Family history of FXTAS is associated with age-related cognitive-linguistic decline among mothers with the FMR1 premutation

Jessica Klusek1*, Amanda Fairchild2, Carly Moser1, Marsha R. Mailick3, Angela John Thurman4 and Leonard Abbeduto4

Abstract

Background: Women who carry a premutation allele of the FMR1 gene are at increased vulnerability to an array of age-related symptoms and disorders, including age-related decline in select cognitive skills. However, the risk factors for age-related decline are poorly understood, including the potential role of family history and genetic factors. In other forms of pathological aging, early decline in syntactic complexity is observed and predicts the later onset of neurodegenerative disease. To shed light on the earliest signs of degeneration, the present study characterized longitudinal changes in the syntactic complexity of women with the FMR1 premutation across midlife, and associations with family history of fragile X-associated tremor/ataxia syndrome (FXTAS) and CGG repeat length.

Methods: Forty-five women with the FMR1 premutation aged 35–64 years at study entry participated in 1–5 longitudinal assessments spaced approximately a year apart (130 observations total). All participants were mothers of children with confirmed fragile X syndrome. Language samples were analyzed for syntactic complexity and participants provided information on family history of FXTAS. CGG repeat length was determined via molecular genetic testing.

Results: Hierarchical linear models indicated that women who reported a family history of FXTAS exhibited faster age-related decline in syntactic complexity than those without a family history, with that difference emerging as the women reached their mid-50s. CGG repeat length was not a significant predictor of age-related change.

Conclusions: Results suggest that women with the FMR1 premutation who have a family history of FXTAS may be at increased risk for neurodegenerative disease, as indicated by age-related loss of syntactic complexity. Thus, family history of FXTAS may represent a personalized risk factor for age-related disease. Follow-up study is needed to determine whether syntactic decline is an early indicator of FXTAS specifically, as opposed to being a more general age-related cognitive decline associated with the FMR1 premutation.

Keywords: Grammatical complexity, Language production, Aging, Fragile X premutation

Over 1 million individuals in the USA (1:151 females and 1:468 men) are carriers of a premutation of the Fragile X Mental Retardation-1 (FMR1) gene, which occurs when the FMR1 trinucleotide CGG sequence expands to 55–200 repeats, compared to the normal range of ≤40 repeats [1–3]. Female carriers of the FMR1 premutation can pass the problematic gene to their children, which may cause fragile X syndrome, an inherited form...
of intellectual disability [4]. Carriers themselves can also experience a substantially increased burden of disease, which is thought to be mechanistically related to over-expressed FMR1 mRNA and associated mitochondrial dysfunction and cell death that occurs in the FMR1 premutation [5–7]. Women with the FMR1 premutation are at elevated risk for a variety of medical conditions, including primary ovarian insufficiency [8, 9]; autoimmune, chronic pain, and endocrine disorders [10–14]; mental health disorders [12, 15–18]; executive dysfunction [19–22]; and increased expression of autism-related traits such as reduced eye contact and social-communication difficulties [23–26]. Additionally, about 15% of women with the FMR1 premutation may be vulnerable to premature age-related decline in cognitive, executive, and language production skills during midlife, although it remains unclear whether these age-related changes represent precursors to FXTAS or a more general decline in functioning associated with the FMR1 premutation [19, 22, 29–31].

Because of the high prevalence of the FMR1 premutation in the general population and the increased disease burden associated with the premutation, the delineation of age-related phenotypes is crucial. At present, a major barrier to the development of effective clinical management strategies is that nearly all evidence of age-related change has been gleaned from cross-sectional data that are insufficient for understanding longitudinal trajectories of the disease. Moreover, the risk factors that predispose individuals to age-related decline are poorly understood. One potential risk factor that has not been studied extensively is a family history of adverse phenotypes. In one preliminary study, women with the FMR1 premutation whose fathers experienced FXTAS reported a higher prevalence of balance problems and menopausal symptoms compared to women whose fathers did not experience FXTAS [32]. Thus, a positive family history of FXTAS may place women with the FMR1 premutation at increased clinical risk. However, there is a need to follow up on these early findings using direct-assessment measures of clinical symptoms, given the reporting biases that can occur with self-report. Gaining a better understanding of the family history of FXTAS as a factor that may mark increased clinical risk is important for identifying personalized risk factors that can be used to tailor counseling and prevention services. Additionally, the study of the aggregation of clinical symptoms within families can lead to a better understanding of etiology, including the effects of shared background genes and environmental factors.

The identification of measures that are sensitive to age-related phenotypes in the FMR1 premutation has been a barrier to this work, as the earliest signs of neurodegeneration are subtle and difficult to capture with traditional standardized measures of cognitive function, self-reported symptoms, and even neurological examinations conducted by a movement disorder specialist [33]. Language sample analysis, which provides insight into multiple dimensions of language production, is a method that may prove useful in identifying age-related phenotypes in carriers of the FMR1 premutation. In other forms of pathological aging, such as Alzheimer’s disease and dementia, subtle language production deficits can be observed early in disease progression before other cognitive deficits are able to be detected using traditional standardized measures [34–36]. Language production is supported by a wide range of cognitive processes, such as semantic storage and retrieval as well as working memory, executive control, and attention [37–39]. Thus, the study of language production can provide a window into “cognition in action” and can serve as an early and sensitive indicator of age-related cognitive changes [36, 40–42].

A decrease in syntactic complexity is a strong predictor of the later onset of neurodegenerative disease in the general population. Syntactic complexity refers to the complexity of the grammatical structures within a sentence (for example, sentences can range from simple one-clause sentences to complex multi-clause sentences that include multiple forms of embedding and subordination). In healthy aging, syntactic complexity is relatively stable through middle adulthood, with apparent decline generally not evident until the 70s, corresponding to age-related degradation of working memory [43–47]. Yet, in pathological aging, such as in dementia and Alzheimer’s disease, a decline in syntactic complexity is evident earlier in life and is a strong predictor of the later development of disease [46, 48–51]. In a landmark study focused on the early autobiographical writings of a cloister of nuns, the syntactic complexity of writings produced when the nuns were young adults (mean age of 23 years) predicted poorer cognitive function and the development of Alzheimer’s disease more than 50 years later when the nuns were evaluated again in old age and post-mortem [52, 53]. Thus, diminished syntactic complexity is a sensitive risk marker for the development of neurodegenerative disease in late life.

In the present study, we examined syntactic complexity as a feature that may lend new insight into the earliest manifestations of age-related cognitive decline in women with the FMR1 premutation. Specifically, we sought to
determine (a) whether women with the FMR1 premutation demonstrate age-related decline in syntactic complexity and (b) whether a family history of FXTAS and CGG repeat length relate to age-related changes in syntactic complexity. We hypothesized that women with the FMR1 premutation would exhibit a decline in syntactic complexity across age, with the steepest decline observed among those with a family history of FXTAS. We also expected that the decline would be the most pronounced among women with mid-range CGG repeat lengths, consistent with prior reports of curvilinear CGG risk patterns [19, 54, 55]. Understanding potential age-related patterns of cognitive-linguistic decline in women with the FMR1 premutation could assist with the identification of women who are at the greatest risk for neurodegenerative disease prior to the onset of obvious symptoms, allowing for the implementation of prevention measures to prolong health in aging.

**Methods**

**Participants**

Participants were 45 women with the FMR1 premutation who were aged 35 to 64 years at study entry ($M = 47.20, SD = 7.50$). All women were the biological mother to a child with fragile X syndrome ($M$ age of child = 17.78 years, $SD = 6.32$). Participants were drawn from three larger studies that focused on language phenotypes associated with the FMR1 premutation or fragile X syndrome [26, 56]; these studies were linked and followed mirrored protocols for data collection of all variables of interest. The present study made use of a longitudinal convenience sample that represented a unique opportunity to analyze age-related trajectory of syntactic complexity in mothers with the FMR1 premutation across midlife. Participants completed 1–5 longitudinal assessments ($Md_n = 3, M = 2.9$), for a total of 130 observations. The number of observations across participants varied, given the inclusion of data drawn from multiple studies. For example, seven participants contributed five longitudinal observations, fifteen contributed four observations, four contributed three observations, four contributed two observations, and fifteen contributed one observation. This variability in the number of observations was due to differences in the various study designs of the larger projects from which participants were drawn, rather than attrition.\(^1\) Assessments were spaced approximately a year apart ($M = 1.24$ years, $SD = 0.56$). All mothers spoke American English as their native language and none had received a clinical diagnosis of FXTAS, per participant report. The racial identity of the sample was primarily White (91%) or Black (5%). The reported educational level of participants was a high school education or less (9%); some college (36%); a bachelor’s degree (33%); and a graduate degree (22%). FMR1 premutation status ($55–200$ CGG repeats on the 5’UTR of FMR1) was confirmed through molecular genetic testing. Recruitment methods included social media posts targeted towards families of children with fragile X syndrome, word of mouth, advertisements through the National Fragile X Foundation, referrals from other ongoing studies of fragile X syndrome being conducted at the University of South Carolina [57], and outreach through the IDDRG Research Participant Registry of the University of North Carolina at Chapel Hill.

**Procedures**

Assessments were completed in a university laboratory setting. The language assessment was the first behavioral task administered in the protocol. The entire assessment protocol, which included measures beyond those relevant to the present study, lasted approximately 3 h. Questionnaires, including a demographic form inquiring about a family history of FXTAS, were sent to participants about two weeks prior to their appointment and were completed ahead of time. The Parenting Stress Index-4 Short Form [58] and biospecimens for genetic analysis were collected at a single time point and thus were treated as time-invariant covariates in analyses. Biospecimens were collected at the end of the study visit via either buccal swab or blood sample. Participants were also provided the option to have their blood drawn by their local physician at a time that was convenient for them. All participants provided informed consent and procedures were approved by the Institutional Review Board of the University of South Carolina.

**Measures**

**Syntactic complexity**

Syntactic complexity was evaluated from language produced during the Five Minute Speech Sample [59], in which participants were asked to talk about “what kind of person their child is” and “how they get along” with their child, for five minutes without any interjections from the examiner. This sampling context is ideal for capturing syntactic skills because the prompt elicits a spontaneous, uninterrupted spoken language sample of adequate length to ensure stability of analyses and has been used for similar purposes in previous work [30, 54, 60]. The ensuing data were transcribed using the conventions of Systematic Analysis of Language Transcripts [61] by research assistants who were trained to >80% inter-rater agreement on morphemes and utterance segmentation.

---

\(^1\) Inference across the presented models did not change when cases were restricted to those with more than one data point.
on three consecutive training files. Inter-rater reliability conducted by an independent transcriber on 20% of randomly selected transcripts was at 98% for morpheme-morpheme agreement and 84% for the segmentation of utterances into C-units.

Syntactic complexity was evaluated from the transcripts using Coh-Metrix 3.0 [62], a computational linguistics and discourse processing software that integrates a variety of natural language processing tools to analyze texts, including part-of-speech taggers [63], lexicons, syntactic parsers, latent semantic analysis, and pattern classifiers [64]. Although a variety of different metrics have been used in prior research to index syntactic complexity (e.g., counts of left-branching clauses, hand-scoring methods such as IPSYN), the use Coh-Metrix has implementation advantages given it does not require specialized software, programming expertise, or laborious hand-coding or tagging. The syntactic simplicity Z score (“PCSYMz”) was used as an index of the complexity of syntactic structures. This score is a principal component-derived text complexity index based on the analysis of over 37,500 texts spanning thirteen grade levels and various genres [65, 66]. The syntactic simplicity Z score indicates the degree to which the sentences contain fewer words and use simpler syntactic structures as reflected by the number of words per sentence, the number of words before the main verb, the ratio of function words to content words, the number of words per sentence, and the syntactic similarity across sentences [66]. To facilitate interpretation, the sign of the syntactic simplicity Z score was reversed so that a higher score denoted greater syntactic complexity.

Family history of FXTAS
Information on the family history of FXTAS was collected as part of a standard demographic questionnaire. Participants responded “yes” or “no” to the question “Has anyone in your family been diagnosed with FXTAS?” A blank space was provided for participants who responded “yes” to provide information about their relationship to the diagnosed relative. This information was collected at each assessment. If a new FXTAS case in the family emerged as the study progressed, that family history was considered positive for all preceding time points.

FMR1 CGG repeat number
CGG repeat DNA analysis was conducted as part of the larger studies from which the present sample was drawn. Specifically, these data derive from the MIND Institute at the University of California Davis Health (54% of samples), Rush University Medical Center (25% of samples), and the New York State Institute for Basic Research in Developmental Disabilities (21% of samples). CGG repeat size analysis of the 5’-UTR of FMR1 was conducted on DNA derived from peripheral blood lymphocytes (Qiagen, Valencia, CA), whole blood dried blood spots [67], or buccal swabs. Polymerase chain reaction (PCR) amplification of the FMR1 CGG repeat region was conducted with Amplidex® FMR1 PCR (RUO) reagents (Asuragen, Austin, TX 78,744 USA). PCR products were analyzed by capillary electrophoresis and GeneMapper software for FMR1 allele CGG repeat sizing (ABI 3130 Genetic Analyzer, Applied Biosystems, Foster City, CA) [68]. Inter-lab reliability was evaluated on 24% of samples, where seven participants submitted samples to two of the labs and three participants submitted samples to all three labs. Intraclass correlation coefficients (ICC [1, 3]) indicated excellent reliability at 0.97 across the labs.

Covariates
Education level was collected via a standard demographic form and coded as a four-level categorical variable: ≤ high school, some college, bachelor’s degree, some graduate school or higher. This variable was included as a covariate because educational attainment is thought to represent a neuroprotective factor against the development of dementia [69] and is also associated with some measures of verbal output, such as mean length of utterance [70]. The Parenting Stress Inventory-4 Short Form (PSI-4 SF; [58]) was also collected as a covariate, given the high levels of parenting stress experienced by mothers with the FMR1 premutation [71], and the understanding that stress may contribute to vulnerability in normal and pathological aging [72]. The PSI-4 SF is a 32-item questionnaire that captures child, parent, and situational/demographic characteristics that contribute to parenting stress. This scale shows good test–retest reliability of 0.84 over 6 months, high internal consistency (α = 0.94), and high concordance when validated against the full length PSI-4 [58]. Internal consistency in the present sample was (α = 0.91). The Total Stress percentile score was used in analyses.

Data analysis
Analyses were conducted in SAS v9.4 (SAS Institute, 2013). First, descriptive statistics were computed and the variables examined for normal distribution. One case exhibited a value for the syntactic complexity variable that was an extreme outlier (3.10) relative to both the sample as a whole, as well as to the other longitudinal datapoints for that case and was thus top-coded to 1.73 (a value slightly above the next highest observation in
the sample; 1.72). Top-coding allowed for a normal distribution of the syntactic complexity outcome and also minimized undue influence of this extreme outlier on the models. Across all statistical models, age was centered at 50 years, total parenting stress percentile score was centered at the mean of 58, and CGG repeat length was centered at the mean of 97.

To address the research questions, a series of random intercept, hierarchical linear models (HLMs) were fit using PROC MIXED. In line with contemporary methodological recommendations, a model-building approach was used where an unconditional means model was first considered to provide a null baseline model. Several more gradually complex models were then estimated to consider the influence of various predictors of interest, in line with each research question [73]. At each step, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) deviance-based statistics were examined to evaluate overall improvement in model fit. All models were estimated with maximum likelihood estimation, which is a contemporary approach to handle missing data that uses all available information on each variable to optimize the overall likelihood function of the data while yielding unbiased parameter estimates [74]. Unstructured covariance matrices were specified to allow variance components to be freely estimated. Denominator degrees of freedom were calculated using the Ken-wood-Roger approximation [75]. Chronological age was nested within participant as the marker of change over time. The parenting stress and genetic variables were treated as time-invariant in the statistical models.

To investigate the first research question on change in syntactic complexity across age, the fixed effect of age was added as a predictor and fit was compared to the null, baseline model. Fixed effects for education level and parenting stress were added in a third model, but deviance-based model fit statistics did not indicate any improvement in model fit and neither variable accounted for significant variance. Thus, these covariates were not included in the final model.

The final research question on the relationship between CGG repeat length and syntactic complexity was addressed using a similar model-building process in which a series of random intercept HLMs were considered. An unconditional means model was first estimated. Then a model including the fixed effects of age and linear CGG repeat length was estimated and overall model fit was compared to the unconditional, baseline model. Finally, two nonlinear models that considered the interaction between age and CGG and the quadratic effect of CGG were estimated and evaluated, respectively [19, 54, 55]. In addition to the continuous CGG analyses, models were also run using a categorical CGG variable, with CGG length coded as low (55–89), mid-size (90–110), and high (111–200) categories, consistent with prior reports (Allen et al., 2007; Mailick et al., 2014; Sullivan et al., 2005). An analogous model-building approach was employed for this variant of the data, with unconditional baseline, main effect, and interactive models estimated and compared as they were for the continuous CGG variable. As with the first and second research questions, education level and parenting stress were probed as covariates in the models evaluated for the final research question, as were the interactions involving CGG, education, and parenting stress. Deviance-based fit statistics did not support the inclusion of either variable or their interaction with CGG in the model. Thus, these covariates were not retained in the final models.

---

**Table 1** Descriptive statistics at study entry

| Variable                                                       | M (SD) | Range         |
|---------------------------------------------------------------|--------|---------------|
| Syntactic complexity Z score, Coh-Metrix                      | 0.74 (0.58) | -0.18–3.10    |
| Range                                                         | -0.18–3.10 |               |
| Total stress percentile, Parenting Stress Index-4 Short Form  | 62.00 (20.38) |               |
| Range                                                         | 4.00–94.00 |               |
| CGG repeat length                                             | 96.82 (18.08) | 64.00–170.00 |
| Range                                                         | 64.00–170.00 |               |
| Education level, n (%)                                        |        |               |
| High school education or less                                 | 16 (36%) |               |
| Some college                                                  | 15 (33%) |               |
| Bachelor’s degree                                             | 4 (9%)  |               |
| Graduate degree                                               | 10 (22%) |               |

---

2 Sensitivity analyses indicated that the inference across the models was the same regardless of whether the influential point was retained, omitted, or top-coded.
Table 2 Descriptive statistics by family history of FXTAS

| Variable                                      | Family History of FXTAS |
|-----------------------------------------------|-------------------------|
|                                               | Negative (n = 33)       | Positive (n = 12) |
| Total number of observations                  | 90                      | 40 |
| Observations per participant, M (SD)          | 2.73 (1.63)             | 3.33 (1.30) |
| Age at entry (years), M (SD)                  | 46.88 (7.27)            | 48.10 (8.31) |
| Syntactic complexity Z score, Coh-Metrix, M (SD) | 0.69 (0.45)            | 0.88 (0.86) |
| Total stress percentile, Parenting Stress Index-4, M (SD) | 62.84 (20.76)        | 59.83 (20.08) |
| CGG repeat length, M (SD)                     | 96.30 (19.41)           | 94.14 (14.46) |
| Education level, n (%)                        |                         |               |
| High school education or less                 | 13 (39%)                | 3 (25%) |
| Some college                                  | 9 (27%)                 | 6 (50%) |
| Bachelor's degree                             | 3 (9%)                  | 1 (8%) |
| Graduate degree                               | 8 (24%)                 | 2 (17%) |

Results

Descriptive statistics

Table 1 displays descriptive statistics of the sample at study entry. Twelve participants reported a positive family history of FXTAS. Of these, the majority (75%) reported that the family member who had received a diagnosis of FXTAS was their father. Of the remaining individuals, two participants did not indicate which family member was affected and one reported their brother as the affected family member. Participants with a positive family history of FXTAS (n = 12) contributed 40 longitudinal observations and those with a negative family history (n = 33) contributed 90 longitudinal observations. The subgroups with and without positive family histories of FXTAS did not differ in age at study entry (p = 0.633), age averaged across all observations (p = 0.181), or in the number of observations per individual (p = 0.252). Table 2 shows descriptive statistics across the two subgroups at study entry.

To describe the presence of motor symptoms potentially linked to FXTAS, scores on the Tremor Disability Questionnaire [76] were examined descriptively across the two subgroups at study exit. This self-report questionnaire assesses difficulty completing daily activities due to tremor (e.g., zipping a zipper, typing shoes), with difficulty completing each activity rated on a scale of “0” (no problem), “1” (reduced efficiency), or “2” (need to modify was task is performed; task is difficult). Total scores range from 0 to 60. There were no differences in self-reported functional tremor symptoms across the family history subgroups (p = 0.806), with a mean score of 1.28 (SD = 3.78) in those without a family history and of 1.58 (SD = 3.20) in those with a family history. Therefore, functional tremor symptoms were low overall and did not appear to be elevated among the participants with a family history of FXTAS.

Age-related stability of syntactic complexity

Results indicated that, as a group, mothers with the FMR1 premutation did not exhibit significant changes in syntactic complexity across age (p = 0.292). Model results are presented in Table 3. However, when age and family history of FXTAS were considered together, results indicated that these factors interacted to affect syntactic complexity (p = 0.006; see Table 4), such that those who had a positive family history of FXTAS exhibited faster decline in syntactic complexity across age relative to those without a history of FXTAS in their family (see Fig. 1). For every year of time, on average, mothers with a positive family history of FXTAS showed a 0.05 decrease in the syntactic complexity Z score relative to those without a positive family history. Bonferroni-corrected post-hoc analyses

Table 3 HLM testing age-related change in syntactic complexity

|            | Estimate (SE) | p     |
|------------|---------------|-------|
| Fixed effects |               |       |
| Intercept  | 0.59 (0.06)   | <0.001*|
| Age        | -0.01 (0.01)  | 0.292 |
| Error variance |             |       |
| Level-1    | 0.16 (0.02)   | <0.001*|
| Intercept  | 0.08 (0.03)   | 0.005*|

Notes. Estimation method = maximum likelihood; Kenwood-Roger degrees of freedom. AIC = 177.7. BIC = 184.4
*p < 0.050.
testing group differences in syntactic complexity at 40, 45, 50, 55, and 60 years of age indicated group differences were evident at 55 years old ($t[58.7] = -2.16$, $p = 0.037$) and 60 years of age ($t[58.7] = -2.63$, $p = 0.012$), but were not significantly different at younger ages: 50 years ($t[58.7] = -0.86$, $p = 0.398$), 45 years ($t[58.7] = 0.97$, $p = 0.339$), or 40 years of age ($t[58.7] = 1.95$, $p = 0.059$).

### Table 4 HLM testing age-related change in syntactic complexity by family history of FXTAS

|                  | Estimate (SE) | p       |
|------------------|---------------|---------|
| Fixed effects    |               |         |
| Intercept        | 0.64 (0.07)   | <0.001* |
| Age              | 0.01 (0.01)   | 0.383   |
| Group            | -0.10 (0.12)  | 0.398   |
| Group*age        | -0.05 (0.02)  | 0.006*  |
| Error variance   |               |         |
| Level-1          | 0.16 (0.02)   | <0.001* |
| Intercept        | 0.06 (0.03)   | 0.011*  |

Notes. Estimation method = maximum likelihood; Kenward-Roger degrees of freedom. AIC = 173.6. BIC = 183.8.

*p < 0.050

### Fig. 1 Age-related change in syntactic complexity by family history of FXTAS

### Relationship between CGG repeat length and age-related stability of syntactic complexity

CGG repeat length was not a significant predictor of age-related change in syntactic complexity either when tested as a continuous linear, quadratic variable, or as a categorical variable, and statistical inferences regarding all fixed and random coefficients were consistent across the models. Deviance statistics indicated that the model with the continuous linear CGG term was the best fit among the set and thus results for that parameterization are provided here (see Table 5).

### Discussion

Decline in syntactic complexity is a strong predictor of the later onset of neurodegenerative disease. Through
premutation. This information could be useful in the development of methods to target prevention and detection efforts to those who are at heightened risk for age-related disease. Preserving health with age is particularly meaningful within the context of fragile X syndrome because mothers who carry the FMR1 premutation often continue to provide daily care and assistance for their children with fragile X syndrome throughout midlife.

As a group, mothers with the FMR1 premutation did not exhibit a decline in syntactic complexity across midlife. This suggests that vulnerability to neurodegenerative disease, as reflected by diminished syntactic complexity, was not generalized across all mothers with the FMR1 premutation. However, results indicated that mothers who have a history of FXTAS in their family may be particularly vulnerable. On average, participants who had a relative with FXTAS showed a 0.05 decrease in the syntactic complexity Z score for each year passed relative to those without a diagnosed relative. Although research on family history of FXTAS as a risk factor is sparse, our results are consistent with, and extend through an objective measure, those of Chonchaiya et al. [32], who found that women whose fathers had FXTAS were more likely to report balance and menopausal symptoms than women whose fathers did not have FXTAS. Thus, across these two independent reports and both self-report and direct-assessment measures, there is converging evidence that women with the FMR1 premutation who have a family history of FXTAS may be at elevated risk for clinical involvement. The functional impact of the declining syntactic complexity observed in the present study is unclear, although this type of language production difficulty can be perceived by patients as “word finding problems” or “brain fog” [77], both of which have been reported anecdotally by women with the FMR1 premutation.

It is notable that the difference related to family history of FXTAS did not emerge until older ages. The syntactic complexity of the mothers with a positive family history of FXTAS did not diverge from that of those with a negative family history until the mothers reached their mid-50 s. The finding of age effects is consistent with prior cross-sectional analyses indicating that older age is correlated with increased severity of various symptoms in women with the FMR1 premutation [19, 29, 30]. The present study contributes to the scant longitudinal data on the FMR1 premutation, bolstering the hypothesis that the expression of certain aspects of the FMR1 premutation phenotype are modulated by age.

Future directions of this work could include investigation of potential interactions with other age-related aspects of the FMR1 premutation phenotype, such as early menopause associated with fragile X-associated primary ovarian insufficiency (FXPOI). It is unclear from the present literature whether reduced syntactic complexity is associated with menopause. However, a potential link is plausible given that other cognitive-linguistic skills, such as verbal fluency, appear to be negatively related to menopause [78–80]. Chonchaiya et al. [32] reported increased menopausal symptoms in women whose fathers had FXTAS, and therefore, it is possible that the syntactic complexity decline in those with a family history of FXTAS could be related to hormonal differences occurring within this subgroup. This hypothesis should be explored in future research.

Given that prior research has shown that diminished syntactic complexity is linked with neurodegenerative diseases such as Alzheimer’s disease and dementia, it is possible that the decline in syntactic complexity observed in the present study marks vulnerability for age-related neurodegeneration of some type [46, 48–51]. Additional research is needed to determine whether the observed decline in syntactic complexity marks vulnerability for FXTAS specifically or for more generalized premutation-associated neurodegeneration that is distinct from FXTAS. Additionally, the mechanisms by which family history of FXTAS is associated with loss of syntactic complexity are yet unknown and should be explored in future research. Regardless, the results of this study do suggest that mothers who have a family history of FXTAS may be at increased risk for pathological aging. This raises questions about pathologic processes associated with FXTAS that may be shared within families, beyond CGG repeat length. It is possible that the familial risk patterns observed here may reflect a common set of secondary genetic or other vulnerabilities that predispose the participants and their family members to FXTAS. For example, the APOE ε4 allelotype is a genetic risk factor for dementia-producing diseases that also appears to

| Table 5 | HLM testing CGG repeat as a predictor of age-related change in syntactic complexity |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Continuous CGG model (linear) | Fixed effects | Intercept | 0.56 (0.06) | <0.001* | Age | −0.01 (<0.01) | 0.502 | CGG | <0.01 (<0.01) | 0.547 | CGG*age | <0.01 (<0.01) | 0.933 |
| Error variance | Level-1 | 0.16 (0.03) | <0.001* | Intercept | 0.07 (0.03) | 0.009* |

*Notes. Estimation Method = maximum likelihood; Kenwood-Roger degrees of freedom, AIC = 178.2. BIC = 189.1

*p < 0.050
influence FXTAS risk [81]. Environmental risk factors may also be more likely to be shared among relatives. The present study examined education level as an environmental factor that might relate to age-related decline in syntactic complexity, but no relationship was detected. Future studies may explore other factors that may be shared within families and have been linked to risk for neurodegenerative disease, including diet, physical activity, access to healthcare, and vascular disease [82–85].

Adopting a family design in future studies may be helpful in identifying the mechanisms that contribute to risk for developing FXTAS within families.

Although preliminary, the present study has potential clinical implications that may pave the way for future research. It is common for women with *FMR1* premutation who have seen a family member experience FXTAS to express concerns about their own risk for health problems as they get older. Counseling and prevention efforts for these women have been hampered by poor understanding of risk factors for age-related symptom aggravation, including the role of family history. While the clinical implications from this study are preliminary, findings suggest that mothers with a family history of FXTAS may be at increased risk for age-related decline relative to those without a family history. Clinical monitoring, particularly as individuals reach late midlife, may be useful in establishing baseline performance and detecting the early signs of degeneration. It may also be advisable to take a more proactive approach to prevention, given that it is known that about 15% of women with the *FMR1* premutation will develop FXTAS [13, 27] and many others will experience increased symptom expression with age, regardless of FXTAS status [19, 22, 29–31]. There are several modifiable factors that can be targeted to preserve cognitive health with aging, such as exercise, smoking cessation, maintaining social engagement, and clinical management of medical problems like hypertension and depression [86, 87]. It is likely that these factors would also promote healthy aging within the context of the *FMR1* premutation. Stress management may also be particularly important for mothers with the *FMR1* premutation, who experience high levels of parenting stress and may experience increased risk as a consequence [16, 71, 88, 89].

The present study also has numerous strengths. One notable strength is the use of a longitudinal design, which allowed us to model change within the same cohort of individuals across time. Most prior studies of age-related change in the *FMR1* premutation have relied on cross-sectional data, which provide only a snapshot into time and are insufficient for delineating longitudinal trajectories. Another advantage of the use of a repeated measures design is that it requires fewer participants to achieve statistical power relative to a between-participants design, as it allows researchers to disentangle variance due to individual differences from error variance in the model. Thus, although participants with a positive family history of FXTAS consisted of a relatively small subgroup of 12 participants, these participants contributed a total of 40 longitudinal observations to analysis. Future replication in larger samples will inform generalizability across more nuanced dimensions not examined here, such as variation related to background gene effects or environmental factors (e.g., diet, smoking).

Another strength is the use of automatic language processing software, Coh-Metrix, to index syntactic complexity. Although a variety of other methods for indexing syntactic complexity exist, the implementation advantages of automated natural language processing software are substantial because this method does not require programming expertise or time-consuming hand-coding or tagging. Such an approach could be easily scalable for potential clinic-based applications in the future. For example, modern automated transcription and language processing software would allow patients to provide a brief language sample that could be transcribed and analyzed for syntactic complexity within minutes, making it feasible to monitor changes in syntactic complexity during routine check-ups. Our focus on syntactic complexity is also a strength, given the strong connection between the reduced syntactic complexity and the later development of neurodegenerative disease in other populations, as well as evidence that language production deficits represent some of the earliest detectable signs of disease, sometimes emerging before other cognitive deficits are able to be detected using traditional standardized measures [34–36]. Because this study capitalized on a rare corpus of longitudinal language samples from women with the *FMR1* premutation originally gathered for other purposes, we did not have access to other measures of neuropsychological performance to complement the cognitive-linguistic data. The inclusion of cognitive test performance measures in future work could inform the cognitive factors that relate to the loss of syntactic complexity within women with the *FMR1* premutation. Likewise, we did not have access to FXTAS outcome data on the participants themselves and therefore cannot draw conclusions as to whether the observed decline in syntactic complexity reflects general neurodegeneration associated with the *FMR1* premutation genotype versus risk for FXTAS specifically. Finally, the inclusion of other *FMR1*-related indices in future work, such as messenger RNA, Fragile X Mental Retardation Protein, or information on mosaicism or activation ratio, would also enhance understanding of potential *FMR1* associations beyond CGG.
Our use of participant self-report data to evaluate FXTAS family history is a limitation. Direct assessment of FXTAS in family members would have been more reliable, as we cannot rule out the possibility that a relative had FXTAS that had yet to be clinically identified. Another limitation of relying on participant report is that this method assumes that the participant is informed of their extended family members’ medical problems. Additionally, because of the late onset of FXTAS, it is possible that some participants will have a family member develop FXTAS in the future. The challenge of an incomplete observation period could have resulted in the inclusion of some individuals in the “negative family history” subgroup who may eventually go on to have a relative diagnosed with FXTAS, which could have attenuated the observed effects.

Regarding the sample, it also should be noted that all participants were mothers caring for a child with fragile X syndrome, and therefore, caution is needed when generalizing patterns to the broader population of women with the FMR1 premutation. Studies aimed at understanding FMR1 premutation-associated risk as manifested in mothers of children with fragile X syndrome are highly important because clinical problems in mothers impact outcomes for both the mother and her children. However, mothers with the FMR1 premutation represent a subgroup of individuals who, on average, will show higher CGG repeat lengths than the broader population of females with the FMR1 premutation [90] and may be at heightened risk for FXTAS and the expression of other premutation-associated phenotypes as a result. Mothers of children with fragile X syndrome also experience high levels of parenting stress which is also associated with increased vulnerability for symptom expression [16, 71, 88, 89]. In this study, neither parenting stress, indexed via the PSI-4 SF, nor the interaction between parenting stress and CGG repeat length were significant predictors of syntactic complexity in any of our analyses. However, follow-up studies are needed to obtain a more comprehensive understanding of the potential impact of parenting a child with fragile X syndrome on age-related patterns, including the inclusion of more varied indices of objective and subjective stress and indicators of child disability severity. Potential CGG-stress interactions should be pursued in future research with larger samples, as we may have been underpowered to detect such an effect. Additionally, our focus on mothers of children with fragile X syndrome may have resulted in ascertainment bias of participants who were more intimately familiar with the effects of fragile X syndrome within families and the full spectrum of fragile X-associated conditions, including FXTAS. If so, this may be viewed as a weakness (decreased generalizability to the larger population) or a strength (knowledge of fragile X-associated conditions may have been enhanced the validity of the FXTAS variable in this study). Finally, it should be noted that the participants enrolled in this study were primarily of White racial identity, which is a limiting factor in generalizing findings to the larger population of individuals with the FMR1 premutation. Inadequate minority representation in participant samples remains a challenge in research involving neurodevelopmental disorders [91], including fragile X syndrome [92], and should be explicitly addressed in future work.

In conclusion, the results of the present study suggest that family history of FXTAS may be associated with heightened risk for neurodegenerative disease, as marked by accelerated age-related decline in syntactic complexity. Thus, the present study sheds light on the family history of FXTAS as a potential personalized risk factor that could prove useful for identifying those who are most at risk to better target prevention efforts, potentially even before the onset of symptoms. Preserving the health of mothers with the FMR1 premutation as they age is important for both the outcomes of the mothers and for their children with fragile X syndrome.

Abbreviations
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FMR1: Fragile X Mental Retardation-1; FXTAS: Fragile X-associated tremor/ataxia syndrome; HLMs: Hierarchical linear models; PCR: Polymerase chain reaction; PSI-SF: Parenting Stress Inventory-4 Short Form.

Acknowledgements
We would like to thank the women who participated in this study.

Authors’ contributions
JK was responsible for the conceptualization of the study. JK wrote the original draft and AF, CM, MM, AJT, and LA reviewed and edited the manuscript. JK, AF, and CM were responsible for the data curation, methodology, and formal analysis. All authors supported the interpretation of the data and read and approved the final manuscript.

Funding
This research was supported by the National Institutes of Health: R03HD098291, R21DC017804, F32DC013934 (PI: Klusek); R01HD024356 and P50HD103526 (PI: Abbeduto); and the Research Participant Registry Core of the Carolina Institute for Developmental Disabilities (P50HD103573).

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate.
The study was approved by the Institutional Review Board at the University of South Carolina. Informed written consent was obtained from all participants. Consent for publication. Not applicable.

Declarations
Competing interests
LA has received funding to develop and implement outcome measures for clinical trials from F. Hoffman-LaRoche, Ltd., Roche TCRC, Inc, Neuren Pharmaceuticals Limited, Inc, and the LuMind IDSC Foundation. AJT has received funding to develop and implement outcome measures from Fulcrum Therapeutics. MM serves as the chair of the Scientific Advisory Board of the
John Merck Fund Developmental Disabilities Program. The authors have no other relevant conflicts of interest to disclose.

Author details
1 Department of Communication Sciences and Disorders, Arnold School of Public Health, University of South Carolina, 1705 College Street, SC 29208, Columbia, USA. 2 Department of Psychology, University of South Carolina, 1512 Pendleton Street Columbia, SC 29208, USA. 3 Waisman Center, University of Wisconsin-Madison, 1500 Highland Ave, Madison, WI 53705, USA. 4 Department of Psychiatry and Behavioral Sciences and MIND Institute, University of California Davis Health, 2825 50th Street, Sacramento, CA 95817, USA.

Received: 30 April 2021 Accepted: 2 January 2022 Published online: 14 January 2022

References
1. Maddalena A, Richards CS, McGinniss MJ, Brothman A, Desnick RJ, Grier RE, et al. Technical standards and guidelines for fragile X: the first of a series of disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics, Genet Med. 2001;3(2):200–5.
2. Seltzer MM, Baker MW, Hong J, Maenner M, Greenberg J, Mandel D. Prevalence of CGG repeats in the FMR1 gene in a US population-based sample. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(5):589–97.
3. Maenner MJ, Baker MW, Broman KW, Tian J, Barnes JK, Atkins A, et al. FMR1 CGG expansions: prevalence and sex ratios. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(2):66–73.
4. Lubin HA, Stevenson RE, Schwartz CE, Fragile X and X-linked intellectual disability: four decades of discovery. The American Journal of Human Genetics. 2012;90(4):579–90.
5. Kraan CM, Goddler DE, Amor DJ. Epigenetics of fragile X syndrome and fragile X-related disorders. Dev Med Child Neurol. 2019;61(2):121–7.
6. Goehl D, Sripada L, Praapatit P, Currim F, Roy M, Singh K, et al. Expression of expanded FMR1-CGG repeats alters mitochondrial miRNAs and modulates mitochondrial functions and cell death in cellular model of FXTAS. Free Radic Biol Med. 2021;165:100–10.
7. Uslin K, Kumari D. Repeat-mediated epigenetic dysregulation of the FMR1 gene in the fragile X-related disorders. Front Genet. 2015;6:192.
8. Allen E, Sullivan A, Marcus M, Small C, Dominguez C, Epstein M, et al. Examination of reproductive aging milestones among women who carry the FMR1 premutation. Hum Reprod. 2007;22(8):2142–52.
9. Sullivan SD, Welt C, Sherman S, editors. FMR1 and the continuum of primary ovariyan insufficiency. Semin Reprod Med; 2011: © Thieme Medical Publishers.
10. Coffey SM, Cook K, Tartaglia N, Tassone F, Nguyen DV, Pan R, et al. Expanded clinical phenotype of women with the FMR1 premutation. Am J Med Genet A. 2008;146B(10):1009–16.
11. Winarni TI, Chonchaiya W, Sumekar TA, Ashwood P, Morales GM, Tassone F, et al. Immune-mediated disorders among women carriers of fragile X premutation alleles. Am J Med Genet A. 2012;158(10):2473–81.
12. Moraghad A, Page D, Brilliant M, Baker MW, Greenberg J, Hong J, et al. Data-driven phenotype discovery of FMR1 premutation carriers in a population-based sample. Science Advances. 2019;5(8):eaav7195.
13. Rodriguez-Revenga L, Madrigal I, Pagonabarraga J, Xuncia M, Badeucas N, Kulisvsky J, et al. Penetrance of FMR1 premutation associated pathologies in fragile X syndrome families: Eur J Hum Genet. 2009;17(10):1359–62.
14. Leehey MA, Legg W, Tassone F, Hagerman R. Fibromyalgia in fragile X mental retardation 1 gene premutation carriers. Rheumatology (Oxford). 2011;50(12):2233–6.
15. Roberts JE, Tonnsen BL, McCary LM, Ford AL, Golden RN, Bailey DB. Trajectory and predictors of depression and anxiety disorders in mothers with the FMR1 premutation. Biol Psychiatry. 2016;79(10):850–7.
16. Roberts JE, Bailey DB, Mankowski J, Ford A, Weisenfeld LA, Heath TM, et al. Mood and anxiety disorders in females with the FMR1 premutation. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(1):130–9.
17. Allen EG, Charen K, Hipp HS, Stubeck L, Amin A, He W, et al. Clustering of comorbid conditions among women who carry an FMR1 premutation. Genet Med. 2020;1–9.
18. Kenna HA, Tartter M, Hall SS, Lightbody AA, Nguyen Q, de los Angeles CP, et al. High rates of comorbid depressive and anxiety disorders among women with premutation of the FMR1 gene. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2013;162B(8):872–8.
19. Kluske J, Hong J, Sterling A, Berry-Kravis E, Mallick MR. Inhibition deficits are modulated by age and CGG repeat length in carriers of the FMR1 premutation allele who are mothers of children with fragile X syndrome. Brain Cogn. 2020;139:105511.
20. Shelton AL, Cornish KM, Kraan CM, Lozano R, Bui M, Fielding J. Executive dysfunction in female FMR1 premutation carriers. The Cerebellum. 2016;15(5):565–9.
21. Kraan CM, Hocking DR, Bradshaw JL, Fielding J, Cohen J, Georgiou-Karistianis N, et al. Neurobehavioural evidence for the involvement of the FMR1 gene in female carriers of fragile X syndrome. Neurosci Biobehav Rev. 2013;37(3):522–47.
22. Moser C, Schmitt L, Schmidt J, Fairchild A, Kluske J. Response inhibition deficits in women with the FMR1 premutation are associated with age and fall risk. Brain Cogn. 2021;148:105675.
23. Losh M, Kluske J, Martin GE, Sideris J, Parlier M, Piven J. Defining genetically meaningful language and personality traits in relatives of individuals with fragile X syndrome and relatives of individuals with autism. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(6):660–8.
24. Kluske J, Schmidt J, Fairchild AJ, Porter A, Roberts JE. Altered sensitiv- ity to social gaze in the FMR1 premutation and pragmatic language competence. J Neurodev Disord. 2017;9:31.
25. Kluske J, Ruber A, Roberts JE. Impaired eye contact in the FMR1 premutation is not associated with social anxiety or the broad autism phenotype. Clin Neuropsychol. 2018;32:1337–52.
26. Kluske J, Fairchild AJ, Roberts JE. Vagal tone as a putative mechanism for pragmatic competence: an investigation of carriers of the FMR1 premutation. J Autism Dev Disord. 2019;49:197–208.
27. Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syn- drome—features, mechanisms and management. Nat Rev Neurol. 2016;12(7):403–12.
28. Jacquesmont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, et al. Penetration of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. The Journal of the American Medi- cal Association. 2004;306:461–568.
29. Goodrich-Hunsaker NJ, Wong LM, McLennan Y, Srivastava S, Tassone F, Harvey D, et al. Young adult female fragile X premutation carriers show age- and genetically-modulated cognitive impairments. Brain Cogn. 2011.
30. Sterling AM, Mallick M, Greenberg J, Warren SF, Brady N. Language dysfunctions in females with the FMR1 premutation. Brain Cogn. 2013;82(1):84–9.
31. Goodrich-Hunsaker NJ, Wong LM, McLennan Y, Tassone F, Harvey D, Rivera SM, et al. Adult female fragile X premutation carriers exhibit age- and CGG repeat length-related impairments on an attentionally-based enumeration task. Front Hum Neurosci. 2011;5.
32. Chonchaiya W, Nguyen D, Au J, Campos L, Berry-Kravis E, Lohse K, et al. Examination of reproductive aging milestones among women who carry the FMR1 premutation. The Journal of the American Med- ical Association. 2010;294:1915–1926.
33. Chonchaiya W, Nguyen D, Au J, Campos L, Berry-Kravis E, Lohse K, et al. Clinical involvement in daughters of men with fragile X-associated tremor ataxia syndrome. Clin Genet. 2010;78(1):58–46.
34. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging. 2005;26(3):341–7.
35. Mueller KD, Kosciuk RL, Herrmann BP, Johnson SC, Turkstra LS. Declines in connected language are associated with very early mild cogni- tive impairment: results from the Wisconsin Registry for Alzheimer’s Prevention. Front Aging Neurosci. 2018;10:437.
36. McCullough KC, Bayles KA, Boulton ED. Language performance of individuals at risk for mild cognitive impairment. J Speech Lang Hear Res. 2019;62(3):706–22.
37. Taler V, Phillips NA. Language performance in Alzheimer’s disease and mild cognitive impairment: a comparative review. J Clin Exp Neuropsychol. 2008;30(5):501–56.

38. Barker MS, Nelson NL, Robinson GA. Idea formulation for spoken language production: the interface of cognition and language. J Int Neuropsychol Soc. 2020;26(2):226–40.

39. Mueller KD, Hermann B, Mecollari J, Turkstra LS. Connected speech and language in mild cognitive impairment and Alzheimer’s disease: a review of picture description tasks. J Clin Exp Neuropsychol. 2018;40(9):917–39.

40. Ye Z, Zhou X. Executive control in language processing. Neurosci Biobehav Rev. 2009;33(8):1168–77.

41. Bayles K, McCullough K, Tomaoka CK. Cognitive-communication disorders of MCI and dementia: definition, assessment, and clinical management: Plural Publishing, 2018.

42. Rogers SL, Friedman RB. The underlying mechanisms of semantic memory loss in Alzheimer’s disease and semantic dementia. Neuropsychologia. 2008;46(1):12–21.

43. Nippold MA, Cramond PM, Hayward-Mayhew C. Spoken language production in adults: examining age-related differences in syntactic complexity. Clin Linguist Phon. 2014;28(3):195–207.

44. Kemper S, Sumner A. The structure of verbal abilities in young and older adults. Psychol Aging. 2001;16(2):312–22.

45. Sung JE. Age-related changes in sentence production abilities and their relation to working-memory capacity: evidence from a verb-final language. PLoS One. 2015;10(4):e0119424.

46. Kemper S, Thompson M, Marquis J. Longitudinal change in language production: effects of aging and dementia on grammatical complexity and semantic content. 2001.

47. Kemper S, Herman R, Lian C. Age differences in sentence production. J Gerontol B Psychol Sci Soc Sci. 2003;58(S5):P260–8.

48. Pakhomov S, Chacon D, Wicklund M, Gundel J. Computerized assessment of syntactic complexity in Alzheimer’s disease: a case study of Iris Murdoch’s writing. Behav Res Methods. 2011;43(1):136–44.

49. Illes J. Neurolinguistic features of spontaneous language production dissociate three forms of neurodegenerative disease: Alzheimer’s, Huntington’s, and Parkinson’s. Brain Lang. 1998;63(4):628–42.

50. Bates E, Harris C, Marchman V, Wulfeck B, Kitchevsky M. Production of complex syntax in normal ageing and Alzheimer’s disease. Lang Cognit Process. 1995;10(5):487–539.

51. Sand Aronsson F, Kuhlmann M, Jelic V, Ostberg P. Is cognitive impairment associated with reduced syntactic complexity in writing? Evidence from automated text analysis. Aphasiology. 2020:1–14.

52. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, et al. Infant social avoidance predicts autism but not anxiety in fragile X syndrome. Front Psych. 2019;10:199.

53. McNamara DS, Graeser AC, McCrory PD, Edmunds L, Zubieta J-K, et al. Hormonal environment affects cognition independent of age during the menopausal transition. J Clin Endocrinol Metab. 2012;97(9):E1686–94.

54. Silva F, Rodriguez-Revejaga L, Madrigal I, Alvarez-Mora MI, Oliva R, Millà M. Cognitive computational phenotypes. Sci Rep. 2017;7:2674.

55. Miller JS, Chapman RS. Systematic Analysis of Language Transcripts (SALT) Madison, WI: University of Wisconsin-Madison, Waisman Center, 2008. p. Computer Software.

56. McMinn MA, Graeser AC, McCrory PD, Cameron LA, Zubieta J-K, et al. Gender differences in sentence production and their relation to working-memory capacity: evidence from a verb-final language. PLoS One. 2015;10(4):e0119424.

57. Rogers SL, Friedman RB. The underlying mechanisms of semantic memory loss in Alzheimer’s disease and semantic dementia. Neuropsychologia. 2008;46(1):12–21.

58. Rogers SL, Friedman RB. The underlying mechanisms of semantic memory loss in Alzheimer’s disease and semantic dementia. Neuropsychologia. 2008;46(1):12–21.
84. Landgrave-Gómez J, Mercado-Gómez O, Guevara-Guzmán R. Epigenetic mechanisms in neurological and neurodegenerative diseases. Front Cell Neurosci. 2015;9:58.
85. Marras C, Canning CG, Goldman SM. Environment, lifestyle, and Parkinson’s disease: implications for prevention in the next decade. Mov Disord. 2019;34(6):801–11.
86. Livingston G, Sommerlad A, Orgeta V, Costa-Freda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The Lancet. 2017;390(10113):2673–734.
87. Fratiglioni L, Qiu C. Prevention of common neurodegenerative disorders in the elderly. Exp Gerontol. 2009;44(1):46–50.
88. Hartley SL, Seltzer MM, Hong J, Greenberg JS, Smith L, Almeida D, et al. Cortisol response to behavior problems in FMR1 premutation mothers of adolescents and adults with fragile X syndrome: a diathesis-stress model. Int J Behav Dev. 2012;36:53–61.
89. Smith LE, Seltzer MM, Greenberg JS. Daily health symptoms of mothers of adolescents and adults with fragile X syndrome and mothers of adolescents and adults with autism spectrum disorder. J Autism Dev Disord. 2012;42(9):1836–46.
90. Kraan CM, Bui QM, Field M, Archibald AD, Metcalfe SA, Christie LM, et al. FMR1 allele size distribution in 35,000 males and females: a comparison of developmental delay and general population cohorts. Genet Med. 2018.
91. West EA, Travers JC, Kemper TD, Liberty LM, Cote DL, McCollow MM, et al. Racial and ethnic diversity of participants in research supporting evidence-based practices for learners with autism spectrum disorder. The Journal of Special Education. 2016;50(3):151–63.
92. Johnson VA, Edwards KKA, Sherman SL, Stephens LD, Deer-Smith MH. Decisions to participate in fragile X and other genomics-related research: Native American and African Am

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.