scores and cytosine-guanine-guanine (CGG) repeats, unadjusted and adjusted for age and full-scale intelligence quotient, among male and female participants[a]

	Male group (N=42)						Female group (N=31)					
	Unadjusted CGG repeats			Adjusted CGG repeats			Unadjusted CGG repeats			Adjusted CGG repeats		
SCL-90-R subscale	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Anxiety	−0.18	0.1	0.069	−0.33	0.1	0.003[b]	−0.02	0.12	0.851	−0.16	−0.13	0.221
Depression	−0.13	0.11	0.213	−0.23	0.11	0.048	0.03	0.1	0.806	−0.15	−0.09	0.127
GSI	−0.15	0.1	0.143	−0.25	0.11	0.027	0.06	0.12	0.645	−0.14	−0.11	0.216
Hostility	−0.13	0.08	0.136	−0.14	0.1	0.152	0.03	0.12	0.822	−0.19	−0.1	0.071
Interpersonal sensitivity	−0.09	0.1	0.381	−0.2	0.11	0.071	0.01	0.14	0.938	−0.24	−0.12	0.057
OC symptoms	−0.05	0.11	0.668	−0.13	0.12	0.298	0.06	0.13	0.622	−0.14	0.12	0.264
Paranoid ideation	−0.06	0.1	0.542	−0.13	0.11	0.231	−0.02	0.13	0.851	−0.2	0.13	0.123
Phobia	−0.08	0.07	0.263	−0.15	0.07	0.058	0.12	0.11	0.295	−0.04	0.11	0.722
PSDI	−0.03	0.09	0.741	−0.12	0.09	0.21	−0.03	0.1	0.803	−0.11	0.11	0.3
PST	−0.15	0.09	0.112	−0.23	0.1	0.024	0.11	0.12	0.369	−0.1	0.1	0.354
Psychoticism	−0.12	0.09	0.195	−0.21	0.1	0.044	0.12	0.11	0.273	−0.05	0.11	0.63
Somatization	−0.12	0.11	0.291	−0.22	0.12	0.066	0.08	0.12	0.517	−0.08	0.12	0.527

[a] GSI=Global Severity Index; OC=obsessive-compulsive; PSDI=Positive Symptom Distress Index; PST=Positive Symptom Total score.
[b] $p<0.05$ (remained significant at a false discovery rate <0.05 after correction for multiple comparisons).

memory that refers to the acquisition of sequence-specific motor skills through practice. Initial impairments in motor procedural learning were also reported in Parkinson's disease (24). Some brain regions are thought to be related to motor procedural learning deficits, such as the basal ganglia, cerebellum, and frontal cortex (25).

Our results suggest that motor procedural learning is a specific early neurocognitive correlate among FXTAS patients. Because parkinsonism is commonly seen in FXTAS and is correlated with FXTAS stage, *FMR1* mRNA level, and cerebellar ataxia (26), the relationship between parkinsonism and motor procedural learning capacity among FXTAS patients and other possible clinical and neurocognitive correlates of motor procedural learning warrant further investigation.

The pathophysiology of psychiatric symptoms in fragile X-associated conditions has been explored previously. Reduced activation in the amygdala and hippocampus, elevated *FMR1* mRNA levels, and reduction in FMRP were found among individuals with psychiatric symptoms among premutation carriers (12). It is believed that the lifetime accumulation of RNA toxicity and oxidative stress are further aggravated by aging and make the brain more vulnerable to comorbid psychiatric illness and degenerative changes (27). These presentations have different phenotypes between men and women. This gender difference in clinical phenotype may be affected by the presence of a normal allele on the active intact X chromosome among female carriers. This intact X chromosome may exert a putative protective effect among female premutation carriers and may thus account for the lower levels of neurocognitive impairment that are often seen among female premutation carriers.

Brain imaging of the typical middle cerebellar peduncle sign was more common among men (60%) than women (11%); however, other diagnostic imaging hallmarks of FXTAS, including hyperintensity in the splenium of the corpus callosum and diffuse cerebral deep white matter changes, were similarly prevalent in both genders (18, 28). Women are believed to have milder motor symptoms, and the relative sparing of corticocerebellar afferents among women may explain a protective effect on cerebellar manifestations among female FXTAS patients (18). However, the diffuse white matter disease likely leads to varied neuropsychiatric aspects in both genders, with a more notable affective component among women and primarily changes associated with subcortical dementia among men, a pattern of results that was also seen in our study.

We attempted to verify other related factors that may contribute to the psychiatric presentations seen in FXTAS. Our study explored the relationships between psychiatric symptoms and executive function and found a correlation only between obsessive-compulsive symptoms and BDS-II total scores after adjustments for age and intelligence, with higher obsessive-compulsive symptoms correlated with poorer global executive function among male participants only. There were no significant correlations among the various psychiatric symptoms and motor procedural learning, the component in which the scores declined among our study participants.

There have been several studies examining correlations among motor, other psychiatric, and neurocognitive symptoms among premutation carriers with or without FXTAS. In the Grigsby et al. (29) study, the psychiatric symptoms of anxiety, depression, somatization, obsessive-compulsive symptoms, irritability, apathy, and aggression were more commonly seen among men with FXTAS but not among asymptomatic premutation carriers. Executive impairment affected the levels of depression, apathy, irritability, disinhibition, hostility, and, to a lesser extent, psychoticism.

Hocking et al. (30) reported significant correlations between motor rating scale scores and the scores for global cognitive decline, processing speed, immediate memory, depression, and anxiety among men with FXTAS. For non-FXTAS female carriers, poorer nonverbal reasoning and response inhibition ability correlated with more depression, anxiety, hostility, and global severity as well as poorer motor performance.

Another study showed subtle impairments in response inhibition among female premutation carriers and their association with depression, anxiety, and attention-deficit hyperactivity disorder (31). A non-FXTAS study of obsessive-compulsive disorder, panic disorder, and major depressive disorder among premutation carriers and control participants demonstrated impairment in spatial working memory, spatial recognition, and motor initiation and execution in the group with obsessive-compulsive disorder (32).

Our results show consistency in the psychiatric and neurocognitive profiles in FXTAS and their strong relationship with motor function but inconsistency in the correlations between psychiatric symptoms and dysexecutive function. The inconsistency may be attributable to the FXTAS stages and the measurements or tools used. Our results highlight the importance of motor symptoms in both noncognitive psychiatric presentations and executive function, as well as the limited intercorrelated effects of executive function on other psychiatric presentations, in the early to middle stages of FXTAS. These phenomena were observed across genders.

Disease-modifying treatment that targets slowing the progression of FXTAS motor stages may be helpful for both the motor and psychiatric symptoms in FXTAS. Concurrently, conventional multimodal psychiatric interventions (psychotropic medications, psychotherapy, and neuromodulation for treatment-resistant symptoms) should be offered, with caution to minimize adverse cognitive side effects of somatic psychiatric interventions. The significant correlation between obsessive-compulsive symptoms and executive function also suggests that obsessive-compulsive symptoms in FXTAS are critical symptoms to monitor and treat to preserve executive function and vice versa.

Genetic factors, including the CGG repeat numbers, *FMR1* mRNA level, and activation ratio, have also revealed contributions to the development of neuropsychiatric presentations (12, 30, 33). Previous studies have demonstrated the role of CGG repeat number in predicting the age at onset of FXTAS and performance in neuromotor domains, such as gait, attention, and inhibition (34, 35). Higher CGG repeat numbers correlated with a risk of major neurocognitive disorder or dementia in FXTAS (33). However, the evidence for a role in psychiatric symptoms has been sparse. In the present study, the first to our knowledge that points out its relationship with anxiety among men, we found a significant negative correlation between anxiety and CGG repeat numbers among male participants, after adjustments for age and cognitive function.

There were several limitations to this study. First, the data are cross-sectional but not longitudinal; therefore, we should be cautious in interpreting the comparisons across stages. Second, participants in the study were enrolled through referral from physicians or family members who already had awareness of the *FMR1* premutation, and therefore the cohort may have been biased and thus not representative of FXTAS in the general population. We also included stage 1 for carriers where the tremor was minimal or subclinical, and thus this represents the earliest stage of FXTAS. Third, the SCL-90-R is a self-report questionnaire, and the reliability may have been influenced by subjectivity and cognitive ability. Finally, the BDS-II is a general instrument to measure executive function; therefore, more subtle neuropsychological function changes may have not been detected.

CONCLUSIONS

In summary, various psychiatric symptoms were more notable across genders among patients when comparing early to middle FXTAS stages. Because of the likelihood of progression of motor deficits in FXTAS, serial monitoring of motor and neuropsychological function among FXTAS patients is important. The effects of motor symptoms on the progression of these psychiatric symptoms were much stronger than the effects of executive function and CGG repeat numbers per se. Motor procedural learning is a candidate correlate here; however, its role warrants further investigation.

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