

Genetic and Environmental Influences on Self-Reported Cognitive Functioning: Associations of Diverse Measures of Stress across the FMR1 CGG Repeat Range

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Abstract

Background : The FMR1 gene is essential for neural development and healthy synaptic function. The modal number of CGG repeats in FMR1 is 30, but the range is large with the reported copy number extending down to as few as 6 CGGs and up to over 200 CGGs, conferring fragile X syndrome. Prior work suggests that behavioral phenotypes, including cognitive function, may vary along the continuum of the FMR1 CGG repeat range. Stress may negatively influence cognitive function; however, it is not known whether FMR1 -related variability (i.e., CGG repeat length), in addition to stress, independently influences cognitive function across the CGG range.

Methods : Participants included 1275 mothers who had CGGs ranging from 18 to 123 repeats. Participants completed self-report measures of executive function (BRIEF-A), memory, subjective stress (i.e., perceived stress), and objective stress (i.e., number of life events, parenting a child with a disability). Stress and FMR1 -related variability (i.e., CGG repeat length) were examined as predictors of self-reported executive function and memory difficulty.

Results : Each measure of stress (i.e., perceived stress, life events, and parenting a child with a disability) significantly predicted greater self-reported difficulties in executive function and the likelihood of memory problems, net of age and level of education. Additionally, above and beyond stress effects, CGG repeat number significantly predicted executive functioning and memory difficulties. There was a linear association of CGG repeat number with executive functioning limitations. The association of CGGs with memory difficulties was curvilinear, with participants in the premutation range having the greatest likelihood of reporting such difficulties.

Conclusions : These findings suggest that CGG repeat length confers independent contributions to self-reported executive function difficulty and memory problems over and above indices of stress, suggesting additive effects of genetic variation and environmental exposure.

Keywords : Stress, Cognitive Function, Executive Function, Memory, FMR1 , CGG Repeats

Background

The fragile X mental retardation 1 (FMR1) gene is essential for healthy synaptic function and neural development, as well as the regulation of mRNA throughout the genome (1). Located on the X chromosome, an expansion of more than 200 cytosine-guanine-guanine (CGG) trinucleotide repeats in the 5' untranslated region of the FMR1 mRNA causes fragile X syndrome (FXS). Mothers of children with FXS are often carriers of the FMR1 premutation (PM; i.e., 55–200 CGG repeats), which is relatively common in the general population (~ 1 in 150–209 females; ~1 in 430–470 males (2, 3). Prior work exploring genotype-phenotype associations has largely focused on individuals who carry CGG expansions (i.e., full mutations, premutations, intermediate expansions (4–8). However, the CGG repeat is highly polymorphic, ranging from as few as 6 repeats to over 200 (9–13). A small body of literature highlights the importance of evaluating the possibility of involvement of CGG repeats continuously across this range with respect to both biological (9, 14, 15) and behavioral phenotypes (16, 17). Thus, consideration of the FMR1 CGG repeat number continuously across

the range below FXS has the potential to elucidate phenotypic variation at the population-level. Of additional importance is the examination of environmental circumstances that may influence phenotypic variation. Prior work suggests that stress, such as parenting a child with a disability, may uniquely influence health outcomes across the CGG range (16). The present study aimed to characterize environmental and genetic predictors of self-reported cognitive function, specifically executive function and memory, across the CGG repeat range.

Cognitive Function and FMR1-related Variability

Executive function and memory encompass higher-order mental processes required for goal-directed behavior (e.g., planning, inhibition, performance monitoring) and retrieval (18). Although difficulties in these domains have been implicated as part of the PM phenotype (5, 6, 19), there remains some controversy regarding the extent to which variation in phenotypes may be due to CGG repeat expansions, or may be explained by ascertainment bias, namely the inclusion in research of PM carriers who also have children with FXS (20–22). To better tease apart these effects, one fruitful approach has been to examine the FMR1 CGG range (normal through premutation expansions) in relationship to variation in executive function and memory. In a large sample of both males and females under 50 years of age who had normal (≤ 40 repeats), intermediate (41–60 repeats), and premutation (61–~180) CGG repeats, Hunter and colleagues (22) examined whether FMR1 CGG repeat length predicted factor scores reflecting aspects of executive function and memory. In the full female sample (i.e., normal through premutation repeats), they found that greater CGG repeat length was predictive of higher factor scores indicative of self-reported inattention and impulsivity, as well as direct-assessment processing speed, but not other factors (e.g., memory, response fluency). Though these findings were interpreted as marginal after correcting for multiple comparisons, this work set the stage for continued exploration of executive function variability along the CGG repeat continuum. Likewise, prior work from Debrey and colleagues (23) identified a subgroup of individuals with intermediate CGG repeats who demonstrated clinically significant memory problems. Building on this prior work, the present study examines cognitive functioning (i.e., self-reported executive function and memory) in individuals across the CGG repeat range (excluding the full mutation).

Stress And Cognitive Function

Heightened levels of stress, both subjective and objective, have been reported in observational studies to be associated with executive dysfunction across multiple populations, including individuals with disabilities, individuals exposed to trauma, older adults, and healthy adult controls (18, 24–29). Greater perceived stress, a measure of subjective stress in response to external stressors, has been found to be associated with poorer cognitive functioning including attentional control, processing speed, and working memory (24, 26). Likewise, objective indices of stress (e.g., life events, parenting a child with a disability) may prompt similar aberrations in executive function across diverse populations (28, 29). These objective stressors have also been found to be associated with cognitive dysfunction (including poorer episodic memory) (30), decreased well-being (31), poor mental health (32, 33), as well as changes to biological mechanisms, such as dampened cortisol-awakening-responses (34–36), and alterations to the neural structures that underlie stress-related responses (25, 26, 37).

Parenting stress, or adverse psychological responses to parenting obligations (38), may be observed at increased rates in parents of children with disabilities due to unique and chronic caregiving demands. Meta-analyses (39, 40) suggest that parents of a child with a developmental disability experience higher rates of parenting stress than do parents of typically developing children. Parenting stress may also be observed at increased rates in parents of children with other health conditions. For instance, having a child with a chronic physical (e.g., epilepsy) or mental health (e.g., bipolar disorder) condition has been associated with higher parenting stress compared to the parenting stress of raising typically developing children (41–43). Parents of adult children with developmental or mental health conditions have been exposed to this unique stressor for many years (32) and have been shown to have particularly high levels of parenting stress.

Past research has suggested that mothers may be more negatively affected by parenting stress than fathers (44–46). Therefore, the present study focused on mothers and examined the effects of multiple indices of stress on executive function and memory in mothers across the CGG repeat range (below the full mutation). In addition to stress, it is possible that other factors may contribute to variability in executive function and memory, namely age and education (47–49). These individual factors are therefore incorporated into the study as covariates to account for sociodemographic features that may influence variation in cognitive function. We hypothesized that subjective and objective stressors, as well as increased FMR1 CGG repeat number, would each independently predict executive function and memory difficulty, net of age and education.

Methods

Participants and Procedures

Participants included 1275 mothers with CGG repeats ranging from 18 to 123.

The majority of these participants ($n = 1152$) were drawn from the Marshfield Clinic Personalized Medicine Research Project (PMRP) (50), a 20,000-person population-based biobank. Over half of the PMRP members were female ($n = 11,556$) and DNA was available for 99.7% of them. For a previous investigation (51), the DNA samples of all 20,000 PMRP members were screened for FMR1 CGG repeats, which formed the basis for the current study's sampling plan. We invited all PMRP females who had CGG expansions (41 or greater CGGs) as well as all of those who had at least one allele below the normal range (defined here as 25 or fewer CGGs) to participate in the present study. Additionally, based on a power analysis, a random sample of females with normal-range CGGs was selected for inclusion in the present research. Thus, by design, the recruited sample included all females in the population biobank who had expanded or low numbers of CGGs but fewer females in the normal range than in the full population biobank. The response rate of the recruited females was 77.4%. We further restricted the current analysis to data obtained from mothers who had at least one biological or adopted child.

The CGGs of the participants from PMRP ranged from 18–100 repeats, although per IRB they were not aware of their CGG repeat number. To extend the range of FMR1 CGG repeat length, clinically-ascertained mothers of children diagnosed with FXS were included in the present analysis ($n = 123$, with 67–123 CGGs). Participants from the clinically-ascertained samples were recruited from fragile X clinics, via local media,

newsletters, brochures, and disability registries (52, 53). All participants (PMRP and clinically-ascertained) completed a questionnaire that provided information on whether they had a child with a developmental or mental health condition (see Table 1), as well as all other non-genetic measures for the current study.

Table 1
Developmental or mental health conditions of children of participating mothers

Condition	Frequency	Percentage (%)
None	721	56.5%
Anxiety/depression	150	11.8%
Fragile X Syndrome ¹	124	9.7%
ADHD	116	9.1%
Learning disabilities	27	2.1%
Other developmental disabilities ²	25	2.0%
Autism spectrum disorders	22	1.7%
Bipolar disorder	21	1.6%
Seizures	16	1.3%
Other mental health problems ³	10	0.8%
Schizophrenia	5	0.4%
Other ⁴	38	3.0%
Total	1275	100.0%
¹ 123/124 cases of FXS were derived from the clinically-ascertained sample.		
² including cerebral palsy, Down syndrome, intellectual disabilities.		
³ including PTSD, emotional disorder, eating disorder, mental disability, OCD, ODD.		
⁴ including sensory loss, alcohol/drug problems, mild mental health conditions, mutism, and speech delay.		

The Institutional Review Boards at the University of Wisconsin-Madison and the Marshfield Clinic approved all procedures and all participants signed informed consents.

Measures

Stress.

Perceived Stress Scale. The Perceived Stress Scale (PSS) (54) is a 10-item, self-report measure that quantifies an individual's appraisal of stressful experiences from the past month. Examples include "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?"

and “In the last month how often did you feel nervous or stressed?” Each item was scored on a scale of 0 (never) – 4 (very often); four positively-stated items were reverse-coded. The total score represents a sum across items; higher numbers indicate a greater degree of perceived stress (i.e., subjective stress). Age- and gender-based norms were previously established in prior work ($n = 1406$ females; $M = 13.7$, $SD = 6.6$) with a Cronbach α coefficient of .78 (55). In previous work, higher PSS scores have been linked to poorer health including greater risk of developing depressive symptoms following life events and vulnerability to the common cold (55).

Life Events. Participants reported life events (positive and negative) that they personally experienced during the past year (adapted from Abidin’s Parenting Stress Index; (56)). Participants selected events from a list of 22 items, such as divorce, going into debt, and the birth of a child. Higher scores indicate a greater number of personal life events.

Parenting Status. Participants reported whether their child had a developmental or mental health condition (0 = no, 1 = yes). Fully 43.5% of the present sample had children with developmental or mental health conditions, while the other mothers in the sample had children who did not have such diagnoses.

Cognitive function.

Executive Function. Participants completed the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) (57, 58), a well-validated self-report measure of executive function in daily life for adults. The BRIEF-A consists of 75-items that yields an overall raw score of executive function (Global Executive Composite; GEC), made up of two indices: Behavior Regulation Index (BRI) and Metacognitive Index (MI). Participants indicated the extent to which they experienced problems across nine domains: Inhibit, Shift, Emotional Control, Self-Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials, which together comprise the GEC (see Table 2 for definitions). Each item was rated from 1 (never) to 3 (often). Raw scores for each domain were converted into t-scores, with higher scores suggestive of greater executive difficulties in daily life. T-scores that exceeded 65 on any domain indicated clinically-significant executive dysfunction in that area. In order to ensure that respondents did not indicate excessively negative self-perception about their own executive function, the Negativity scale was examined to ensure that no participant met or exceeded a total score of six (57).

Table 2
Standard definitions of the BRIEF-A domains (57, 58, 72).

Domain	Definition
Inhibit	The Inhibit domain assesses inhibitory control and impulsivity. This can be described as the ability to resist impulses and the ability to stop one's own behavior at the appropriate time.
Shift	The Shift domain assesses the ability to move with ease from one situation, activity, or aspect of a problem to another as the circumstances demand. Key aspects of shifting include the ability to (a) make transitions; (b) tolerate change; (c) problem-solve flexibly; (d) switch or alternate attention; and (e) change focus from one mindset or topic to another.
Emotional Control	The Emotional Control domain measures the impact of executive function problems on emotional expression and assesses an individual's ability to modulate or control his or her emotional responses.
Self-Monitor	The Self-Monitor domain assesses aspects of social or interpersonal awareness. It captures the degree to which an individual perceives himself as aware of the effect that his or her behavior has on others.
Initiate	The Initiate domain reflects an individual's ability to begin a task or activity and to independently generate ideas, responses, or problem-solving strategies.
Working Memory	The Working Memory domain measures "on-line representational memory," that is, the capacity to hold information in mind for the purpose of completing a task, encoding information, or generating goals, plans, and sequential steps to achieving goals. Working memory is essential to carry out multistep activities, complete mental manipulations such as mental arithmetic, and follow complex instructions.
Plan/Organize	The Plan/Organize domain measures an individual's ability to manage current and future-oriented task demands. The domain consists of two components: plan and organize. The Plan component captures the ability to anticipate future events, to set goals, and to develop appropriate sequential steps ahead of time in order to carry out a task or activity. The Organize component refers to the ability to bring order to information and to appreciate main ideas or key concepts when learning or communicating information.
Task Monitor	The Task Monitor domain reflects the ability to keep track of one's problem-solving success or failure, and to identify and correct mistakes during behaviors.
Organization of Materials	The Organization of Materials domain measures orderliness of work, living, and storage spaces (e.g., desks, rooms).

The BRIEF-A was previously standardized on a representative population sample of 1136 adults (age 18–90) with Cronbach α coefficients ranging from .93-.96 and test-retest reliability ranging from .93-.94 across domains, with utility demonstrated in both clinical and non-clinical samples (57–60). The BRIEF-A has been shown to correlate significantly with direct-assessment measures of executive function (e.g., go/no go and trail making tests) in healthy adults (61) and in individuals with disorders associated with executive dysfunction (62–64). The present study used the GEC t-score as the indicator of executive functioning.

A subset of participants in our sample were over 85 years old ($n = 42$). Given that the BRIEF-A was standardized on participants up to age 90, we checked all findings excluding participants over 85 ($n = 30$) and

over 90 years (n = 12), which did not change results. Thus, the findings reported below include all participants.

Self-reported Memory Problems. Participants answered the question: Do you have problems with memory? This question was rated as 0 (no problems with memory), 1 (undiagnosed problems with memory), or 2 (diagnosed memory problems). Due to skewness in the data (as very few mothers reported diagnosed memory problems), all “2” responses were collapsed to 1.

FMR1 -related variation. DNA samples from all participants were analyzed for CGG repeats in FMR1. Assays were completed at Kimball Genetics, Inc., the Wisconsin State Laboratory of Hygiene, and the Rush University Medical Center Molecular Diagnostics Laboratory. PM mothers who were mosaic for the full mutation were excluded from analyses given previously reported differences in cognitive function in this subsample of PM carriers (53).

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics, version 26 (65). Descriptive statistics and Pearson correlations among all study variables are presented in Table 3. Maternal age and education were controlled in all subsequent analyses. To control for potential effects of the second FMR1 allele (as females carry two X chromosomes), the “shorter” allele (i.e., the allele with the lower number of CGG repeats) was included as a covariate in all regression analyses.

Table 3
Correlations between cognitive function, age, education, stress, and CGG repeat length

Variable	Age	Education	Perceived Stress	Life Events (Self)	Parenting Status	CGG Long Allele	Self-Reported Memory Problems	GEC
Age	–							
Education	– .273**	–						
Perceived Stress	– .205**	– .021	–					
Life Events	– .168**	< .001	.332**	–				
Parenting Status	– .032	.102**	.176**	.142**	–			
CGG Long Allele	– .004	.194**	.090*	– .027	.308**	–		
Self-Reported Memory Problems	.124**	– .076*	.232**	.106**	.140**	.143**	–	
BRIEF-A GEC	.115**	– .132**	.560**	.224**	.139**	.084*	.355**	–
M (SD)	57.83 (14.90)	2.74 (.74)	13.22 (7.39)	1.25 (1.42)	0.435 [#]	42.14 (18.64)	.25 (.43)	50.44 (10.60)
**p < .001; *p < .01								
[#] Represents percentage of mothers of a child with a disability								
Note: Parenting status is dichotomized (0 = no child with a disability, 1 = child with a disability); Education was recoded to 1 (less than high school), 2 (high school degree), 3 (college degree or equivalent), 4 (master's degree or above) GEC: Global executive composite								

For the domain of executive function, the primary analysis involved three hierarchical regressions (one for each type of stressor) that assessed the key prediction that stress and FMR1 CGG repeat length would each uniquely contribute to self-reported executive function difficulties. For memory problems, three logistic regressions (one for each type of stressor) were completed to test if stress and FMR1 CGG repeat length would predict the likelihood of a self-reported memory problem. For both executive function and memory problem models, maternal age, education, the shorter allele, and each stress measure were entered into the first block; CGG repeat length (the long allele) was entered into the second block. In the third block, a separate term (CGG squared) was included in all regression models to evaluate potential curvilinear CGG effects within the sample. A significant curvilinear effect would suggest that components of the CGG distribution (e.g.,

premutation expansions) would potentially be driving the CGG effect, whereas if the curvilinear effect is not significant, this would suggest that the CGG effect is linear.

Results

Descriptive Findings

As shown in Table 3, participants' ages ranged from 28–98 years ($M = 57.83$, $SD = 14.90$). Almost all mothers self-identified as white (99.2%). The majority of the mothers (62.3%) had graduated from college. Their children ranged in age from < 1 year to 71 years ($M = 30.30$, $SD = 13.81$). The number of children in each family ranged from 1 to 13 ($M = 2.79$, $SD = 1.50$); the number of children in each family with a developmental or mental health condition ranged from 0 to 6 ($M = .38$, $SD = .78$). As noted, 43.5% of the mothers had a child with a developmental or mental health condition. Perceived stress ranged from 0 to 39 ($M = 13.22$, $SD = 7.39$), similar to the normative population. Most participants (62.2%) had experienced at least one life event in the past year ($M = 1.25$, $SD = 1.42$, Range = 0–9). GEC t-scores on the BRIEF-A ranged from 35 to 93 ($M = 50.44$, $SD = 10.60$), again similar to the normative population. Only 11% of participants exceeded clinical cutoff on the GEC (i.e., t-score > 65). Approximately 25% of participants self-reported a memory problem.

Correlations among study variables are depicted in Table 3. Notably, the stress measures were significantly inter-correlated (p -values < .001), although the strengths of these associations were small to moderate ($r_s = .142$ – $.322$), indicating that the three measures represented somewhat distinct aspects of stress. Both executive function difficulty and memory problems were significantly positively associated with each measure of stress and CGG repeat length (p -values < .001). Executive function difficulty and memory problems were significantly positively correlated with each other, with moderate effects ($r = .355$; $p < .001$).

Multivariate Findings

The key predictions of the study were that measures of stress would influence executive function and memory function, and that an effect of FMR1 CGG repeat length would be associated with these measures of cognitive function above and beyond indices of stress.

Executive Function. Curvilinear CGG effects were not significant in any model of executive function (p -values > .589); thus, linear effects are reported below. As presented in Table 4, perceived stress (PSS) significantly predicted variance in the global executive composite (GEC) of the BRIEF-A ($b = .866$, $p < .001$), such that higher levels of perceived stress was associated with greater problems in executive functioning. There was an additional significant effect of CGG repeat length ($b = .036$, $p = .011$; see Fig. 1). Similarly, total number of life events significantly predicted higher GEC ($b = 1.786$, $p < .001$) with additional significant CGG effects ($b = .073$, $p < .001$; see Fig. 2). Finally, higher GEC was significantly predicted by parenting a child with a developmental or mental health condition ($b = 2.869$, $p < .001$) and by greater CGG repeat length ($b = .045$, $p = .012$; see Fig. 3).

Table 4
Unstandardized Regression Coefficients: Stress and CGG Repeat Length Predict Global Executive Function

	Predictors	b	S.E.	p	R ²
Perceived Stress					
Model 1	(Constant)	31.986	2.103	< .001	.371
	Age	.163	.018	< .001	
	Maternal Ed.	-.800	.349	.022	
	CGG Short allele	-.018	.046	.700	
	PSS	.874	.035	< .001	
Model 2	(Constant)	32.149	2.099	< .001	.374
	Age	.161	.018	< .001	
	Maternal Ed.	-.994	.356	.005	
	CGG Short allele	-.051	.048	.287	
	PSS	.866	.035	< .001	
	CGG Long allele	.036	.014	.011	
Life Events					
Model 1	(Constant)	47.539	2.449	< .001	.077
	Age	.091	.022	< .001	
	Maternal Ed.	-1.331	.422	.002	
	CGG Short allele	-.033	.056	.556	
	Life Events (Self)	1.755	.214	< .001	
Model 2	(Constant)	47.485	2.430	< .001	.093
	Age	.089	.022	< .001	
	Maternal Ed.	-1.725	.429	< .001	
	CGG Short allele	-.102	.058	.078	
	Life Events (Self)	1.786	.213	< .001	
	CGG Long allele	.073	.017	< .001	
Parenting Status					

Note: Significant p-values are noted in bold for key predictors (i.e. Stress, CGG long allele)

	Predictors	b	S.E.	p	R²
Model 1	(Constant)	50.414	2.394	< .001	.049
	Age	.063	.022	.004	
	Maternal Ed.	-1.789	.425	< .001	
	CGG Short allele	- .007	.056	.898	
	Parenting Status	3.345	.608	< .001	
Model 2	(Constant)	50.501	2.388	< .001	.054
	Age	.061	.022	.005	
	Maternal Ed.	-1.990	.432	< .001	
	CGG Short allele	- .049	.059	.403	
	Parenting Status	2.869	.636	< .001	
	CGG Long allele	.045	.018	.012	
Note: Significant p-values are noted in bold for key predictors (i.e. Stress, CGG long allele)					

Estimated regression lines indicate the independent influences of CGG repeat length and increased number of life events on executive function difficulty. Trend lines represent a subset of participants with high life events (> 1 SD above the mean) and low life events (< 1 SD below the mean).

Estimated regression lines indicate the independent influences of CGG repeat length and parenting a child with a disability on executive function difficulty.

Memory Problems. Second, we predicted that stress and FMR1 CGG repeat length would independently predict the likelihood of self-reported memory problems. The curvilinear term was tested and found to be significant in all models reported below. As shown in Table 5, PSS significantly predicted self-reported memory problems (OR = 1.084, $p < .001$), with additional significant curvilinear CGG effects (OR = 1.000, $p = .049$). Total number of life events significantly predicted self-reported memory problems (OR = 1.227, $p < .001$), with additional significant curvilinear CGG effects (OR = 1.000, $p = .021$). Last, self-reported memory problems were predicted by parenting status (OR = 1.742, $p < .001$), with additional significant curvilinear CGG effects (OR = 1.000, $p = .031$). Visually, these curvilinear effects were most apparent above 80 CGG repeats (see Figs. 4–6). Thus, the effects were most pronounced in the premutation range.

Table 5

Logistic Regressions: Stress and CGG Repeat Length Predict the Presence of Self-Reported Memory Problems

	Predictors	Odds Ratio	S.E.	p	Pseudo R ²	95% CI (Lower, Upper)
Perceived Stress						
Model 1	(Constant)	.023	.014	< .001	.075	.007, .077
	Age	1.030	.005	< .001		1.019, 1.040
	Maternal Ed.	.898	.087	.267		.742, 1.086
	CGG Short Allele	1.002	.013	.910		.976, 1.028
	PSS	1.088	.011	< .001		1.068, 1.109
Model 2	(Constant)	.035	.015	< .001	.091	.007, .080
	Age	1.029	.005	< .001		1.019, 1.040
	Maternal Ed.	.806	.081	.032		.661, .982
	CGG Short Allele	.987	.014	.333		.961, 1.014
	PSS	1.085	.011	< .001		1.064, 1.106
	CGG Long Allele	1.017	.004	< .001		1.010, 1.024
Model 3	(Constant)	.046	.032	< .001	.093	.012, .181
	Age	1.030	.005	< .001		1.019, 1.040
	Maternal Ed.	.807	.082	.034		.662, .984
	CGG Short Allele	1.000	.014	.765		.968, 1.024
	PSS	1.084	.011	< .001		1.063, 1.105
	CGG Long Allele	.980	.019	.290		.943, 1.018
	Curvilinear CGG (Long)	1.000	< .001	.049		1.000, 1.001
Life Events						
Model 1	(Constant)	.089	.051	< .001	.028	.029, .271
	Age	1.022	.005	< .001		1.012, 1.032
	Maternal Ed.	.894	.085	.239		.742, 1.077
	CGG Short Allele	1.003	.013	.815		.978, 1.029
	Life Events (Self)	1.218	.056	< .001		1.112, 1.333
Note: Significant p-values are noted in bold for key predictors (i.e. Stress, curvilinear CGG)						

	Predictors	Odds Ratio	S.E.	p	Pseudo R ²	95% CI (Lower, Upper)
Model 2	(Constant)	.082	.048	< .001	.051	.027, .257
	Age	.102	.005	< .001		1.012, 1.032
	Maternal Ed.	.791	.078	.018		.652, .960
	CGG Short Allele	.985	.013	.257		.959, 1.011
	Life Events (Self)	1.229	.058	< .001		1.121, 1.348
	CGG Long allele	1.020	.004	< .001		1.013, 1.027
Model 3	(Constant)	.175	.115	.008	.055	.048, .637
	Age	1.023	.005	< .001		1.013, 1.033
	Maternal Ed.	.794	.079	.020		.654, .965
	CGG Short Allele	.996	.014	.759		.968, 1.024
	Life Events (Self)	1.227	.058	< .001		1.118, 1.346
	CGG Long allele	.976	.019	.214		.940, 1.014
	Curvilinear CGG (Long)	1.000	< .001	.021		1.000, 1.001
Parenting Status						
Model 1	(Constant)	.119	.065	< .001	.038	.041, .348
	Age	1.019	.005	< .001		1.009, 1.029
	Maternal Ed.	.819	.078	.035		.680, .987
	CGG Short Allele	1.003	.013	.828		.978, 1.028
	Parenting Status	2.131	.291	< .001		1.631, 2.784
Model 2	(Constant)	.123	.068	< .001	.051	.041, .363
	Age	1.019	.005	< .001		1.009, 1.028
	Maternal Ed.	.753	.074	.004		.622, .912
	CGG Short Allele	.989	.013	.397		.964, 1.015
	Parenting Status	1.793	.259	< .001		1.351, 2.380
	CGG Long Allele	1.015	.004	< .001		1.008, 1.023
Model 3	(Constant)	.245	.156	.027	.054	.071, .852
	Age	1.019	.005	< .001		1.009, 1.029

Note: Significant p-values are noted in bold for key predictors (i.e. Stress, curvilinear CGG)

Predictors	Odds Ratio	S.E.	p	Pseudo R ²	95% CI (Lower, Upper)
Maternal Ed.	.754	.074	.004		.622, .914
CGG Short Allele	.999	.014	.930		.972, 1.027
Parenting Status	1.742	.254	< .001		1.309, 2.318
CGG Long Allele	.976	.018	.194		.941, 1.012
Curvilinear CGG (Long)	1.000	< .001	.031		1.000, 1.001
Note: Significant p-values are noted in bold for key predictors (i.e. Stress, curvilinear CGG)					

Covariates. Both age and education were significant predictors of executive function difficulty across all models (p-values $\leq .022$). Age and education were significant predictors of self-reported memory problems in all models that included CGG repeat length (p-values $\leq .034$).

Discussion

The present study evaluated the influence of distinct dimensions of stress, and the independent effects of FMR1 CGG repeat length (up to but excluding the full mutation), on self-reported cognitive functioning (i.e., executive function and memory). Importantly, CGG repeat length accounted for small, but statistically significant elevations in executive function difficulty and memory problems, above and beyond stress, age and level of education. To date, this study represents the largest sample in which the association between cognitive function and FMR1 CGG repeat length has been studied. By taking a continuous approach to evaluating FMR1-related effects on cognitive function, and by assessing mothers of non-disabled children as well as children with a diverse range of disability conditions, this study advances understanding of how both environmental and genetic factors influence self-reported cognitive functioning.

Historically, examination of behavioral phenotypes associated with FMR1-related variability (e.g., CGG repeat length) have largely focused on individuals with full mutation fragile X syndrome or the premutation, with some exceptions (16, 17, 22, 66). Many prior assessments of cognition associated with the FMR1 gene involved group comparisons, typically between PM carriers and those with modal numbers of CGG repeats (4, 6, 7, 22). With consideration of the continuous nature of the CGG repeat range, as in the present study, the interpretation of the relationship between FMR1-related variation and phenotypic expression can be advanced.

Our findings revealed linear effects of CGG repeat length on executive functioning and curvilinear effects of CGG repeat length on memory problems. Higher incidence of memory problems was evident at approximately 80 CGG repeats, suggesting that repeats in the premutation range may be driving this effect. The divergent results observed between limitations in executive functioning and memory problems suggest that these constructs may represent distinct aspects of cognition. Higher scores on the BRIEF-A reflect day-to-day difficulties with a broad array of tasks other than memory problems, including difficulties sitting still and waiting, the propensity to make untactful remarks, and the tendency to complete tasks in a hurried manner.

One question that remains is why increasing numbers of CGG repeats across the full range are associated with problems with cognitive functioning. As noted previously, there is evidence to suggest that executive dysfunction is more common among PM carriers and possibly among those in the intermediate range (4, 6, 17, 67, 68). However, our findings are in contrast with other research literature suggesting that FMR1 translation may be most efficient at ~ 30 CGGs, with less efficient translation of FMRP at both higher and lower repeat numbers (9, 69). Replication of the current findings is necessary, and research examining the basic biological functions of the FMR1 CGG repeat is needed to fully understand these effects.

In this study, we observed associations between multiple measures of stress and cognitive functioning, both objective and subjective, with each measure of stress providing unique insights about how stress is associated with cognitive functioning. For example, the life events that were endorsed from the past year encompassed a variety of events that are not necessarily “negative”, such as the birth of a child, increased income, and moving to a new home. Luhmann and colleagues (31) conducted a meta-analysis on relationships between life events and subjective well-being, including cognitive well-being. Similar to our study, they found that cognitive well-being varied in response to the presence of life events, both positive and negative, which may simply be an indication that life change is stressful and can affect cognition.

Though parenting status was a significant predictor of higher self-reported problems with executive function and memory, it predicted less variance than perceived stress and life events. The conditions of the children represented in the sample varied considerably. Whereas some mothers had children with developmental conditions typically present at birth or in early childhood (e.g., Down syndrome), other conditions are later in onset (e.g., schizophrenia). Furthermore, while some conditions were rare, most conditions were relatively common, as the majority of affected children had conditions such as anxiety, depression, or ADHD. The differences in duration and severity of stress exposure to these varied conditions may have influenced the magnitude of variance in cognitive function predicted by parenting a child with a developmental or mental health condition. These factors warrant further attention in future work.

In the present analysis, age and education each significantly contributed to variance in cognitive function in addition to stress and CGG repeat effects, as suggested in prior research (47, 48). Prior work suggests that age-related cognitive problems are most pronounced for individuals with lower levels of education (49). The present research suggests that studies of the relationships between variation in the FMR1 gene and behavioral phenotypes should continue to consider additional individual and environmental factors to accurately evaluate FMR1-related influences.

Study Strengths, Limitations, And Future Directions

This study had several notable strengths. First, the availability of DNA and FMR1 CGG repeat assays across the full range of CGG repeats (up to the full mutation) enabled robust examination of the effects of FMR1-related variability on self-reported cognitive function. Second, we had a large sample size, which drew, in large part, from a population-based sample of participants. Third, this study was strengthened by consideration of multiple measures of stress. Additionally, the inclusion of child disabilities was broad, further contributing to the generalizability of study findings.

This study also had some limitations. Although the sample was diverse with regards to age and the range of FMR1-related variation, the participants in the sample were racially and ethnically homogenous. Additionally, many prior reports of associations between cognitive function and FMR1 expansions have included direct-assessment measures, whereas the present study relied on self-report. The study's large sample size precluded direct testing of > 1200 individuals. It has been suggested that PM carriers may over-report symptoms not evidenced on neurological exam (70). However, there is also extant literature to suggest significant associations between cognitive function and CGG repeat length using both direct-assessment and self-report measures across the CGG range (22, 71), suggesting the validity of self-reported results. Hunter and colleagues (22) have discussed the possibility that individuals who participate in research may be less likely to have cognitive difficulties. Thus, while it is possible that the present findings could reflect potential ascertainment bias in recruited individuals (who are less likely to experience cognitive difficulties), the high response rate from our sample recruitment (77.4%) is indicative of a sample that is largely representative of the population from which participants were drawn.

Another limitation of the present study is that the only FMR1-related biomarker available for the study participants was CGG repeat number. Inclusion of activation ratio, mRNA, and FMRP levels would greatly enhance understanding of the processes investigated here. Additionally, interpretation of these findings can only be extrapolated to females. Given prior work suggestive of age-related cognitive differences in male PM carriers, most obvious in those with motor-related symptoms or signs of FXTAS, it may be that executive function difficulties and memory problems manifest differently in males and females across the CGG range. Future work should examine cognitive function across the CGG range in males, particularly with consideration as to how external stressors may affect profiles, as there may be particular stressors that may be more salient for males than females. This is an important consideration, particularly for male PM carriers, as stress could play an important role in the onset of FXTAS symptoms (72), but further work is needed to investigate this possibility.

Finally, the participants in the present study were recruited using multiple methods, including drawing from a 20,000-person population-based biobank and via a national sample of premutation carriers who were identified clinically after a child was diagnosed with FXS. Although this approach made it possible to include participants with repeats ranging from 18 to 123 CGGs, in future research, it would be advantageous to use a single method of recruitment across diverse samples, but that would require access to much larger population biobanks.

Conclusions

Findings from the present study highlight the importance of separately considering the role of stress and FMR1-related variability in studies of cognitive function. Both stress and CGG repeat length independently predicted variation in self-reported executive function and the likelihood of memory problems. Future work should incorporate multiple dimensions of FMR1-related biomarkers and objective cognitive testing to advance understanding of genotype-phenotype associations at the population level.

Abbreviations

BRIEF-A
Behavior rating inventory of executive function-adult version
FMR1
Fragile X mental retardation 1
FXS
Fragile X syndrome
PM
Premutation
PSS
Perceived Stress Scale

Declarations

Ethics approval and consent to participate

The Institutional Review Boards at the University of Wisconsin-Madison and the Marshfield Clinic approved all procedures and all participants signed informed consents prior to participation.

Consent for publication

Consent for publication is not applicable.

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

Competing interests

MM is the Chair of the Scientific Advisory Board of the John Merck Fund.

EBK has received funding from Seaside Therapeutics, Novartis, Roche, Alcobra, Neuren, Cydan, Fulcrum, GW, Neurotrope, Marinus, Zynerba, BioMarin, Ovid, Tetra, Retrophin, Yamo, Acadia, Avexis, Ionis, Ultragenyx, Lumos, GeneTx, and Vtesse/Sucampo/Mallinckrodt Pharmaceuticals to consult on trial design or development strategies and/or conduct clinical trials in FXS or other NDDs or neurodegenerative disorders, and from Asuragen Inc to develop testing standards for FMR1 testing. All funding to EBK is directed to Rush University Medical Center to support rare disease programs. EBK receives no personal funds.

The remaining authors declare they have no competing interests.

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Authors' contributions

MM, LSD, and JH designed the larger study from which the data were derived and supervised the data collection. NM and JH analyzed the data. NM, LSD, and MM wrote the first draft and made edits to the manuscript. MHB contributed the DNA samples and facilitated the collection of data from the participants in Marshfield PMRP. MWB and EB-K conducted the CGG repeat assays. All authors contributed to interpretation of the data and approved the final manuscript.

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Figures

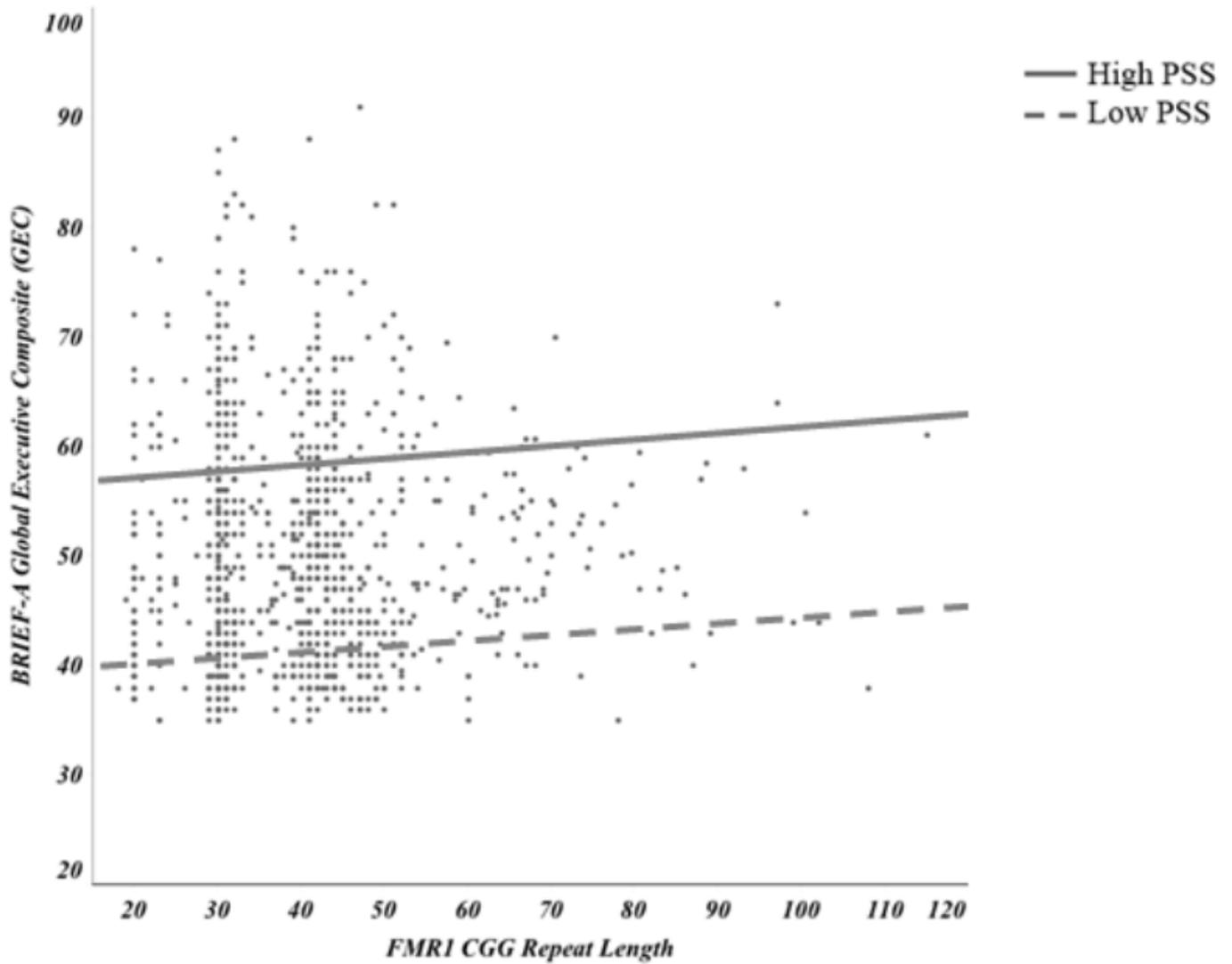


Figure 1

Perceived stress and CGG repeats predict GEC. Estimated regression lines indicate the independent influences of CGG repeat length and increased perceived stress (PSS) on executive function difficulty. Trend lines represent a subset of participants with high PSS (>1 SD above the mean) and low PSS scores (<1 SD below the mean).

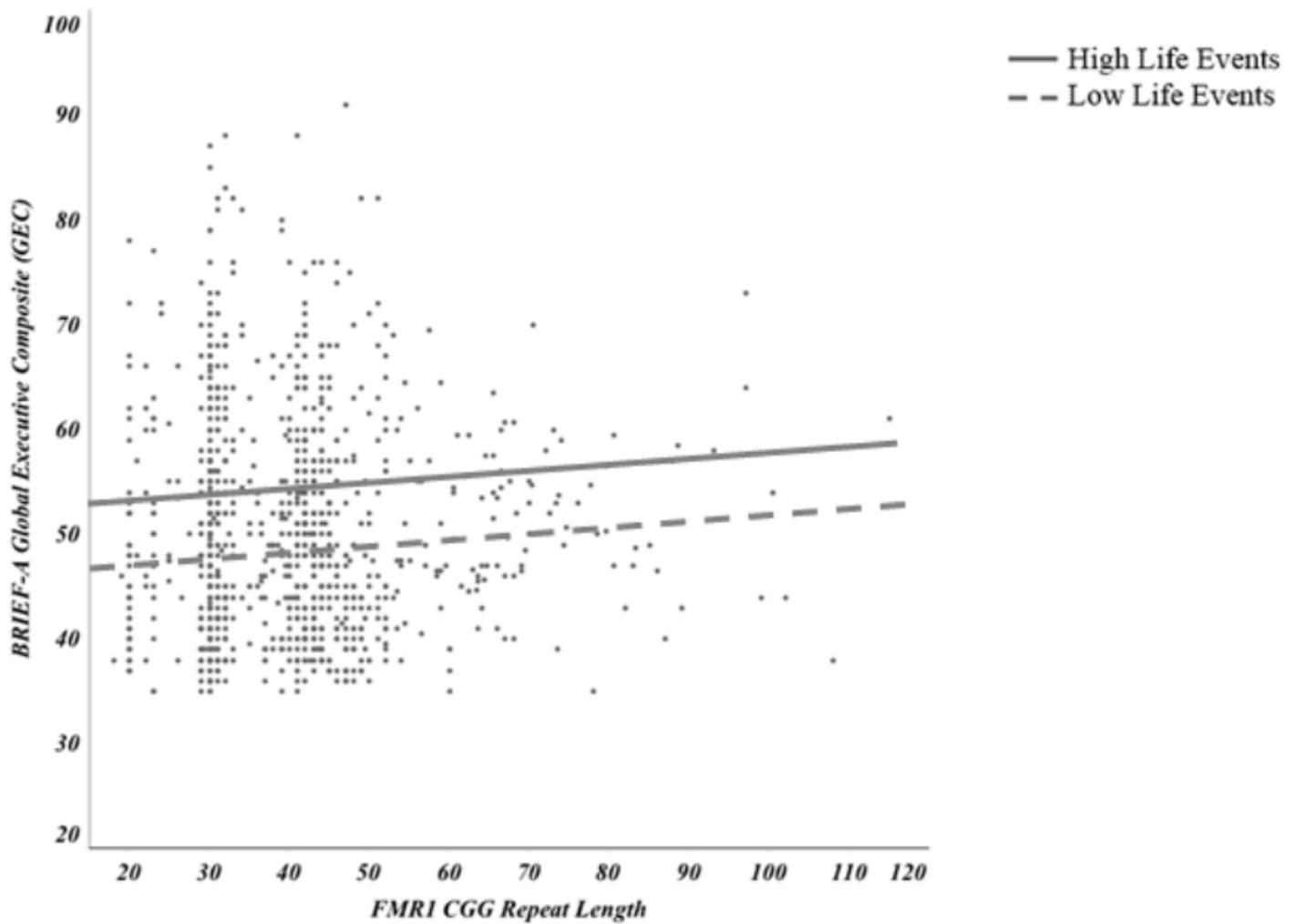


Figure 2

Life events and CGG repeats predict GEC. Estimated regression lines indicate the independent influences of CGG repeat length and increased number of life events on executive function difficulty. Trend lines represent a subset of participants with high life events (>1 SD above the mean) and low life events (<1 SD below the mean).

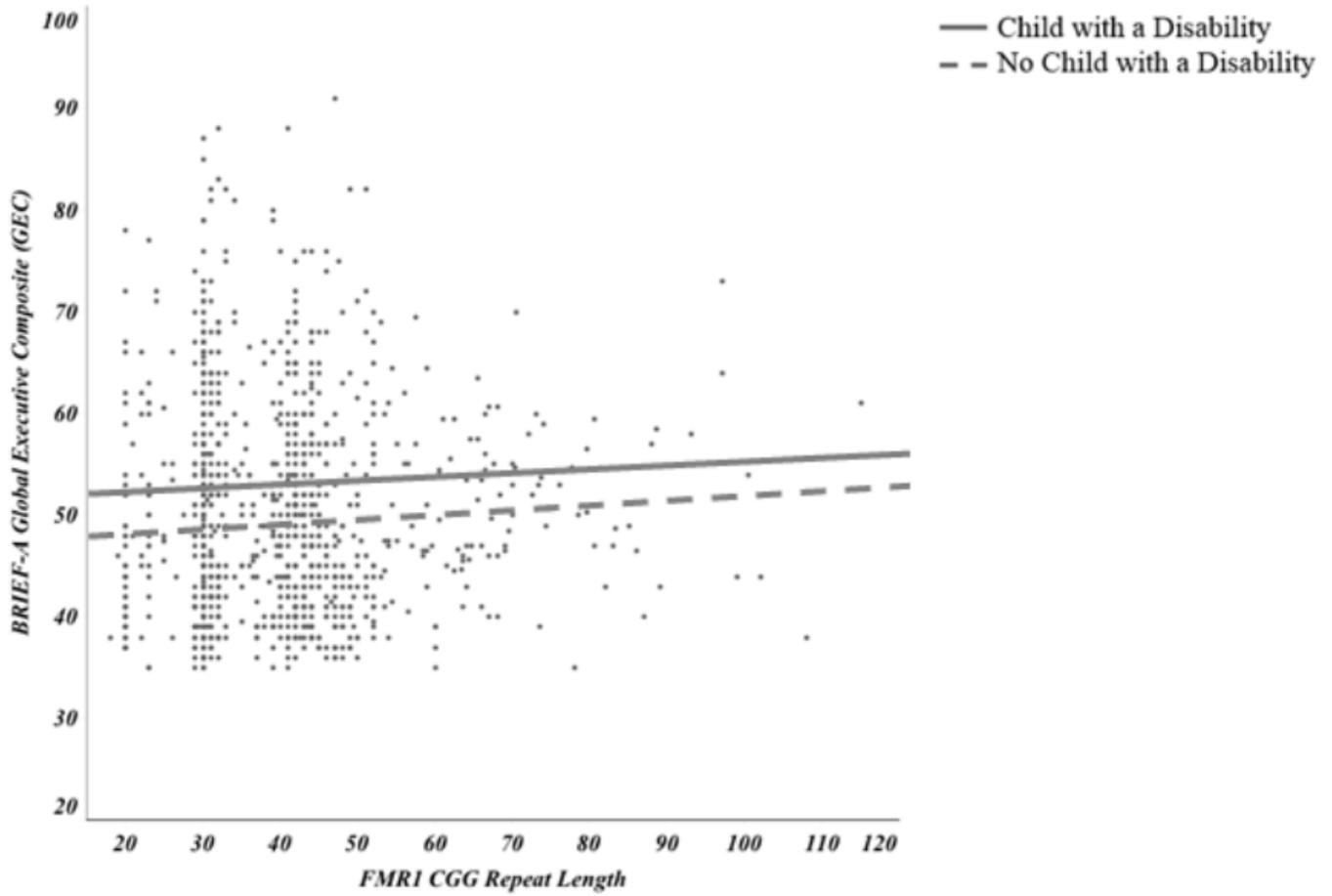


Figure 3

Parenting status and CGG repeats predict GEC. Estimated regression lines indicate the independent influences of CGG repeat length and parenting a child with a disability on executive function difficulty.

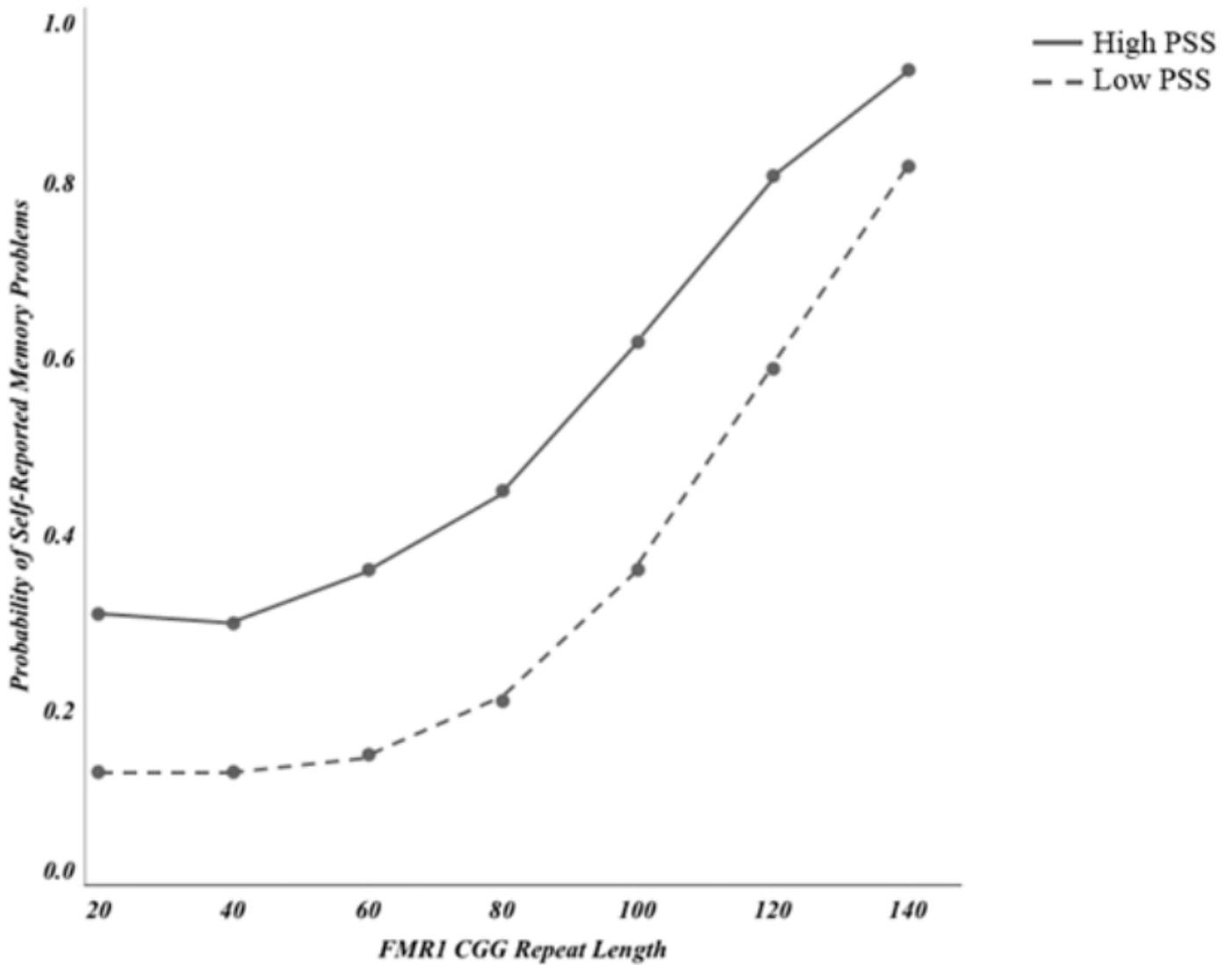


Figure 4

Curvilinear association between CGG repeat length and the probability of self-reported memory problems. Trend lines represent estimated probability for participants with high PSS (>1 SD above the mean) and low PSS scores (<1 SD below the mean).

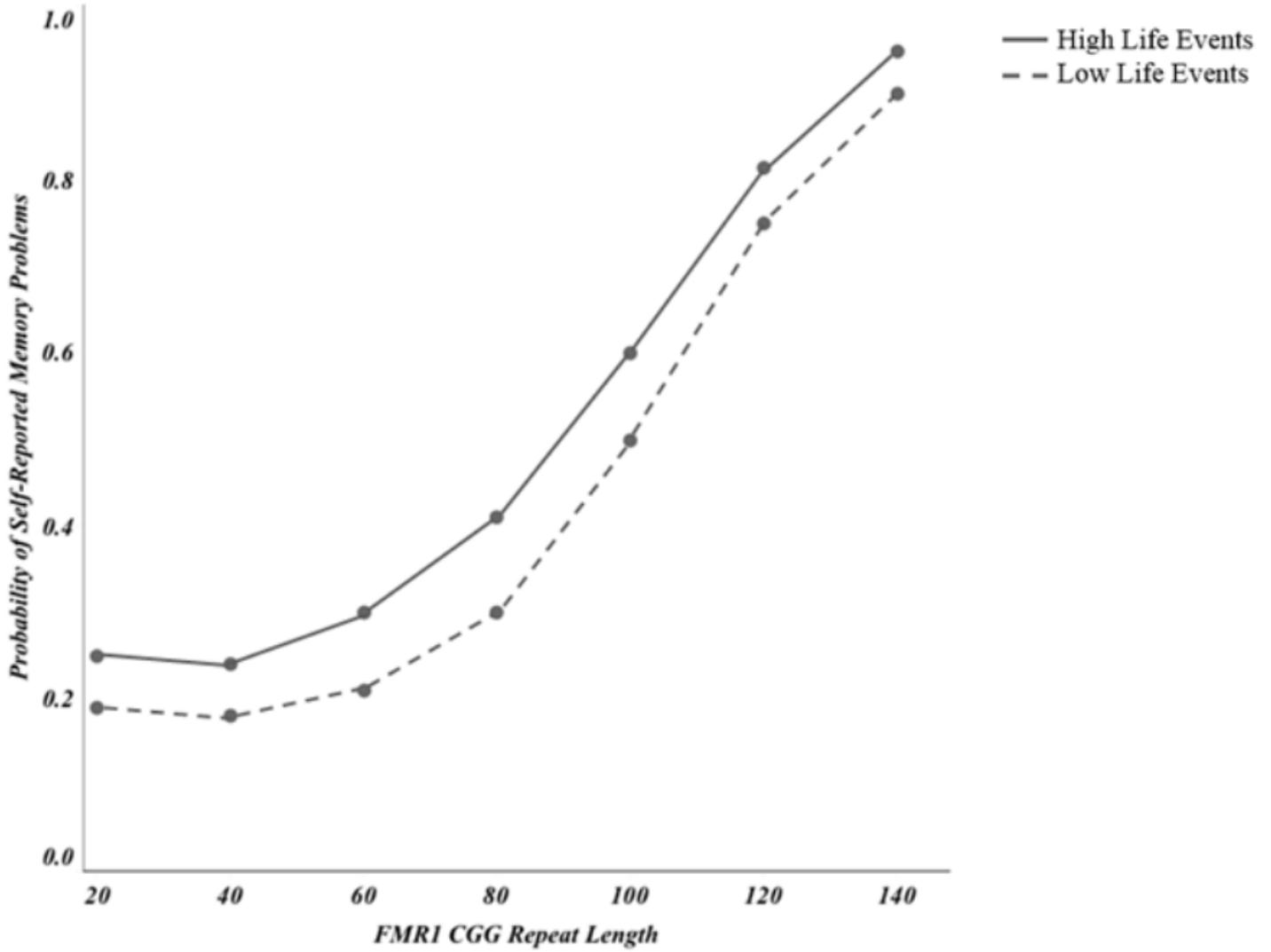


Figure 5

Curvilinear association between CGG repeat length and the probability of self-reported memory problems. Trend lines represent estimated probability for participants with high life events (>1 SD above the mean) and low life events (<1 SD below the mean).

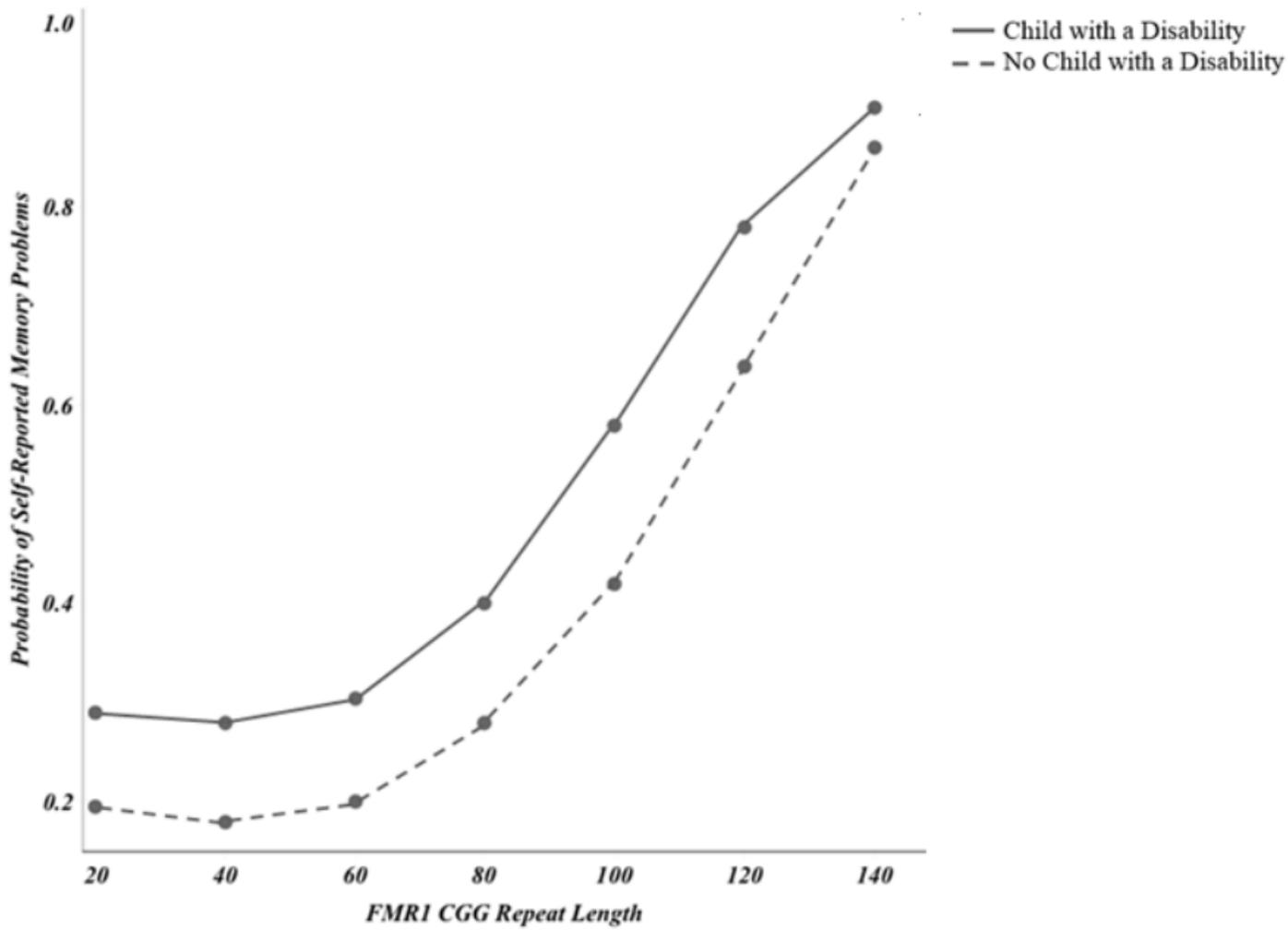


Figure 6

Curvilinear association between CGG repeat length and the probability of self-reported memory problems by parenting status.