Language dysfluencies in females with the FMR1 premutation

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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, Warren, & Darnell, 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 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 et al., 2000).

The full mutation is relatively rare, affecting approximately 1 in every 2500 males, and 1 in every 4000–6000 females (Crawford, Acuna, & Sherman, 2001; Fernandez-Carvajal et al., 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, Barker, and Hong et al., 2012; Seltzer, Barker and Greenberg 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 (FPXO), and a late-onset neurodegenerative disorder (FXTAS), which affects approximately 40% of male and 8% of female premutation carriers (Jacquemont et al., 2004). FXTAS is associated with tremors, gait ataxia, short-term memory and executive function impairments (Bourgeois 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 et al., 2008; Hay, 2008; Kogan & Cornish, 2010). Notably, impairments in working memory and executive function starting in the 30’s are associated with greater risk for FXTAS (Brega 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 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; Coelho, 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 everyday language, the nature and degree of dysfluencies differentiate individuals with typical development from clinical populations (Shadden, 1998; Turkstra, Fuller, Youngstrom, Green, & Ruegeler, 2004). Dysfluencies in language are a hallmark feature of neurocognitive disorders associated with deficits in executive function, such as Parkinson’s disease (Rochester et al., 2004) and Alzheimer’s disease (Swanberg, Trachtenberg, Mohs, Thal, & Commings, 2004). McDowd and colleagues examined verbal fluency in healthy aging, as well as adults with Parkinson’s and Alzheimer’s (McDowd et al., 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 et al., 2004; Blacher & McIntyre, 2006; Eisenhower, Barch, Greenberg et al., 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 FMR1 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, Seltzer, & Smith, 2013; 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 et al., 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 2–3 s, 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.

2.1. Participants

Participants included 363 women, with a mean age of 46 years (25–79 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 et al., 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 FMR1 gene were not included in the analysis.

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Table 1

<table>
<thead>
<tr>
<th></th>
<th>FXPCs (n = 193)</th>
<th>Autism (n = 170)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>46.93</td>
<td>46.62</td>
<td>7.59</td>
<td>.37</td>
</tr>
<tr>
<td>Maternal education</td>
<td>3.17</td>
<td>3.05</td>
<td>.77</td>
<td>1.49</td>
</tr>
<tr>
<td>Child age</td>
<td>17.01</td>
<td>17.73</td>
<td>6.04</td>
<td>.83</td>
</tr>
</tbody>
</table>

Note: Maternal education, 3 = Some college/BA.
The following is an excerpt from an IFPC, including instances of pauses, repetitions, and revisions. 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) did have a lot of time that was (you know) just wonderful.

Table 2: Definitions and examples of language dysfluencies.

<table>
<thead>
<tr>
<th>Type of dysfluency</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphans</td>
<td>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.</td>
<td>I wanted to/go to the store.</td>
</tr>
<tr>
<td>Repetition</td>
<td>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.</td>
<td>He said he said I could go to the store.</td>
</tr>
<tr>
<td>Revision</td>
<td>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.</td>
<td>The girl, I mean, the lady left.</td>
</tr>
<tr>
<td>Total dysfluency</td>
<td>Summary variable including orphans, repetitions, and revisions.</td>
<td>She is a very lovely girl.</td>
</tr>
</tbody>
</table>

Note: Examples drawn from Turkstra et al., 2004.

In order to examine group differences in the language variables, we completed independent samples t-tests between the IFPCs and the comparison group.

Table 3: Partial correlations of maternal age with dysfluencies.

<table>
<thead>
<tr>
<th></th>
<th>IFPCs</th>
<th>Comparison group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>Maternal age</td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>r</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Total dysfluencies</td>
<td>.21*</td>
<td>.00</td>
</tr>
<tr>
<td>Orphans</td>
<td>.16*</td>
<td>.03</td>
</tr>
<tr>
<td>Revisions</td>
<td>.12</td>
<td>.11</td>
</tr>
<tr>
<td>Repetitions</td>
<td>.24*</td>
<td>.00</td>
</tr>
<tr>
<td>Filled pauses</td>
<td>.17</td>
<td>.02</td>
</tr>
</tbody>
</table>

Fig. 1. Relationship between age and dysfluencies in IFPCs.
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, Srivastava, Tassone, Hagerman, & Rivera, 2011) and the corpus callosum and cingulum bundle (Wang, Hessl, Hagerman, Tassone, & Rivera, 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. 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. 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.

The current study may have important clinical implications. The measure used in this study is a short 5-min 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

### Table 4

<table>
<thead>
<tr>
<th>fXPCs</th>
<th>Comparison group</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total dysfluencies</td>
<td>21.60</td>
<td>13.63</td>
</tr>
<tr>
<td>Orphans</td>
<td>1.50</td>
<td>1.73</td>
</tr>
<tr>
<td>Revisions</td>
<td>13.06</td>
<td>8.62</td>
</tr>
<tr>
<td>Repetitions</td>
<td>7.05</td>
<td>6.17</td>
</tr>
<tr>
<td>Filled pauses</td>
<td>12.56</td>
<td>15.13</td>
</tr>
</tbody>
</table>

Fig. 2. Relationship between age and dysfluencies in comparison group.
allows for an examination of the nature of dysfluencies. However, there are limitations. The women in this study were 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 (Breherm, 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 FXAS, future work should involve measures designed to allow for early detection and treatment of either FXAS or other age-related cognitive symptoms.

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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 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.

References


