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Trajectory and Predictors of Depression and Anxiety Disorders in Mothers with the *FMR1* Premutation

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Abstract

Background—Although the *FMR1* premutation is associated with elevated prevalence of psychiatric disorders, the longitudinal course of symptoms has not been established. The present study followed a sample of women with the *FMR1* premutation (1) to characterize the incidence, stability and predictors of mood and anxiety disorders across a 3-year period.

Method—Participants included 83 women with the *FMR1* premutation (mean age=38.35) who completed the *Structured Clinical Interview for the DSM-IV-I*(2) at two time points, three years apart. Additional information was obtained regarding demographic, child, and biomedical (e.g. medication, menopause, CGG repeats) factors.

Results—We found increased prevalence of major depressive disorder (MDD) and anxiety disorders over time, with adverse outcomes predicted by complex interactions among biological, behavioral and environmental risk factors. Lifetime MDD increased from 46% to 54% and lifetime anxiety disorders from 28% to 35%. Mid-range CGG repeats, elevated child problem behavior and divorced marital status conveyed elevated risk for psychiatric diagnoses. Primary ovarian insufficiency was highly prevalent (41%) but did not account for elevated rates of psychiatric diagnoses. Medication use was highly reported (41%), particularly in women with MDD or anxiety, with selective serotonin reuptake inhibitors reported as the most commonly used medication across diagnostic groups.

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Conclusions—The elevated prevalence of depression and anxiety in women with the *FMR1* premutation is a clear and pressing concern given the frequent occurrence of the *FMR1* premutation in the general community and the adverse outcomes – at both an individual and systems levels – associated with psychiatric disorders in this population.

Keywords

fragile X; *FMR1* premutation; depression; anxiety; longitudinal

Expanded CGG trinucleotide repeats in the *FMR1* gene are associated with a spectrum of cognitive and mental health challenges that emerge through dynamic interplay amongst genes, environment and development. Individuals with the *FMR1* premutation exhibit an expansion of between 55–200 CGG repeats on the promoter region of the *FMR1* gene with increased production of mRNA (3; 4). Although premutation carriers were initially thought to be asymptomatic, a number of vulnerabilities have been reported, including elevated rates of mood and anxiety disorders (1,4–6), stress (5; 6), primary ovarian insufficiency (7–9), fragile X-associated tremor and ataxia syndrome (FXTAS) (9–11), and subtle differences in cognitive functions (12–14). Given approximately 1:178–209 women in the United States have the *FMR1* premutation (15; 16), understanding potential vulnerabilities is important to informing public health efforts.

Previous work (1; 5; 17–21) has highlighted the complex mental health vulnerabilities associated with the *FMR1* premutation. In our initial study, we examined mood and anxiety disorders in mothers with the *FMR1* premutation ($n=93$) contrasted to a national comparison sample ($n=2,159$) (1). Women with the *FMR1* premutation endorsed higher rates of lifetime major depressive disorder (MDD) (43% versus 32%) and were more likely to report single versus recurrent MDD compared to the NCS-R sample, with the highest risk among women with lower CGG repeats and those who were never married. The *FMR1* premutation group reported lower rates of lifetime anxiety disorders (29% versus 49%); however, rates of agoraphobia without panic disorder and panic disorder without agoraphobia were higher than in the NCS-R sample. Although we identified a number of predictors of anxiety, including higher number of children with FXS and greater child behavior problems, child factors did not account for elevated rates of MDD in this sample, with almost half (48%) reporting their first major depressive episode prior to the birth of their child with FXS and only a minority (28%) attributing major depressive episodes to FXS-related issues. Thus, although environmental stressors clearly contribute to mental health in the *FMR1* premutation, genetic factors contribute.

Elevated rates of depressive symptoms have been reported by other groups (8; 17; 22–24), with elevations in anxiety symptoms reported in many, but not all, reports (12; 17; 21; 24; 25). Variations in findings (25) likely stem from different methodologies (e.g. continuous versus categorical diagnoses) and clinical samples (e.g. young mothers versus aging adults). Evidence suggests that anxiety is associated with acute factors, such as recent child problem behaviors and life stressors (1; 20), whereas depression relates to less variable factors, such as CGG repeat length (1; 17; 25–27) and marital social support (1). The relationship between CGG repeat length and mental health has been debated with reports of elevated risk

at both lower (1; 27) and higher repeat lengths (17; 25; 26), as well as reports of no association (4; 22; 24). These findings may reflect a complex, bidirectional, and potentially curvilinear association with highest risk among mid-range repeats, a pattern that has been suggested by our group and others (1; 20; 27) but is difficult to test given small samples. Anxiety has not been associated with premutation length (1; 26), but is associated with specific *CRHR1* genotypes implicated in hormonal stress response (18). Notably, recent work indicates improved mental health among women with better executive function skills (12), suggesting subtle *FMR1*-related abnormalities in cognitive functions (12–14) may contribute to or co-occur with psychopathology. Psychiatric vulnerabilities do not appear to be driven by premature ovarian insufficiency (17).

Clearly, a range of involvement presents with the premutation and understanding the phenotype is critical from a public health perspective. However, there are a number of challenges to this work, including evidence that nearly all symptoms present in only a subgroup of the population, lack of biomarkers to establish risk, and limited developmental work characterizing the emergence and onset of symptoms, symptom expression variability in adulthood, and variability in symptoms for those with the premutation versus non-carriers or those with the full mutation.

Despite the increasing recognition of mental health vulnerabilities in the *FMR1* premutation, no study has examined changes in MDD and anxiety disorders over time or identified factors that may convey increased vulnerability to their emergence. The present longitudinal study followed mothers with the *FMR1* premutation over 3 years to address the following research questions: 1) What is the trajectory of MDD and anxiety disorders over time? 2) Do the predictors of MDD and anxiety disorders vary over time? 3) Are there identifiable risk factors that predict the onset of MDD and anxiety disorders?

Methods

Participants

Data were drawn from a longitudinal study of family adaptation in FXS. Of the original sample of 93 mothers (1), 10 did not participate in the 3-year follow-up, resulting in 83 mother-child dyads. Rates of disorder prevalence did not differ between women who declined to participate at Time 2 (60%) versus those who did participate (59%). Enrollment criteria included having at least one child with FXS and a maternal diagnosis of the *FMR1* premutation. Genetic information was unavailable for 4 of the 83 mothers, yielding 79 participants in predictive models. Preliminary analyses indicated no effect of child age.

The average age of participants at Time 2 was 38.35 years ($SD=5.31$), none were older than 50, and the majority were married (67%). Premutation length ranged from 68–163 repeats ($\bar{x}=91.84$, $SD=17.44$). The sample was predominantly Caucasian (80%), with a high proportion completing some college or more (92%). Twenty-five percent met Department of Health and Human Service criteria for being low income. Across the sample, 41% of women ($n=34$) reported primary ovarian insufficiency, defined as experiencing menopause prior to age 40 (39% of the 33 women over 40; 42% of the 50 women under 40). Current psychiatric

medication use was reported by 41% ($n=78$), with an average of 1.23 medications per participant (Table 4).

Measures

Psychiatric disorders—Presence of mood and anxiety disorders was assessed using the *Structured Clinical Interview for the DSM-IV-I* (2), a semi-structured interview designed to evaluate the current and lifetime presence of DSM-IV Axis I disorders. Procedures for completing the SCID are described elsewhere (3). Lifetime presence was defined as meeting diagnostic criteria at any time, including currently. Current presence was defined as meeting diagnostic criteria within the past month. Anxiety disorders were collapsed into one category due to the small number meeting criteria for specific disorders and the overlapping nature across disorders. Major depressive disorder and anxiety disorders were categorically coded as present or absent.

Child behavior—Child problem behavior was measured using the total score from the *Child Behavior Checklist* (28). The CBCL is a parent rating scale designed to assess child problem behavior, with multiple versions accounting for child's age. Test-retest reliability ranges from .68–.94 and inter-reliability from .48–.88.

Maternal demographics—Maternal demographics were collected via demographic form, and menopause and medication history were determined using a semi-structured interview. Menopause was determined by report of no menses in the past year. See Table 4.

Procedure

Data were drawn from a larger dataset that includes multiple child, parent, and parent-child interaction measures. Parents provided written informed consent. The follow-up visit (Time 2) was completed three years after the initial assessment (Time 1). All data were double entered and verified.

Statistical Analyses

Analyses were conducted in SAS statistical software version 9.3 (Cary, NC). Data were screened for normality and outliers, and continuous variables were standardized to reduce multicollinearity. Number of CGG repeats was log transformed to reduce skew.

To identify the trajectory of MDD and anxiety over time, we compared the descriptive proportion of women meeting lifetime diagnostic criteria at Time 2 versus Time 1 using McNemar's Test for Correlated Proportions. To examine the consistency of predictors over time, we conducted a series of logistic regression models. Models included: marital status, CGG repeats, child problem behaviors, and number of children with FXS. CGG repeats were included as a linear main effect, but a quadratic term was also tested given previous evidence of a non-linear relationship. We conducted follow-up models with categorized CGG repeats (low<75; mid-range=75–95; high>95) which is consistent with examinations of these same relationships in recent studies (27; 29). The first series of models parallels the predictive models conducted at Time 1 to establish the stability of these associations at Time 2. We used Fisher's exact test to compare rates of medication usage at Time 2 (coded as

present or absent) across women with and without lifetime MDD and anxiety diagnoses, as well as to compare primary ovarian insufficiency across diagnoses in women over age 40 ($n=33$).

To identify if MDD or anxiety at Time 2 was predicted by specific risk factors from Time 1, we conducted two logistic regression models to assess the association between occurrence of (1) MDD and (2) any anxiety disorder controlling for the presence of MDD and/or anxiety at Time 1. Parallel to our first set of models, marital status, CGG repeats, child problem behaviors, and number of children with FXS were included. To determine whether emergent MDD or anxiety over time was associated with changes in medication usage or menopausal state, we used Fisher's exact test to compare medication use and menopause status across women (1) with initial occurrences of MDD or anxiety at Time 2, versus (2) women whose lifetime MDD and anxiety diagnoses remained stable. See Table 3.

Results

Trajectory of MDD and Anxiety

Figure 1 depicts the four patterns of longitudinal diagnostic trajectories for each MDD and anxiety: "Never" (no diagnosis at Time 1 or Time 2), "Remission" (diagnosis at Time 1 only), "Emergence" (diagnosis at Time 2 only), and "Maintenance" (diagnosis at both Time 1 and Time 2).

MDD—McNemar's Test indicated a significant increase in the proportion of participants meeting current criteria for MDD, $\chi^2(1) = 5.44$, $p = .02$, with prevalence rates increasing from 5% to 13%. Significant increases were observed for lifetime MDD, $\chi^2(1) = 7.00$, $p = .008$ with rates increasing from 46% to 54% (17% change). Seven women without a history of MDD at Time 1 met criteria for either single ($n=6$) or recurrent ($n=1$) MDD across the subsequent 3 years. Thirteen women with a single depressive episode at Time 1 experienced a second episode during the 3 years. Consequently, the proportion of women with recurrent MDD rose from 33% to 58% across our longitudinal study. The average age of onset for MDD was 28.74 ($SD=8.33$, range 13–43) with approximately half (51%) meeting criteria before age 30, including 11% before age 18, and an additional 44% before age 40. Forty seven percent experienced their first MDD episode prior to having a child with FXS.

Anxiety—Rates of current anxiety disorders remained stable from 18% to 19%, $\chi^2(1) = 0.07$, $p = .80$. We observed an increase in lifetime anxiety disorders, $\chi^2(1) = 6.00$, $p = .01$. The proportion meeting lifetime criteria increased from 28% to 35% (25% change). The average age of onset for anxiety disorders was 19.62 ($SD=12.17$, range 2–43) with approximately half (52%) meeting criteria before they turned 18, 24% meeting before age 30 and 17% before age 40. Seventy six percent of women with anxiety disorders first met criteria before the birth of their child with FXS.

Predictors of MDD and Anxiety

MDD—Concurrent variables significantly predicted MDD at Time 2, $\chi^2(5)=12.05$, $p=.03$. Tables 2 and 3 depict model estimates and group means, respectively. Consistent with our

initial findings, the presence of lifetime MDD at Time 2 was associated with lower CGG repeats and higher likelihood of being divorced/separated compared to single/engaged. A quadratic term for CGG repeats was tested but not significant, with categorical analyses of CGG repeats suggesting a trend (model $p=.08$; main effect $p=.12$). Analyses indicated medication usage was higher among women with lifetime MDD (54% versus 27% without MDD; Fisher's $p=.02$), and women over 40 who endorsed premature ovarian insufficiency were marginally more likely to meet criteria for MDD (65%; Fisher's $p=.08$). Of the 32 women who met criteria for MDD between Time 1 and Time 2, diagnoses at Time 1 were: 15 MDD only (47%), 1 anxiety disorder only (3%), 10 both disorders (31%), and 6 neither disorder (19%).

Anxiety—Contrary to hypotheses, concurrent variables did not predict anxiety at Time 2, $\chi^2(5) = 4.92$, $p = .43$, inconsistent with our previous findings that the number of children with FXS and severity of problem behavior predicted anxiety at Time 1. Analyses indicated that medication usage was higher among women with lifetime anxiety (60% medicated versus 32% without anxiety; Fisher's $p=.02$). Premature ovarian insufficiency was not associated with anxiety (41%; Fisher's $p=.22$). Of the 20 women who met criteria for an anxiety disorder between Times 1 and 2, diagnoses at Time 1 were as follows: 5 MDD only (25%), 5 anxiety disorder only (25%), 9 both disorders (45%), and 1 neither disorder (5%).

Earlier Risk Factors Predicting Later Emergence of MDD and Anxiety

Time 1 variables significantly predicted emergence of both lifetime MDD, $\chi^2(6) = 36.81$, $p < .001$, and anxiety, $\chi^2(6) = 28.00$, $p < .001$ at Time 2. The occurrence of a major depressive episode between Times 1 and 2 was associated with the presence of MDD and elevated child problem behaviors at Time 1. The quadratic term for CGG repeats approached significance ($p=.09$), and follow-up analyses indicate significantly higher rates of MDD in mid-range repeats compared to low-range (OR=11.51; $p=.03$) and high-range (OR=6.34; $p=.03$) repeat groups (Figure 1). The occurrence of anxiety was associated with the presence of maternal anxiety at Time 1. Of women with neither MDD nor anxiety at Time 1 ($n=36$), 6 reported initial MDD, anxiety or both prior to Time 2. Women with MDD or anxiety disorder that emerged over the 3 year period were not more likely to have initiated medication use ($p=.19$) or started menopause ($p=.25$). Between Times 1 and 2, 7 women either divorced or separated from their partner. In relation to MDD, 4 of these 7 women did not have MDD at either time point, 1 exhibited remission, and 1 exhibited MDD at both time points. In relation to anxiety disorders, 6 women did not meet criteria for anxiety at either time point, and 1 met criteria at both time points.

Discussion

Given the high prevalence and substantial impact of mental illness on individuals across the lifespan, interest has focused on the identification of specific mechanisms and potential subgroups that may confer increased risk for psychiatric disorders. Identified genetic disorders, such as *FMRI* related conditions, provide a model for elucidating the role of genetics and downstream effects on functional outcomes. The elevation of depression and anxiety in women with the *FMRI* premutation is a clear concern given the frequent

occurrence of the *FMR1* premutation in the community and the significant impairment – at both an individual and systems levels – associated with psychiatric disorders.

We found a significant increase in MDD across a 3-year span, with lifetime rates rising from 46% to 54% and current rates increasing from 5% to 13%. Across three years, we observed the emergence of new cases ($n=7$), a shift from single episode to recurrent ($n=11$), and an additional episode for those with recurrent disorders ($n=13$), indicating an increase in the prevalence and severity of depression over time. The prevalence of lifetime anxiety disorders also increased from 28% to 35%, particularly due to increases in generalized anxiety, with 6 new cases meeting criteria. In contrast, the prevalence of current anxiety symptoms remained stable from 18% to 19%.

Examining the course of psychiatric diagnoses in the *FMR1* premutation is important given the unique set of genetic and experiential risk factors exhibited by this population, including elevated genetic predispositions to psychosocial (1; 17; 30; 31) and medical conditions (7; 9–11), and environmental stressors that may stem from raising a child with FXS (5). Although mothers with the *FMR1* premutation generally report positive adaptation to these challenges (5), they endorse higher rates of stress and psychopathology than women without the premutation (1; 5; 8; 12; 17; 21–25). Our results confirm that these risks become more severe over time in adulthood, with an 18% increase in MDD and 26% increase in anxiety disorders across a 3-year period. These data suggest stressors associated with parenting a child with FXS impact both anxiety and MDD with varying time effects. Given the association between maternal stress and well-being to child anxiety in FXS (32), these data underscore importance of attending to psychiatric health in the family of individuals with *FMR1* mutations.

We identified several exogenous and endogenous predictors of psychiatric outcomes at Time 2. Consistent with our previous report (1), lifetime MDD at Time 2 was associated with being unmarried, likely reflecting the buffering effect of social support on stressors associated with *FMR1* mutations (6). Women with mid-range CGG repeats exhibited moderately higher risk for MDD occurrence between Times 1 and 2 that was implicated in non-linear models ($p=.09$) and confirmed using categorical analyses ($p<.05$). Our findings are consistent with a report indicating an inverse relationship between CGG repeat length and psychiatric symptomology in a large multi-site sample ($n=299$) of women with the premutation (27). Both our study and others (1; 20; 27; 29) note the subtlety of the relationships between mid-level CGG repeats and psychiatric symptoms that are challenging to detect given the relatively small samples of women with larger premutation alleles and a failure to intentionally examine non-linear effects in the presence of linear effects. The lack of replication of these findings in some studies may be due, in part, to these factors as many conduct simple correlations or exclusively linear analyses which obscure detection of non-linear effects and preclude detecting a potential relationship between mid-range repeats and psychiatric symptomology (33; 34).

The mechanisms contributing to mid-range CGG repeat length vulnerability are not clear; however, maximal mRNA toxicity in the mid-premutation range associated with inappropriate protein binding has been proposed (27). Alternatively, undiscovered genetic or

epigenetic factors and mediating cognitive or environmental factors are rival hypotheses given evidence of differential sensitivity to stressful life events in relation to depressive and anxious symptomology in women with midsize CGG repeats (21) and recent discoveries of novel methylation markers associated with anxiety mediated by executive functioning in women with the premutation (33). Progressive mRNA toxicity is an associated putative explanatory mechanism with recognition of the cumulative effects of stress and the presence of protective factors as contributory factors (34).

While elevated problem behavior of children with FXS influences the presence of anxiety and MDD, its course and the specificity of its influence varies. Elevated child problem behaviors were associated with lifetime anxiety at Time 1, however this relationship was more diffuse 3 years later despite an increase in severity of child problem behavior. This pattern suggests that severe child behavior problems affect maternal anxiety but that their effect becomes more complex as problems worsen, reflecting an additive contribution. In contrast, more severe child problem behaviors were not associated with lifetime MDD at either Time 1 or Time 2; however, more severe child problem behavior at Time 1 was associated with the presence of MDD over the course of the 3 year follow-up. Examination of mean levels of child problem behavior (table 3) indicate that it is not concurrent child problem behavior that predicts MDD per se; rather, it is the chronicity of elevated child problem behavior. This is consistent with reports that psychosocial stressors predict MDD recurrence in non-*FMR1* samples (35) and that, within FXS, child problem behaviors are associated with poorer maternal adaptation (5). Recent findings suggest women with mid-range premutation lengths may display more sensitive biological responses to life stressors than women with lower or higher repeat lengths (20). These women display more blunted cortisol awakening responses after stressful life events, yet also show lowest levels of depression and anxiety in the absence of stressful life events. These data complement our findings and support the association between stressful events such as child problem behaviors and MDD emergence.

Despite a trajectory of increasing anxiety disorders over time, predictors of anxiety disorders at the follow-up assessment and for the emergence of anxiety disorders over the 3 years appear non-specific with a history of anxiety identified as the most salient factor. These findings are inconsistent with our previous report that anxiety disorders were associated with higher number of children with FXS and greater child problem behaviors at Time 1. However, it is likely that because factors associated with anxiety at Time 1 were child-related, these environmental variables are more amenable to change or that participants adapted in response to those child-related demands. Because the SCID employs DSM-IV criteria, women must endorse significant impairment to meet criteria for any psychiatric disorder. Given the array of support networks and coping strategies reported by women with the premutation (36), and the high medication usage reported by our sample (60% among those with anxiety disorders), it is possible that anxiety disorder rates were attenuated, resulting in less variability for predictive models or that unmeasured variables account for its occurrence at Time 2.

The biological and environmental associations for psychiatric disorder in the premutation were further supported by medical histories of women in our sample. We observed high

medication utilization and high rates of premature ovarian insufficiency, with 41% of the sample reporting the onset of menopause prior to age 40. Although medication usage was higher among women with MDD and anxiety disorders, increased rates of psychopathology across time points were not accounted for by changes in medication or menopausal status. Rates of MDD and anxiety disorders did not differ between women over age 40 with and without premature ovarian insufficiency, consistent with previous reports (17). Given that none of our participants were 50 years or older and all reported the absence of a FXTAS diagnosis, these findings are not attributed to FXTAS as has been reported in other studies (34; 37). Thus, the accelerating, elevated rates of mood and anxiety disorders we observed do not appear to be secondary effects of medical experiences, underscoring the developmentally complex nature of vulnerabilities.

While this study is critical given that it is the first to characterize the trajectory of MDD and anxiety in women with the *FMR1* premutation, it is limited by the relatively small sample that precludes estimating prevalence rates for specific medication utilization or low-incidence mood and anxiety disorders, as well as to characterize non-linear growth. Assessors were not blind to the genetic status of premutation carriers or their previous psychiatric diagnoses and precise measures of endocrine function were not employed. Future work is needed to examine protective factors related to psychiatric diagnoses in women with the *FMR1* premutation, as well as to examine the mental health of women with the *FMR1* full mutation. Finally, we did not include a comparison sample to assess over time. However, we note that our findings indicating marital status and child problem behavior as predictors of MDD and anxiety over time are consistent with epidemiological reports (38; 39). Our report of an increase in lifetime and current disorders, however, may be at odds with existing literature with community samples as some reports suggest an attenuation of prevalence rates with age and a decrease in initial diagnoses in mid to late adulthood while others indicate a wide range of age in the onset of disorders (see 37,38, for reviews).

In summary, our findings characterize the mental health of women with the *FMR1* premutation to represent escalating risk for MDD and anxiety disorders over time and note that our initial characterization at Time 1 is not straightforward highlighting the value of longitudinal follow-up. We report interactive influences among biological, behavioral, and environmental factors in the development of psychopathology with mid-range CGG repeats, elevated child problem behavior and unmarried status conveying elevated risk in a sample subset. Given that 1 in 178 women carry the *FMR1* premutation (15), our data inform efforts towards improved identification and treatment to reduce, or ultimately prevent, adverse outcomes with women having mid-range repeats potentially at highest risk. Evidence from this study and others clearly indicate that females with an *FMR1* premutation are at risk for several disorders that should be considered as part of their routine health care. We recognize that current treatment efforts are limited to a symptom focus until a useful biomarker is identified to target core mechanisms.

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Figure 1.

Longitudinal Patterns of MDD and Anxiety Disorders

Never (not at Time 1 or Time 2; Remission (present at Time 1 and absent at Time 2);

Emergence (absent at Time 1 and present at Time 2); Maintenance (present at Times 1 and 2).

Table 1

Summary of SCID Longitudinal Data

Lifetime DSM-IV Disorder	<i>FMR1</i> Time 1 (subset of Roberts et al., 2009) % (<i>n</i>)	<i>FMR1</i> Time 2 % (<i>n</i>)	NCS-R Dataset reported in Roberts et al., 2009 (<i>n</i> =2,159) % (<i>n</i>)
Mood Disorders	51.81 (43)	60.24 (50)	37.10 (800)
Major Depressive Disorder	45.78 (38)	54.22 (45)	31.90 (688)
Dysthymia	1.20 (1)	1.20 (1)	1.60 (35)
Bipolar Disorder I or II	4.82 (4)	4.82 (4)	4.70 (101)
Anxiety Disorders	27.71 (23)	34.94 (29)	48.80 (1,054)
Panic Disorder with Agoraphobia	3.61 (3)	6.02 (5)	2.30 (50)
Panic Disorder w/o Agoraphobia	7.23 (6)	8.43 (7)	2.30 (50)
Agoraphobia without Panic	3.61 (3)	3.61 (3)	2.30 (49)
Social Phobia	8.43 (7)	9.64 (8)	22.10 (478)
Posttraumatic Stress Disorder	4.82 (4)	6.02 (5)	15.30 (330)
Specific Phobia	4.82 (4)	7.23 (6)	25.70 (554)
Generalized Anxiety Disorder	6.02 (5)	10.84 (9)	11.30 (243)
Any Mood or Anxiety Disorder	59.04 (49)	66.27 (55)	62.90 (1,357)

Table 2

Logistic Regression Prediction Models of Lifetime and Recent MDD and Anxiety

Predictors	B	S.E.	Wald	p	OR	95% CI	Lifetime MDD from Time 2 Predictors						Lifetime Anxiety from Time 2 Predictors					
Marital Status (vs. divorced)																		
Married	1.00	0.60	2.80	0.09	2.71	0.84–8.71	0.54	0.54	0.99	0.32	1.72	0.59–4.98						
Never Married	2.76	1.29	4.59	0.03	15.78	1.26–196.89	0.98	1.23	0.64	0.42	2.67	0.24–29.76						
CGG Repeats	3.39	1.54	4.85	0.03	29.58	1.45–602.09	0.76	1.41	0.29	0.59	2.13	0.13–33.83						
# Children with FXS	0.29	0.43	0.45	0.50	1.34	0.57–3.14	−0.34	0.44	0.58	0.45	0.72	0.30–1.69						
Child behavior problems	0.04	0.26	0.03	0.87	1.04	0.62–1.75	−0.38	0.27	1.98	0.16	0.68	0.40–1.16						
Recent MDD from Time 1 Predictors													Recent Anxiety from Time 1 Predictors					
MDD/Anxiety at Time 1	2.66	0.67	15.63	<.0001	14.28	3.82–53.34	2.43	0.70	12.11	0.00	11.30	2.88–44.29						
Marital Status (vs. divorced)																		
Married	−0.66	0.87	0.58	0.45	0.52	0.10–2.82	0.61	0.82	0.56	0.45	1.84	0.37–9.15						
Never Married	−0.03	1.49	0.00	0.98	0.97	0.05–18.13	12.93	356.00	0.00	0.97	>.999	--						
* CGG Repeats	1.47	1.79	0.68	0.41	4.37	0.13–145.76	2.26	2.04	1.24	0.27	9.61	0.18–519.05						
# Children with FXS	0.36	0.57	0.38	0.54	1.43	0.46–4.40	−0.30	0.55	0.30	0.58	0.74	0.25–2.16						
Child behavior problems	−0.97	0.37	6.74	0.01	0.38	0.18–0.79	−0.25	0.40	0.38	0.54	0.78	0.36–1.72						

* When quadratic term added to model, effect approached significance, $\beta = -220.4$, $p = .09$

Table 3

Predictive descriptive statistics across groups.

Concurrent Predictors (Time 2)	Lifetime MDD		Lifetime Anxiety	
	Absent (<i>n</i> =38) % or <i>x</i> (<i>sd</i>)	Present (<i>n</i> =45) % or <i>x</i> (<i>sd</i>)	Absent (<i>n</i> =54) % or <i>x</i> (<i>sd</i>)	Present (<i>n</i> =29) % or <i>x</i> (<i>sd</i>)
Marital Status (% total)				
Married	73.68%	60.00%	68.52%	62.07%
Never Married/Engaged	10.53%	4.44%	9.26%	3.45%
Divorced/Separated	15.79%	35.56%	22.22%	34.48%
CGG Repeats [<i>x</i> (<i>sd</i>)]	96.57 (20.18)	87.67 (13.53)	92.71 (18.70)	90.25 (15.06)
# Children with FXS	1.45 (0.60)	1.36 (0.53)	1.39 (0.53)	1.41 (0.63)
Child behavior problems	57.47 (9.10)	58.22 (10.14)	56.44 (9.87)	60.55 (8.68)

Past Predictors (Time 1)	Recent MDD*		Recent Anxiety*	
	Absent (<i>n</i> =51) % or <i>x</i> (<i>sd</i>)	Present (<i>n</i> =32) % or <i>x</i> (<i>sd</i>)	Absent (<i>n</i> =63) % or <i>x</i> (<i>sd</i>)	Present (<i>n</i> =20) % or <i>x</i> (<i>sd</i>)
Diagnosis at Time 1 (% total)	25.49%	78.13%	14.29%	70.00%
Marital Status (% total)				
Married	78.43%	65.63%	77.78%	60.00%
Never Married/Engaged	9.80%	3.13%	9.52%	0
Divorced/Separated	11.76%	31.25%	12.70%	40.00%
CGG Repeats [<i>x</i> (<i>sd</i>)]	94.90 (19.56)	87.10 (12.38)	93.02 (18.23)	88.35 (14.72)
# Children with FXS	1.43 (0.61)	1.31 (0.54)	1.37 (0.52)	1.45 (0.76)
Child behavior problems	53.75 (10.20)	61.47 (8.37)	55.21 (10.21)	61.50 (8.83)

* Recent MDD refers to participants who experienced a depressive episode during the 3 year interval between Times 1 and 2, including a current episode at Time 2. Recent anxiety refers to participants who met for an anxiety disorder or who presented with symptoms of an existing anxiety disorder during the 3 year interval between Times 1 and 2, including currently at Time 2. This analysis looks at variables from Time 1 as predictors of anxiety or MDD at Time 2.

Note. Bold indicates that the variable is a significant predictor.

Table 4

Historic psychiatric medication usage by Lifetime Diagnoses at Time 3

Current Medication	Across sample (n=78 of 83)		No MDD (n=37)		MDD (n=41)		No Anxiety (n=53)		Anxiety (n=25)	
	%	N	%	N	%	N	%	N	%	N
No medication	58.97	46	72.97	27	46.34	19	67.92	36	40.00	10
SSRI	19.23	15	16.22	6	21.95	9	16.98	9	24.00	6
Other antidepress.	14.10	11	8.11	3	19.51	8	9.43	5	24.00	6
SNRI	6.41	5	0	0	12.20	5	3.77	2	12.00	3
Benzodiazapine	2.56	2	2.70	1	2.44	1	0	0	8.00	2
Stimulant	2.56	2	0	0	4.88	2	1.89	1	4.00	1
Other	6.41	5	8.11	3	4.88	2	5.67	3	8.00	2

Note: No incidence of sympatholytic, tricyclic, anxiolytic, or mood stabilizers reported.

Other psychiatric medications included anticonvulsants (n=1), antihistamine (n=1), antipsychotic (n=1), beta blocker (n=1) and hypnotic (n=1).