Published in final edited form as:

Brain Cogn. 2013 June ; 82(1): 84–89. doi:10.1016/j.bandc.2013.02.009.

Language Dysfluencies in Females with the *FMR1* Premutation

Audra M. Sterling¹, Marsha Mailick¹, Jan Greenberg¹, Steven F. Warren², and Nancy Brady²

¹Waisman Center, University of Wisconsin-Madison

²Life Span Institute, University of Kansas

Abstract

Recent evidence suggests that there are age-related neurocognitive implications for fragile X premutation carriers, including deficits in executive function, and that such deficits are more common in male than female premutation carriers. The purpose of the current study is to examine one aspect of executive function, language dysfluencies, in a group of 193 women with the premutation, and to contrast them with a comparison group (mothers of children with autism spectrum disorders). Our results demonstrate a linguistic profile in the female premutation carriers characterized by dysfluencies associated with deficits in organization and planning, with a clear impact of age. The comparison group, matched on both age and education level, did not demonstrate the age effect. Our results suggest dysfluencies could be an early indicator of cognitive aging in some female premutation carriers, and could be used to target early intervention.

1. Introduction

The *FMR1* gene is associated with a continuum of clinical involvement including fragile X syndrome (FXS), fragile X-associated tremor ataxia syndrome (FXTAS), and fragile X primary ovarian insufficiency (FXPOI). These syndromes occur when there is a defect in the *FMR1* gene, located on the long arm of the X chromosome (Verkerk et al., 1991). The gene is located in the 5' untranslated region (locus Xq27.3). *FMR1* directs cells to produce the fragile X mental retardation protein (FMRP), which is believed to play an important role in typical brain development and functioning (Darnell et al., 2004; Rogers, Wehner, & Hagerman, 2001). The *FMR1* gene is made up of trinucleotide (CGG) repeats, and elevated repeats beyond 55 signify either the premutation (55–200 repeats) or the full mutation (> 200 repeats).

Specifically, the full mutation of fragile X syndrome is a neurodevelopmental disorder, and the most common cause of inherited intellectual disability. It occurs when an individual has more than 200 repeats, thus signifying the full mutation (Bailey, Hatton, Skinner, & Mesibov, 2001; Hagerman, 2002). In the case of the full mutation, the elevated repeat sequence reduces or shuts down the methylation of FMRP. However, in most individuals

© 2013 Elsevier Inc. All rights reserved.

Correspondence regarding this manuscript should be addressed to Audra M. Sterling, Waisman Center, University of Wisconsin-Madison, 1500 Highland Ave., Room 481, Madison, WI 53705-2280. asterling@waisman.wisc.edu.

Audra M. Sterling, Waisman Center, University of Wisconsin-Madison; Marsha Mailick, Waisman Center, University of Wisconsin-Madison; Jan S. Greenberg, School of Social Work, University of Wisconsin-Madison; Steven F. Warren, Life Span Institute, University of Kansas; Nancy Brady, Life Span Institute, University of Kansas.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with the premutation, FMRP levels are within normal limits, although *FMR1* mRNA levels are between 2 and 10 times what is seen in unaffected individuals (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor, Gane, Godfrey, & Hagerman, 2000).

The full mutation is relatively rare, affecting approximately 1 in every 2500 males, and 1 in every 4000–6000 females (Crawford et al., 2001; Fernandez-Carvajal, Walichiewicz, Xiaosen, Pan, Hagerman, & Tassone, 2009; Hagerman, 2008). However, the premutation is much more common, with 1 in every 260–813 males and 1 in every 113–259 females estimated to have the premutation (Hagerman, 2008). A recent paper reported the first population-based US study of the prevalence of the premutation, which found that 1 in 151 females and 1 in 468 males had the premutation (Seltzer et al., 2012). Whereas initially, premutation carriers were believed to be unaffected, within the last ten years, research has uncovered the impact of the premutation, including early menopause in 20–28% of premutation carrier women (FXPOI), and a late-onset neurodegenerative disorder (FXTAS), which affects approximately 40% of male and 8% of female premutation carriers (Jacquemont, Hagerman, Leehey, Hall, Levine, Brunberg, et al., 2004). FXTAS is associated with tremors, gait ataxia, short-term memory and executive function impairments (Bourgeois, Coffey, Rivera, Hessel, Gane, Tassone et al., 2009).

Both males and females with the premutation have been found to have clinical risk. Recent research has indicated that there is an aging-related set of cognitive symptoms that are associated with the premutation in males, resulting in either FXTAS or a milder phenotype (Cornish, Li et al., 2008; Hay, 2008; Kogan & Cornish, 2010). Notably, impairments in working memory and executive function starting in the 30s are associated with greater risk for FXTAS (Brega, Goodrich, Bennett, Hessel, Engle, Leehey et al., 2008). Kogan and Cornish (2010) examined executive function in asymptomatic male premutation carriers. A subset of their participants had clinically significant elevations in everyday working memory, with IQs in the average range. The authors note a cognitive profile of executive dysfunction within premutation males that can reliably distinguish premutation carriers from males with typical cognitive performance.

The majority of the research on the cognitive profile of the premutation has focused on male carriers. However, one recent study examined cognitive impairments in females with the premutation (Goodrich-Hunsaker, Wong, McLennan, Srivastava, Tassone, Harvey et al., 2011). They found subtle although statistically significant impairments in cognitive function, measured by a magnitude comparison task. These effects were significantly related to age (range 20–42 years), as well as biological variables (i.e., CGG repeat length). This finding motivated the increasing need for research in this area, given the mounting evidence of neurocognitive dysfunction, which has a longer developmental trajectory than originally anticipated.

The purpose of the present paper is to examine one aspect of neurocognitive dysfunction, language dysfluencies, in female premutation carriers. Past research has shown language dysfluencies to be an indicator of executive functioning deficits, particularly deficits in organization and planning (Chapman et al., 1992; Coehlo, Liles, & Duffy, 1994; VanLeer & Turkstra, 1999). Dysfluencies in language production are defined as “disturbances in the flow of information that result from any one of a number of language and non-language behaviors that impair continuity of language sequencing and information content” (Shadden, 1998, p.52). While dysfluencies occur in every-day language, the nature and degree of dysfluencies differentiate individuals with typical development from clinical populations (Shadden, 1998; Turkstra, Fuller, Youngstrom, Green, & Kuegeler, 2004). Dysfluencies in language are a hallmark feature of neurocognitive disorders associated with deficits in

executive function, such as Parkinson's disease (Rochester, Hetherington, Jones, Nieuwboer, Willems, Kwakkel, & Van Wegan, 2004) and Alzheimer's disease (Swanberg, Tractenberg, Mohs, Thal, & Commings, 2004). McDowd and colleagues examined verbal fluency in healthy aging, as well as adults with Parkinson's and Alzheimer's (McDowd, Rozek, Hoffman, Lyons, Pahwa, Burns, & Kemper, 2011). They found that regardless of the task used, the abnormal pattern of fluency was evident in the adults with Alzheimer's and Parkinson's diseases.

Aside from the biological manifestations of being a premutation carrier, some female carriers are mothers of children with the full mutation of FXS. Children with disabilities in general and specifically those with FXS and autism often exhibit challenging behavioral phenotypes, which can lead to high levels of parental stress (Abbeduto, Seltzer, Shattuck, Krauss, Orsmond, & Murphy, 2004; Blacher & McIntyre, 2006; Eisenhower, Baker, & Blacher, 2005; Smith, Hong, Seltzer, Greenberg, Almeida, & Bishop, 2010). Therefore in order to control for the impact of high levels of stress due to raising a child with a disability, in the present study, we included a comparison group of mothers of children with a similar behavioral phenotype as FXS, i.e., autism spectrum disorders.

Given the emerging cognitive phenotype associated with the premutation, and the limited body of research on female premutation carriers, the current study focused on adult female premutation carriers. We assessed language dysfluencies through commonly used discourse measures collected within a five-minute language sample. We were interested in whether female premutation carriers would exhibit a linguistic profile marked by language dysfluencies, and how this would compare to a group of mothers of similarly-aged individuals with children with a diagnosis of autism spectrum disorders, matched on age and education. Additionally given the relationship noted in past literature between age and cognitive decline in premutation carriers, we were interested in the relationship between age and language dysfluencies, as well as a biological variable, CGG repeat length. We had two research questions. First, is the language phenotype of fXPCs characterized by dysfluencies? Second, is this profile consistent in women without the premutation who also are caregivers for children with developmental disabilities?

2. Method

2.1 Participants

Participants included 363 women, with a mean age of 46 years (25 to 79 years), including 193 fragile X premutation carriers (fXPCs), and 170 members of the comparison group. The fXPC group consisted of premutation carrier mothers of children with the full mutation of FXS, and were part of a larger study, Family Adaptation to FXS (Bailey, Raspa, Olmsted, & Holiday, 2008; Seltzer, Barker, Greenberg, Hong, Coe, & Almeida, 2012; Sterling, Barnum, Skinner, Warren, & Fleming, 2012; Warren, Brady, Sterling, Fleming, & Marquis, 2010). Because the present analysis is focused on mothers with the premutation, mothers participating in the Family Adaptation Study who either had the full mutation or a normal *FMRI* gene were not included in the analysis.

The comparison group included mothers of children with autism spectrum disorders, and were part of a larger study focused on the family impact of autism, Adolescents and Adults with Autism (Barker et al., in press; Seltzer et al., 2011). The two groups were matched overall on maternal age and education, as well as the age of their child (see Table 1). The participants were recruited through the Waisman Center at the University of Wisconsin-Madison and the Lifespan Institute at the University of Kansas. Data collection was completed via in-person assessments for the comparison group, and via in-person

assessments as well as phone interviews for the fXPCs. The institutional review boards at both universities approved the study. Written informed consent was obtained prior to testing.

2.2 Language Characteristics

Language characteristics were coded from the Five Minute Speech Sample (FMSS; Magana, Goldstein, Karno, Miklowitz, Jenkins, & Falloon, 1986). Mothers were instructed to speak about their son or daughter for five minutes without interruption. The specific instructions are as follows:

I'd like to hear your thoughts and feelings about (son/daughter) in your own words and without my interrupting with any questions or comments. When I ask you to begin, I'd like you to speak for five minutes, telling me what kind of person (son/daughter) is and how the two of you get along together. After you being to speak, I prefer not to answer any questions until after the five minutes are over. Do you have any questions before I begin?

The language sample was recorded via audio recorders, and later transcribed and coded for language characteristics using the Systematic Analysis of Language Transcripts (SALT; Miller & Chapman, 2000). Transcription guidelines were based on the conventions stated in the SALT manual. Utterances were segmented according to terminal intonation contour and/or pauses of 2–3s, following the procedures of Miller (1981, p. 14). Reliability was monitored on a continuous basis. The coders were trained to 85% agreement or better on five transcripts prior to beginning independent work. A second transcriber checked transcripts. The minimum reliability was set at 85%; average agreement for reliability was 87%.

The samples were coded for language dysfluencies, including orphans, revisions, repetitions, and filled pauses, based on the conventions set forth in Dollaghan and Campbell (1992) and the SALT manual. An orphan is defined as an utterance that is not completed (i.e., abandoned utterance). Repetitions and revisions were coded at the part word, word, and phrase level. Part word revisions and repetitions were quite rare, with word and phrase level being more common. We created a total dysfluency variable, which included orphans, repetitions, and revisions; it was created by summing the three individual variables, yielding one total score. This is a common summary variable used in language research (Turkstra et al., 2004). Filled pauses are lexical units that do not carry any specific meaning, e.g., um, uh, ah. Definitions and examples are provided in Table 2.

The following is an excerpt from an fXPC, including instances of filled pauses, orphans and repetitions. Language dysfluencies are noted in parentheses; the names of the participants have been changed.

And (we we uh uh did not) Stacy and I did not (orphan). (Uh) you know we butted heads a lot. And (uh) she did not like the control that I exerted. I did not like the way that you know she was (you know) not (uh) acting (uh) appropriately. And (uh you know) there were times that you know we had (uh) a lot of (uh you know uh) problem/s (uh) together. But (uh) doesn't mean that Stacy wasn't always an incredibly loving person. And we were incredibly loving family. And (uh you know we) we did have a lot of time that was (you know) just wonderful.

2.3 Molecular Analysis

fXPC mothers provided past records of molecular genetics analysis, including CGG repeat size or provided a blood sample that was analyzed by Kimball Genetics, Inc. Given the potential for lab-to-lab variability in assays, we restricted the analysis with CGG repeats and

our dependent variables to the 109 samples measured by Kimball Genetics. The mean CGG repeat size was 95 (SD = 18.80).

3. Results

3.1 Within-Group Analysis

In order to answer our research questions on both dysfluencies and group differences, we completed several sets of analyses. We first ran partial correlations in the fXPC sample between the dysfluency variables and maternal age, maternal education, and CGG repeat length, controlling for the amount of talk (i.e., number of utterances) in order to ensure that differences were not due to variability in the amount of language produced within the five minutes. The language variables were not significantly correlated with maternal education or CGG repeat length. However, there was a significant correlation between all of the language dysfluency variables with maternal age, with the exception of revisions (see Table 3 and Figure 1 for one example). In other words, the older the fXPCs, the more dysfluent their language.

We also ran the correlations with maternal age and education for the comparison group, controlling for the amount of talk. Much like the fXPCs, we did not find significant associations between maternal education and the language dysfluency variables. However, in contrast to the fXPCs, there were no significant correlations between age and language dysfluencies in the comparison group (see Figure 2 for one example).

3.2 Group Differences

In order to examine group differences in the language variables, we completed independent samples *t*-tests between the fXPCs and the comparison group on each of the dysfluency variables. Table 4 displays the means and significance values for each *t*-test completed. For all of the variables, the fXPCs had a significantly more dysfluent pattern of speech compared to the comparison group.

4. Discussion

The current study examined language dysfluencies in fXPCs. The purpose was to characterize the language phenotype in terms of dysfluencies, and to explore the relationship between dysfluencies and age, as well as a biological variable. We had two main research questions: (1) Is the language phenotype of fXPCs characterized by dysfluencies? (2) Is this profile consistent in women without the premutation who were also caregivers of children with developmental disabilities? We found significant group differences on all of the measures of language dysfluencies, with the same trend. The fXPCs had a more dysfluent pattern of language compared to the mothers of similarly-aged children with autism spectrum disorders. Additionally there was a significant effect of age for the majority of the dysfluency measures for the fXPCs, with an increase in dysfluencies in older ages. However, this age effect was not observed for the comparison group. The dysfluency variables were not related to CGG repeat length.

The impact of age on language dysfluency adds to the growing body of literature indicating an age-related cognitive phenotype noted in both male and female fXPCs, including deficits in executive function and working memory (Goodrich-Hunsaker et al., 2011). The research on male fXPCs has demonstrated an aging-related set of cognitive symptoms that either results in FXTAS or a milder phenotype. In terms of non-FXTAS female fXPCs, the Goodrich-Hunsaker et al. (2011) study noted impairments in cognitive function that were related to both age and CGG repeat length. While we did not find significant associations between CGG repeat length and our variables, we did find a significant impact of age. The

dysfluencies measured in this study are indicators of deficits in organization and planning, aspects of executive function. Deficits in executive function are noted in individuals with FXTAS; it could be that some female fXPCs, much like some male fXPCs, demonstrate an age-related decline in cognitive symptoms regardless of diagnosis of FXTAS. Future research is needed to investigate the biological mechanisms that contribute to these deficits in executive dysfunction in female fXPCs.

In light of the recent behavioral findings, there have been a handful of studies examining brain structure as well as the integrity of white matter tracts in the premutation. Studies of brain volume in the premutation carriers have generally found reduced brain volume in premutation carriers (Cohen et al., 2006; Murphy et al., 1999) and decreased cerebellar gray matter (Adams et al., 2007). Two DTI studies in the premutation carriers have demonstrated decreased white matter microstructure of the cerebellar white matter tracts (Hashimoto et al., 2011) and the corpus callosum and cingulum bundle (Wang et al., 2012). Therefore, there appear to be atypicalities of the brain structure in premutation carriers. Pathology of the cerebellum may be pronounced in the premutation carriers, and may be highly related to age-related motor and cognitive symptoms. Notably Wang et al. (2012) found widespread age-related deterioration in structural connectivity in older carriers with FXTAS, as well as subtle white matter structural changes in the young premutation carriers without FXTAS. This is particularly relevant to the findings from this study, given the broad age range of the participants. Both DTI studies included only male premutation carriers. Given the current findings, future research should replicate these important DTI studies, including female premutation carriers with and without FXTAS.

The fXPCs had a more dysfluent pattern of language compared to mothers of children with autism spectrum disorders, and the age effect was only found in the fXPCs. All of the women in this study were mothers of children with a developmental disability. We know that the life-course of raising a child with a disability results in physical and mental health problems above and beyond what is seen in the typical population (Smith, Seltzer, & Greenberg, 2011). By including mothers of children with autism spectrum disorders, we were able to control for one environmental factor, the stress associated with parenting a child with a developmental disability, in order to examine if the observed language phenotype is specifically related to the *FMR1* gene, or rather the impact of stressful caregiving.

This study may have important clinical implications. The measure used in this study is a short five-minute language sample that can be administered either in person or over the phone, in any location (Hastings, Daley, Burns & Beck, 2006; Hastings & Lloyd, 2007). It is easy to administer, and relatively easy to transcribe and analyze. We found in this sample that it is sensitive to age in fXPCs, and detected significant group differences when compared to mothers of similar aged children with autism spectrum disorders. Future studies should explore the relationship of these dysfluencies with other aspects of the cognitive phenotype in order to determine the pattern of dysfluencies observed is an early indicator of cognitive decline in some fXPCs.

This study represents the first examination of the language phenotype in female fXPCs; the large sample size and broad age range allows for an examination of the nature of dysfluencies. However, there are limitations. The women in this study were mainly well-educated, white women. Future research should include a more diverse sample in terms of SES and racial/ethnic composition. We did not have information on FXTAS status, which should be included in future studies; additionally a more comprehensive profile of cognitive abilities would greatly enhance this set of findings, and should be included in future research. There are several important additional crucial areas of future direction. A

longitudinal examination of the changes in cognitive function is needed in female fXPCs in order to see if, much like male fXPCs, there is a diverging pathway with some female fXPCs experiencing cognitive decline and/or FXTAS, and others remaining relatively unaffected.

There is a growing body of evidence indicating age-related impairments in executive function related to the *FMR1* gene. Recent research has demonstrated the effects of cognitive training programs for improving executive functioning in individuals with mild and severe disabilities as well as people without disabilities (Brehmer, Westerberg, & Backman, 2012; Roughan & Hadwin, 2011). It is possible that such cognitive training programs would be of benefit to fXPCs as they age. Measures that are relatively easy to collect such as the FMSS used in this study could allow for easier screening and identification. While we cannot say based on the findings from this study that the dysfluencies noted are early indicators of FXTAS, future work should involve measures designed to allow for early detection and treatment of either FXTAS or other age-related cognitive symptoms.

Acknowledgments

We are extremely appreciative of the families who participated in this study, without whom our research would not have been possible. We would like to thank the National Fragile X Foundation for providing informational materials to share with families. We would also like to thank Leonard Abbeduto and Lyn Turkstra for their contributions to the language analyses.

Funding

This research is supported in part by a grant from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development to the University of North Carolina (P30 HD003100-S1) to support a Fragile X Research Center at three additional sites (Research Triangle Institute International, the University of Kansas, and the University of Wisconsin-Madison), which is led by Donald B. Bailey, Jr. The present analyses were based on data collected at the UW-Madison Waisman Center site (M. Mailick, PI) and the University of Kansas site (S. Warren, PI). Additionally, this research was supported by a grant from the National Institute on Aging (R01 AG08768 to M. Mailick). We are also grateful for the support we received from the Kansas and Waisman Center Core Grants (P30 HD002528, J. Colombo, PI; P30 HD03352, M. Mailick, PI).

References

- Abbeduto L, Seltzer MM, Shattuck PT, Krauss MK, Orsmond GI, Murphy MM. Psychological well-being and coping in mothers of youths with autism, Down syndrome, or fragile X syndrome. *American Journal of Mental Retardation*. 2004; 109:237–254. [PubMed: 15072518]
- Adams JS, Adams PE, Nguyen D, Brunberg JA, Tassone F, Zhang W, Koldewyn K, Rivera SM, Grigsby J, Zhang L, DeCarli C, Hagerman PJ, Hagerman RJ. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). *Neurology*. 2007; 69:851–859. [PubMed: 17724287]
- Bailey DB, Hatton DD, Skinner M, Mesibov G. Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *Journal of Autism and Developmental Disorders*. 2001; 31:165–174. [PubMed: 11450815]
- Bailey DB Jr, Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: Findings from a national parent survey. *American Journal of Medical Genetics*. 2008; 146a:2060–2069. [PubMed: 18570292]
- Barker, ET.; Seltzer, MM.; Smith, LE. Chronic parenting stress in mothers of adolescents and adults with autism: Vulnerability and resilience. In: Martin, CR.; Preedy, VR.; Patel, VB., editors. *The Comprehensive Guide to Autism*. London: UK: Springer; (in press).
- Blacher J, McIntyre LL. Syndrome specificity and behavior disorders in young adults with intellectual disability: Cultural differences in family impact. *Journal of Intellectual Disability Research*. 2006; 50:184–198. [PubMed: 16430730]

- Bourgeois J, Coffey S, Rivera SM, Hessel D, Gane LW, Tassone F, Greco C, Finucane B, Nelson L, Berry-Kravis E, Grigsby J, Hagerman PJ, Hagerman RJ. Fragile X premutation disorders – expanding the psychiatric perspective. *Journal of Clinical Psychiatry*. 2009; 70(6):852–862. [PubMed: 19422761]
- Brega AG, Goodrich G, Bennett RE, Hessel D, Engle K, Leehey MA, Bounds LS, Paulich MJ, Hagerman RJ, Hagerman PJ, Cogswell JB, Tassone F, Reynolds A, Kookan R, Kenny M, Grigsby J. The primary cognitive deficit among males with fragile X-associated tremor/ataxia syndrome (FXTAS) is a dysexecutive syndrome. *Journal of Clinical and Experimental Neuropsychology*. 2008; 30(8):853–869. [PubMed: 18608667]
- Brehmer Y, Westerberg H, Backman L. Working-memory training in younger and older adults: Training gains, transfer, and maintenance. *Frontiers in Human Neuroscience*. 2012; 6:1–7. [PubMed: 22279433]
- Chapman SB, Culhane KA, Levin HS, Harward H, Mendelsohn D, Ewing-Cobbs L, et al. Narrative discourse after closed head injury in children and adolescents. *Brain and Language*. 1992; 43:42–65. [PubMed: 1643511]
- Coelho, CA.; Liles, BZ.; Duffy, RJ. Cognitive framework: A description of discourse abilities in traumatically brain-injured adults. In: Bloom, RL.; Obler, LK.; DeSanti, S.; Ehlich, JS., editors. *Discourse Analysis and Applications*. Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc.; 1994. p. 95–110.
- Cohen S, Masyn K, Adams J, Hessel D, Rivera S, Tassone F, Brunberg J, DeCarli C, Zhang L, Cogswell J, Loesch D, Leehey M, Grigsby J, Hagerman PJ, Hagerman RJ. Molecular and imaging correlates of the fragile X-associated tremor/ataxia syndrome. *Neurology*. 2006; 67:1426–1431. [PubMed: 17060569]
- Cornish KM, Li L, Kogan CS, Jacquemont S, Turk J, Dalton A, Hagerman RJ, Hagerman PJ. Age-dependent cognitive changes in carriers of the fragile X syndrome. *Cortex*. 2008; 44:628–636. [PubMed: 18472033]
- Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: Human genome epidemiology review. *Genetics in Medicine*. 2001; 3:359–371. [PubMed: 11545690]
- Darnell J, Warren S, Darnell R. The fragile X mental retardation protein, FMRP, recognizes G-quartets. *Mental Retardation and Developmental Disabilities Research Reviews*. 2004; 10:49–52. [PubMed: 14994288]
- Dollaghan CA, Campbell TF. A procedure for classifying disruptions in spontaneous language samples. *Topics in Language Disorders*. 1992; 12:56–68.
- Fernandez-Carvajal I, Walichiewicz P, Xiaosen X, Pan R, Hagerman PJ, Tassone F. Screening for expanded alleles of the FMR1 gene in blood spots from newborn males in a Spanish population. *Journal of Medical Diagnostics*. 2009; 11:324–329.
- Goodrich-Hunsaker NJ, Wong LM, McLennan Y, Srivastava S, Tassone F, Harvey D, Rivera SM, Simon TJ. Young adult female fragile X premutation carriers show age- and genetically-modulated cognitive impairments. *Brain and Cognition*. 2011; 75:255–260. [PubMed: 21295394]
- Hagerman PJ. The fragile X prevalence paradox. *Journal of Medical Genetics*. 2008; 45:498–499. [PubMed: 18413371]
- Hagerman, RJ. The physical and behavioral phenotype. In: Hagerman, RJ.; Hagerman, PJ., editors. *Fragile X syndrome: Diagnosis, treatment, and research*. 3rd Edition. Baltimore, MD: The Johns Hopkins University Press; 2002. p. 3–109.
- Hashimoto R, Srivastava S, Tassone F, Hagerman RJ, Rivera SM. Diffusion tensor imaging in male premutation carriers of the fragile X mental retardation gene. *Movement Disorders*. 2011; 26:1329–1336. [PubMed: 21484870]
- Hastings RP, Daley D, Burns C, Beck A. Maternal distress and expressed emotion: Cross-sectional and longitudinal relationships with behavior problems of children with intellectual disabilities. *American Journal on Mental Retardation*. 2006; 111:48–61. [PubMed: 16332156]
- Hastings RP, Lloyd T. Expressed emotion in families of children and adults with intellectual disabilities. *Mental Retardation and Developmental Disabilities Research Reviews*. 2007; 13:339–345. [PubMed: 17979206]

- Hay DA. Fragile X – A challenge to the models of the mind and to best clinical practice. *Cortex*. 2008; 44:626–627. [PubMed: 18472032]
- Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, Zhang L, Jardini T, Gane LW, Harris SW, Herman K, Grigsby J, Greco CM, Berry-Kravis E, Tassone F, Hagerman PJ. Penetrance of the fragile X-Associated tremor/Ataxia syndrome in a premutation carrier population. *The Journal of the American Medical Association*. 2004; 291:460–469.
- Kogan CS, Cornish KM. Mapping self-reports of working memory deficits to executive dysfunction in fragile X mental retardation 1 (FMR1) gene premutation carriers asymptomatic for FXTAS. *Brain and Cognition*. 2010; 73:236–243. [PubMed: 20573435]
- Loesch DZ, Bui QM, Huggins RM, Mitchell RJ, Hagerman RJ, Tassone F. Transcript levels of the intermediate size or grey zone fragile X mental retardation 1 alleles are raised and correlate with the number of CGG repeats. *Journal of Medical Genetics*. 2007; 44:200–204. [PubMed: 16905681]
- Loesch DZ, Khaniani MS, Slater HR, Rubio JP, Bui QM, Kotschet K, Horne M. Small CGG repeat expansion alleles of FMR1 gene are associated with parkinsonism. *Clinical Genetics*. 2009; 76:471–476. [PubMed: 19796183]
- Magana AB, Goldstein MJ, Karno M, Miklowitz DJ, Jenkins J, Falloon IRH. A brief method for assessing expressed emotion in relatives of psychiatric patients. *Psychiatry Research*. 1986; 17:203–212. [PubMed: 3704028]
- McDowd J, Rozek E, Hoffman L, Lyons KE, Pahwa R, Burns J, Kemper S. Understanding verbal fluency in healthy aging, Alzheimer's disease, and Parkinson's disease. *Neuropsychology*. 2011; 25(2):210–225. [PubMed: 21381827]
- Miller, JF. Assessing language production in children. Baltimore, MD: University Park Press; 1981.
- Miller, J.; Chapman, R. Systematic Analysis of Language Transcripts. Research Version 6.1. Madison: Language Analysis Lab, University of Wisconsin; 2000. [Computer software].
- Murphy DGM, Mentis MJ, Pietrini P, Grady CL, Moore CJ, Horwitz B, Hinton V, Dobkin CS, Schapiro MB, Rapoport SI. Premutation female carriers of fragile X syndrome: A pilot study on brain anatomy and metabolism. *Journal of the American Academy on Child and Adolescent Psychiatry*. 1999; 38:1294–1301.
- Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems A, Kwakkel G, Van Wegen E. Attending to the task: Interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Archives of Physical Medicine and Rehabilitation*. 2004; 85:1578–1585. [PubMed: 15468014]
- Rogers SJ, Wehner EA, Hagerman R. The behavioral phenotype in fragile X: Symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioral Pediatrics*. 2001; 22:409–417. [PubMed: 11773805]
- Roughan L, Hadwin JA. The impact of working memory training in young people with social, emotional and behavioural difficulties. *Learning and Individual Differences*. 2011; 21:759–764.
- Seltzer MM, Baker MW, Hong J, Maenner M, Greenberg JS, Mandel D. Prevalence of CGG expansions of the FMR1 gene in a US population-based sample. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*. 2012
- Seltzer MM, Barker ET, Greenberg JS, Hong J, Coe C, Almeida D. Differential sensitivity to life stress in FMR1 premutation carrier mothers of children with fragile X syndrome. *Health Psychology*. 2012
- Seltzer, MM.; Greenberg, JS.; Taylor, JL.; Smith, LE.; Orsmond, GI.; Esbensen, A.; Hong, J. Adolescents and adults with autism spectrum disorders. In: Amaral, DG.; Dawson, G.; Geschwind, D., editors. *Autism spectrum disorders*. New York, NY: Oxford University Press; 2011. p. 241-252.
- Shadden, BB. Sentential/surface-level analysis. In: Cherney, LR.; Shadden, BB.; Coelho, CA., editors. *Analyzing discourse in communicatively impaired adults*. Gaithersburg, MD: Aspen Publishers, Inc.; 1998.

- Smith LE, Hong J, Seltzer MM, Greenberg JS, Almeida DM, Bishop S. Daily experiences among mothers and adolescents and adults with ASD. *Journal of Autism and Developmental Disorders*. 2010; 40:167–178. [PubMed: 19655239]
- Smith LE, Seltzer MM, Greenberg J. Daily health symptoms of mothers of adolescents and adults with fragile X syndrome and mothers of adolescents and adults with autism spectrum disorder. *Journal of Autism and Developmental Disabilities*. 2011 Epub ahead of print.
- Sterling A, Barnum L, Skinner D, Warren SF, Fleming K. Parenting young children with and without fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. 2012; 117:194–206. [PubMed: 22716262]
- Swanberg MM, Tractenberg RE, Mohs R, Thal LJ, Cummings JL. Executive dysfunction in Alzheimer disease. *Archives of Neurology*. 2004; 61:556–560. [PubMed: 15096405]
- Tassone F, Hagerman RJ, Chamberlain WD, Hagerman PJ. Transcription of the FMR1 gene in individuals with fragile X syndrome. *American Journal of Medical Genetics*. 2000; 97:195–203. [PubMed: 11449488]
- Tassone F, Hagerman RJ, Taylor AK, Gane LW, Godfrey TE, Hagerman PJ. Elevated levels of FMR1 mRNA in carrier males: A new mechanism of involvement in the fragile X syndrome. *American Journal of Human Genetics*. 2000; 66:6–15. [PubMed: 10631132]
- Turkstra LS, Fuller T, Youngstrom E, Green K, Kuegeler E. Conversational fluency and executive function in adolescents with conduct disorder. *Neuropsychologia*. 2004; 2:70–85.
- VanLeer E, Turkstra L. Effect of narrative elicitation procedure on cohesion and coherence in traumatically brain-injured adolescents. *Journal of Communication Disorders*. 1999; 32:327–349. [PubMed: 10498013]
- Verkerk A, Pieretti M, Sutcliffe JS, Fu Y, Kuhl D, Pizzuti A, Reiner O, Richards S, Victoria M, Zhang F, Eussen B, van Ommen G, Blonden L, Riggins G, Chastain J, Kunst C, Galjaard H, Caskey CT, Nelson D, Oostra B, Warren S. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*. 1991; 65:905–914. [PubMed: 1710175]
- Wang JY, Hessler DH, Hagerman RJ, Tassone F, Rivera SM. Age-dependent structural connectivity effects in fragile X premutation. *Archives of Neurology*. 2012; 69(4):482–489. [PubMed: 22491193]
- Warren SF, Brady N, Sterling AM, Fleming K, Marquis J. The role of maternal responsivity in the development of young children with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. 2010; 115:63–84.

Highlights

We examined language dysfluencies in female premutation carriers (fXPCs).

fXPCs had more language dysfluencies compared to the comparison group.

Language dysfluencies and age were significantly and positively correlated in fXPCs.

Language dysfluencies could be an early indicator of cognitive aging in fXPCs.

Figure 1.
Relationship between age and dysfluencies in fXPCs.

Figure 2.
Relationship between age and dysfluencies in comparison group.

Table 1

Participant Information

	FXPCs (n = 193)		Autism (n = 170)		t	p
	Mean	SD	Mean	SD		
Maternal Age	46.93	8.76	46.62	7.59	.37	.71
Maternal Education	3.17	.66	3.05	.77	1.49	.14
Child Age	17.01	8.53	17.73	6.04	.83	.41

Note. Maternal Education, 3 = Some College/BA

Table 2

Definitions and Examples of Language Dysfluencies

Type of Dysfluency	Definition	Example
Orphans	An utterance that is abandoned. The speaker does not complete his/her thought/utterance but has not been interrupted.	<i><u>I wanted to</u></i> We're watching a movie.
Repetition	The exact duplication of a linguistic unit of any length, from a word to an entire clause, with no other utterances besides fillers [such as um or uh] allowed in between.	He said <i><u>he said</u></i> I could go to the store.
Revision	Reliably recognizable modifications of an utterance already produced by the speaker. The revision may be to correct an error or to add, delete, or change information.	<i><u>The girl, I mean,</u></i> the lady left.
Total Dysfluency	Summary Variable including orphans, repetitions, and revisions	
Filled Pause	Words or vocalizations that fill in a pause, e.g., um, ah, oh.	She is <i><u>uh</u></i> a very <i><u>uh</u></i> lovely girl.

Note. Examples drawn from Turkstra et al., 2004

Table 3

Partial Correlations of Maternal Age with Dysfluencies

	fXPCs Maternal Age		Comparison Group Maternal Age	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Total Dysfluencies	.21**	.00	-.02	.81
Orphans	.16*	.03	-.01	.26
Revisions	.12	.11	.05	.53
Repetitions	.24**	.00	-.07	.34
Filled Pauses	.17*	.02	-.13	.11

Table 4

Group Differences on Dysfluency Variables

	FXPCs		Comparison Group		Group Differences	
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i>
Total Dysfluencies	21.60	13.63	16.85	10.40	3.75	.00
Orphans	1.50	1.73	.50	.84	7.01	.00
Revisions	13.06	8.62	10.97	6.47	2.63	.01
Repetitions	7.05	6.17	5.38	5.62	2.69	.01
Filled Pauses	32.56	15.13	25.15	15.41	4.62	.00