

An Analysis of Challenging Behavior, Comorbid Psychopathology, and Attention-Deficit/Hyperactivity Disorder in Fragile X Syndrome.

Isabel Newman

Geraldine Leader

June L. Chen

Arlene Mannion

National University of Ireland, Galway

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Corresponding author: Geraldine Leader, Ph.D., Irish Centre for Autism and Neurodevelopmental Research, School of Psychology, National University of Ireland, Galway, Ireland. Tel: 00353 49 3434, Fax: 00353 91 521355

**Abstract**

The present study sought to investigate the relationship between challenging behavior, comorbid psychopathology, and Attention-Deficit/Hyperactivity Disorder (AD/HD) in Fragile X Syndrome (FRAX). Additionally, this study sought to examine how such disorders are predicted by gender, presence of Autism Spectrum Disorder (ASD), and presence of Intellectual Disability (ID). A total of 47 children and adolescents with FRAX were assessed. Results revealed high levels of challenging behavior and AD/HD symptoms within the sample, with some participants exhibiting symptoms of comorbid psychopathology. Further analysis revealed that challenging behavior and comorbid psychopathology were positively correlated, with stereotypy correlating most strongly with comorbid psychopathology. In addition, ASD was found to predict challenging behavior, and gender was found to predict AD/HD symptoms. The implications of these findings are discussed.

*Keywords:* Fragile X syndrome, challenging behavior, comorbid psychopathology, Attention-Deficit/Hyperactivity Disorder, comorbidity

An Analysis of Challenging Behavior, Comorbid Psychopathology, and Attention-Deficit/Hyperactivity Disorder in Fragile X Syndrome.

## 1. Introduction

Fragile X Syndrome (FRAX) is one of the most common causes of inherited intellectual disability (ID) in males and to a lesser extent, females (Cornish, Turk, & Hagerman, 2008). FRAX is caused by the silencing of the Fragile X Mental Retardation 1 (FMR1) gene which affects the production of FMR1 mRNA and in turn disturbs Fragile X Mental Retardation Protein (FMRP) production (Hagerman, 2008). The resultant FRAX phenotype exhibited involves a varied spectrum of symptoms (Hagerman & Hagerman, 2002).

The prevalence of FRAX has been assessed in a number of population-based studies. In a screening of new-born males, Coffee et al. (2009) found that 7 of 576 males screened positive for FRAX, revealing a FRAX incidence of 1 in 5,161 males. The prevalence of FRAX in females has not been calculated (Coffee et al., 2009); however two studies have been conducted examining the prevalence of the FMR1 pre-mutation in females. Crawford, Acuña, and Sherman (2001) estimated that 1 in every 246 – 461 females are carriers of the pre-mutation, whilst Rousseau, Rouillard, Morel, Khandjian, and Morgan (1995) estimated this figure to be 1 in every 259 females tested.

The expression of FRAX varies in accordance with a number of individual factors such as FMR1 mutation status, gender, presence of ID, and presence of autism spectrum disorder (ASD). This has led Hagerman & Hagerman (2002) to characterise FRAX as a ‘spectrum of involvement’. Within this spectrum, the molecular status of the FMR1 mutation (full mutation, pre-mutation, FMR1 mosaicism) has a significant impact upon the presentation of FRAX, especially with regards to ID (Hagerman & Hagerman, 2002).

The FMR1 full mutation is associated with an 85% incidence of ID in males and 25% incidence of ID in females (Hagerman & Hagerman, 2002; Loesch, Huggins, & Hagerman, 2004). A number of physical features associated with the full mutation are observed, especially in males. These include large ears, long narrow faces, hyperextensible finger joints, and abnormal connective tissue structure (Hagerman & Hagerman, 2002; Hull & Hagerman, 1993). In contrast to the high incidence of ID seen in the full mutation, carriers of the FMR1 pre-mutation typically have normal to near-normal IQ (Tassone et al., 2000). Whilst those with the FMR1 pre-mutation may not present with ID, a number of associated problems may be exhibited such as learning deficits, social anxiety, and social withdrawal (Hagerman & Hagerman, 2002).

FMR1 mosaicism falls somewhere between the FMR1 full mutation and FMR1 pre-mutation and describes individuals with FRAX who have both full and pre-mutation cell expansion (Nolin, Glicksman, Houck, Brown, & Dobkin, 1994). Whilst intellectual functioning in mosaic males has been found to be similar to that of full mutation males (Rousseau et al., 1994), mosaic males have been found to exhibit fewer deficits in adaptive functioning than males with the full mutation (Cohen et al., 1996). This would suggest that mosaic FRAX males may have a better prognosis than males with the full mutation.

The expression of FRAX is mediated not only by FMR1 mutation status and associated presence and severity of ID, but also by the individual factors of gender and presence of ASD. The gender of the individual with FRAX impacts significantly upon the expression of this syndrome due to the fact that FRAX is caused by a mutation on the X chromosome (Hessl et al., 2001). Females are protected from FRAX to some degree due to the presence of one unaffected X chromosome (Hessl et al., 2001). As a result, intellectual functioning in such females may not be impaired, with ID typically ranging from mild ID to no significant impairment (Bennetto & Pennington, 1996; Hagerman & Sobesky, 1989). In

contrast, males are often more severely affected than females and may present with ID in the moderate to severe range (Bennetto & Pennington, 1996; Hagerman & Sobesky, 1989).

ASD is a further condition found to commonly co-occur with FRAX. Whilst only 4% of ASD cases are believed to be associated with FRAX (Belmonte & Bourgeron, 2006), it has been estimated that 35% of young males with FRAX meet the diagnostic criteria for ASD (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). Research has investigated the impact of comorbid ASD in FRAX by comparing individuals with comorbid ASD to those with FRAX only. Such research has reported lower IQ (Hagerman et al., 1986), greater deficits in adaptive functioning (Turk & Graham, 1997), and greater deficits in socialisation (Hernandez et al., 2009) in those with comorbid ASD when compared to those with FRAX only. This research suggests that presence of comorbid ASD in FRAX may result in a poorer prognosis. The above research demonstrates that the expression of FRAX is dependent upon the complex interaction of a number of individual factors. It is not surprising therefore, that the behavioral phenotype of FRAX is also highly varied. The classic behavioral phenotype has been described by Hagerman and Hagerman (2002) as involving issues with challenging behavior, comorbid psychopathology, and symptoms of Attention-Deficit/Hyperactivity Disorder (AD/HD).

Within this behavioral phenotype, challenging behavior has been found to be a common co-occurring condition. Challenging behaviors such as aggression towards others, self-injurious behavior (SIB), and stereotypy have been reported to be highly prevalent in FRAX. Bailey, Raspa, Olmsted, and Holiday (2008) estimate that 38% of males and 14% of females with the FMR1 full mutation engaged in aggressive behavior. A nationwide study conducted by Symons et al. (2010) found that 41% of males and 16% of females with the FMR1 full mutation engaged in SIB. This study also found that the onset of SIB occurred around the age of three years, with no gender differences found regarding the age of onset

reported. Repetitive and stereotyped behavior has also been noted as posing a significant issue in FRAX. A study examining repetitive and stereotyped behavior in FRAX was conducted by Hagerman et al. (1986). This study, consisting of a sample of 50 males, found that 88% of participants engaged in repetitive and stereotyped behavior.

Psychopathology is a further condition found to co-occur with FRAX with disorders such as anxiety and depression being prevalent (Tranfaglia, 2011). The behavioral expression of anxiety in FRAX may include poor eye-contact, gaze aversion, and shyness (Tranfaglia, 2011). Moreover, anxiety may manifest itself in the form of challenging behavior such as SIB and aggression towards others in this population (Boyle & Kaufmann, 2010). A parent survey conducted by Bailey et al. (2008) reported that 70% of males and 22% of females with the FMR1 full mutation experienced anxiety. The same study found that 12% of males and 22% of females with the FMR1 full mutation exhibited symptoms of depression. An additional study conducted by Cordiero, Ballinger, Hagerman, and Hessler (2011) examined the incidence of anxiety disorders in a sample of 97 participants between the ages of 5 and 33 years of age. Results revealed that 86% of males and 77% of females met the criteria for an anxiety disorder, with social anxiety and specific phobias reported to be the most common disorders. Older age and comorbid ASD were associated with an increased prevalence of anxiety within the sample.

The most commonly diagnosed comorbid condition in FRAX however is AD/HD (Tranfaglia, 2011). High levels of AD/HD are typically seen in early childhood. As the individual matures, symptoms of AD/HD are found to decrease, although deficits in attention may persist (Tranfaglia, 2011). In a national parent survey, Bailey et al. (2008) found that 66% of males and 30% of females with the FMR1 full mutation exhibited significant issues with hyperactivity. The same study found that 84% of males and 67% of females with the FMR1 full mutation exhibited considerable problems with attention. In their entirety, the

research such as these described suggests that challenging behavior, comorbid psychopathology, and symptoms of AD/HD are significant problems in FRAX.

The assessed research has revealed that factors such as gender, presence of ASD, and presence of ID produce some variability with regards to symptoms across individuals. Furthermore, the expression of challenging behavior, comorbid psychopathology, and AD/HD symptoms in FRAX has been assessed. Despite our knowledge of these distinct factors, the interaction between them has not been fully examined. Further research examining this relationship is of importance in order to gain a greater understanding of the ‘spectrum of involvement’ in FRAX.

The overarching aim of the present thesis is to expand our knowledge of the interaction between individual factors and comorbid disorders. This will be achieved by examining the relationship between challenging behavior, comorbid psychopathology, and AD/HD symptoms in FRAX and will be supplemented by an investigation of whether such disorders are predicted by gender, presence of ASD, and presence of ID.

## **2. Method**

### **2.1. Participant Demographics**

Participants in this study were 47 children and adolescents with a diagnosis of FRAX. These participants were recruited via online forums and support groups. The mean age of the sample was 7.84 ( $SD = 4.19$ ) and the age ranged from 2 to 17 years. Within the sample, 75% were males ( $n=35$ ) and 25% were females ( $n=12$ ). Of the sample, 85% had an FMR1 full mutation ( $n=40$ ), 9% had an FMR1 pre-mutation ( $n=4$ ), and 6% had FMR1 mosaicism ( $n=3$ ). A total of 89% of participants had an ID ( $n=42$ ). A mild ID was reported in 20% of males ( $n=7$ ) and 25% of females ( $n=3$ ). A moderate ID was reported in 46% of males ( $n=16$ ) and 50% of females ( $n=6$ ). A severe ID was reported in 23 % of males ( $n=8$ ) and 8% of females

( $n=1$ ). A profound ID was reported in 3% of males ( $n=1$ ). Furthermore, 43% of the sample had a diagnosis of ASD ( $n=20$ ), of whom 95% were male ( $n=19$ ) and 5% were female ( $n=1$ ).

## **2.2. Measures**

**2.2.1. Participant Demographic Questionnaire.** Participant age, gender, FMR1 mutation status, presence and severity of ID and presence of ASD were determined using a self-constructed demographic questionnaire.

**2.2.2. The Behavior Problems Inventory – Short Form (BPI-S).** The BPI-S (Rojahn et al., 2012a) is a condensed version of the BPI-01 (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001) and consists of three subscales: the self-injurious behavior scale consisting of eight items; the aggressive/destructive behavior scale consisting of 10 items; and the stereotyped behavior scale consisting of 12 items. Symptoms are rated using a Likert rating scale (never = 0, monthly = 1, weekly = 2, daily = 3, hourly = 4) and a 4-point severity scale (no problem = 0, slight problem = 1, moderate problem = 2, severe problem = 3). Internal consistency values on the BPI-S frequency subscale have been found to range from fair (self-injurious behavior) to good (aggressive/destructive behavior and stereotyped behavior; Rojahn et al., 2012b).

**2.2.3. Autism Spectrum Disorders – Comorbidity for Children (ASD-CC).** The ASD-CC (Matson & González, 2007), is a 39-item, informant-based rating scale designed to assess symptoms of psychopathology and emotional disturbances which commonly occur with ASD. Each symptom is rated on the extent to which it has been a recent problem (0 = not a problem or impairment, not at all, 1 = mild problem or impairment, 2 = severe problem or impairment, or X = does not apply or don't know). Mean scores and standard deviations for the subscales within the ASD-CC are calculated and compared to the established cut-offs of no/minimal impairment, moderate impairment, and severe impairment (Thorson &



Matson, 2012). Factor analysis yielded seven subscales in the ASD-CC: (1) tantrum behavior, (2) repetitive behavior (3) worry/depressed, (4) avoidant behavior, (5) under-eating, (6) conduct and (7) over-eating (Matson & González, 2007). Inter-rater and test-retest reliability for the ASD-CC has been found to be moderately good, with good internal consistency reported (Matson & Dempsey, 2008).

**2.2.4. The Conners 3 – Parent Short Version.** The Conners 3 – Parent Short Form is a 43-item informant-based assessment of symptoms of AD/HD in children and adolescents aged between 6 and 18 (Conners, 2008). The form contains six subscales which measure for inattention, hyperactivity/impulsivity, executive functioning, learning problems, defiance/aggression, and peer/family relations (Conners, 2008). Positive impression and negative impression validity scales are also included within the short form (Conners, 2008). Responses are rated on a 4-point Likert scale from 0 = not true at all (never, seldom), 1 = Just a little true (occasionally), 2 = Pretty much true (often, quite a bit), 3 = very much true (very often, very frequently). Test-retest reliability and internal consistency for this measure have been found to be good, with high levels of internal consistency reported (Conners, 2008). In the present research, the inattention and hyperactivity/impulsivity subscales were utilised in order to achieve a measure of AD/HD symptoms.

**2.2.5. The Conners Early Childhood – Parent Short Version.** The Conners Early Childhood – Parent Short Version consists of a 49-item informant-based assessment for children aged between 2 and 6 years of age (Conners, 2013). The form contains 6 subscales including inattention/hyperactivity, social functioning/atypical behaviors, anxiety, mood/affect, physical symptoms, and sleep problems (Conners, 2013). Positive impression and negative impression validity scales are also included within the short form (Conners, 2013). Responses are rated on a 4-point Likert scale from 0 = not true at all (never, seldom), 1 = Just a little true (occasionally), 2 = Pretty much true (often, quite a bit), 3 = very much

true (very often, very frequently). Test-retest reliability values have been found to be good, with high levels of internal consistency reported (Conners, 2013). In the present research, the inattention/hyperactivity subscale was utilised to achieve a measure of AD/HD symptoms.

### **2.3. Informants**

Informants were parents of children diagnosed with Fragile X Syndrome. Rating scales were completed independently by the parents in accordance with the instructions provided at the top of each questionnaire.

## **3. Results**

### **3.1. Prevalence of Challenging Behavior**

Challenging behavior, namely SIB, aggression, and stereotypy, was measured using the BPI-S. The mean scores and standard deviations for the BPI-S were calculated for the three subscales. These scales did not have specific cut-off points. Table 1 displays that 80% of participants ( $n = 38$ ) engaged in SIB, 85% ( $n = 40$ ) engaged in aggression, and 100% ( $n = 47$ ) engaged in stereotypy. Of the sample, 6% ( $n = 3$ ) engaged in only one of the three behaviors, 21% ( $n = 10$ ) engaged in two of the three behaviors, and 72% ( $n = 34$ ) engaged in all three behaviors. A summary of the results from the BPI-S are presented in Table 1.

\*\*\*Insert Table 1 about here\*\*\*

### **3.2. Prevalence of Comorbid Psychopathology**

Behaviors associated with psychopathology were measured using the ASD-CC. Mean scores and standard deviations for the subscales within the ASD-CC were calculated and compared to the established cut-offs of no/minimal impairment, moderate impairment, and severe impairment. All mean scores were found to fall within the range of no/minimal impairment, suggesting that at a group level, comorbid psychopathology was not a significant

issue. Table 2. provides a summary of scores for each factor and corresponding level of impairment.

\*\*\*Insert Table 2 about here\*\*\*

At an individual level, prevalence of comorbid psychopathology was as follows: tantrum behavior: 23%,  $n = 11$ ; repetitive behavior: 17%,  $n = 8$ ; worry/depressed: 17%,  $n = 8$ ; avoidant behavior: 34%,  $n = 16$ , under-eating 9%,  $n = 4$ ; conduct 21%,  $n = 10$ ; and over-eating 40%,  $n = 19$ . Table 3. provides a summary of individual scores for each factor and corresponding level of impairment.

\*\*\*Insert Table 3 about here\*\*\*

**3.2.1. Anxiety Subscale.** Behaviors associated with anxiety can be assessed by the ASD-CC by combining the worry/depressed and avoidant subscales within the ASD-CC (Davis et al., 2011; Rieske et al., 2013). Within the current sample, 80% of participants ( $n = 38$ ) displayed no/minimum impairment, 14% had a moderate impairment ( $n = 7$ ), and 4% had a severe impairment ( $n = 2$ ). This demonstrates that 19% of the sample exhibited symptoms of anxiety.

### 3.3. Prevalence of Symptoms of AD/HD

Subscales within the Conners 3 – Parent Short form and the Conners Early Childhood – Parent Short form were used to tabulate the prevalence of AD/HD symptoms. The Conners 3 – Parent Short form consists of two AD/HD subscales measuring for inattention and hyperactivity respectively, whilst the Conners Early Childhood – Parent Short form consists of only one subscale which measures for inattention/hyperactivity. For this reason, the two AD/HD subscales within the Conners 3 – Parent Short form were collapsed by calculating a mean score for AD/HD symptomology for each participant. Raw scores for the AD/HD

symptoms subscale were then converted into *T*-scores for each participant. A *T*-score of  $\leq 40$  indicated a low score, a *T*-score of 40-59 indicated an average score, a *T*-score of 60-64 indicated a high average score, a *T*-score of 65-69 indicated an elevated score, and a *T*-score of  $\geq 70$  indicated a very elevated score. Validity scores were calculated using the positive impression and negative impression scales, with 100% of respondents not reporting either a positive impression or negative impression (raw score =  $< 5$ ).

Within the sample, 83% of participants ( $n = 39$ ) reported very elevated *T*-scores ( $T = \geq 70$ ), indicating many more concerns than typically reported. Within this cohort, 71% were male ( $n = 28$ ) and 28% were female ( $n = 11$ ). A further 6% of participants ( $n = 3$ ) reported elevated *T*-scores ( $T = 65-69$ ), indicating more concerns than are typically reported. Within this cohort, 66% were male ( $n = 2$ ) and 33% were female ( $n = 1$ ). A further 10% of the sample ( $n = 5$ ) reported a high average *T*-score ( $T = 60-64$ ) suggesting that AD/HD symptoms may be an issue. This cohort was made up of males only. None of the sample reported average *T*-scores ( $T = 45-59$ ) or low *T*-scores ( $T = \leq 40$ ). These results indicate that symptoms of AD/HD were highly prevalent within the assessed sample.

#### **3.4. Correlations between comorbid symptoms**

A series of Pearson's product-moment correlation coefficient (Pearson's *r*) were conducted to test for associations between challenging behavior, comorbid psychopathology, and AD/HD. A large positive correlation between challenging behavior and comorbid psychopathology was reported,  $r(47) = .59, p < .001$ , with high levels of challenging behavior associated with high levels of comorbid psychopathology. However, an association between challenging behavior and AD/HD symptoms ( $p = .30$ ) and comorbid psychopathology and AD/HD symptoms ( $p = .71$ ) was not found. Furthermore, anxiety was found to have a

medium positive correlation with challenging behavior,  $r(47) = .34, p = .02$ , although anxiety was not found to correlate with symptoms of AD/HD ( $p = .95$ ).

The above correlations revealed that higher levels of challenging behavior were associated with comorbid psychopathology. These results were further investigated using Pearson's  $r$  correlations in order to examine if a particular topography of challenging behavior (SIB, aggression, or stereotypy) correlated with comorbid psychopathology. A medium positive correlation was reported between SIB and comorbid psychopathology,  $r(47) = .44, p = .002$ . A medium positive correlation was reported between aggression and comorbid psychopathology,  $r(47) = .33, p = .02$ . A large positive correlation was reported between stereotypy and comorbid psychopathology,  $r(47) = .601, p < .001$ . Anxiety did not correlate with SIB ( $p = .12$ ) or aggression ( $p = .47$ ), however a medium positive correlation was found between anxiety and stereotypy,  $r(47) = .48, p = .001$ , suggesting that higher levels of anxiety was associated with higher levels of stereotypy.

### 3.5. Independent Samples $t$ -tests

Independent samples  $t$ -tests were conducted in order to examine the relationship between the individual factors of ASD, gender, and ID, and the comorbid disorders of challenging behavior, comorbid psychopathology, and AD/HD.

**3.5.1. Challenging Behavior.** Independent samples  $t$ -tests revealed a significant difference in challenging behavior symptoms between individuals with ASD and those without ASD,  $t(45) = 2.07, p = .04$ . Individuals with ASD ( $M = 40.70, SD = 20.80$ ) exhibited higher rates of challenging behavior than those without ASD ( $M = 28.76, SD = 18.89$ ). The degree of difference between these means was found to have practical significance, with a moderate to large effect size revealed ( $d = 0.61$ ). Table 4. shows that significant differences in challenging behavior were not found between males and females ( $p$

= .51) or between individuals with ID compared to those without ID ( $p = .19$ ). However, the degree of difference between these means was found to have practical significance, with a moderate to large effect size ( $d = 0.74$ ) found between those with ID and those without ID. A small effect size value between males and females was also reported ( $d = 0.12$ ).

\*\*\*Insert Table 4 about here\*\*\*

**3.5.2. Comorbid Psychopathology.** Table 5. shows that independent samples  $t$ -tests did not reveal a significant differences in comorbid psychopathology between individuals with ASD and those without ASD ( $p = .08$ ), however a small to moderate effect size value was reported,  $d = 0.52$ . Significant differences in comorbid psychopathology between those with ID compared to those without ID was not reported ( $p = .39$ ), although a small to moderate effect size value was reported,  $d = 0.42$ . A significant difference in comorbid psychopathology between males and females was not found ( $p = .51$ ), however a small effect size value was reported,  $d = 0.23$ . Table 5. provides a summary of these results.

\*\*\*Insert Table 5 about here\*\*\*

**3.5.3. AD/HD Symptoms.** Independent samples  $t$ -tests revealed a significant difference in AD/HD symptoms between males and females,  $t(45) = 2.49$ ,  $p = .02$ . Females ( $M = 83.42$ ,  $SD = 7.42$ ) exhibited more AD/HD symptoms than males ( $M = 76.69$ ,  $SD = 8.29$ ). This mean difference was found to have practical significance, with a moderate to large effect size value revealed,  $d = 0.86$ . Table 6. shows that significant differences in AD/HD symptoms were not reported between those with ASD and those without ASD ( $p = .56$ ), or between those with ID and those without ID ( $p = .87$ ). This table also reveals that effect size values between these factors were not found to have practical significance.

\*\*\*Insert Table 6 about here\*\*\*

### 3.6. Hierarchical Regression Analysis of Challenging Behavior

A hierarchical linear regression was conducted in order to examine if gender, presence of ASD, and presence of ID predicted challenging behavior. Presence of ASD was entered in the first block of the model, followed by gender in the second block and presence of ID in the third block. The first block, with presence of ASD as a predictor, was significant,  $F(1, 45) = 4.28, p = .05, R^2 = .087$ , indicating that presence of ASD accounted for 9% of variance in challenging behavior scores. The addition of gender in the second block of the model did not lead to a significant change in the model ( $p = .13$ ). Similarly, the addition of presence of ID in the third block of the model did not lead to a significant change in the model ( $p = .21$ ). Outcomes of the regression are displayed on Table 7.

Whilst the regression found that gender and presence of ID were not significant predictors of challenging behavior, presence of ASD was found to be a significant predictor of challenging behavior, with the  $t$ -test demonstrating that those with ASD exhibited higher levels of challenging behavior than those without ASD.

\*\*\*Insert Table 7 about here\*\*\*

### 3.7. Hierarchical Regression Analysis of Comorbid Psychopathology

A hierarchical linear regression was conducted in order to examine if gender, presence of ASD, and presence of ID predicted comorbid psychopathology. Presence of ASD was entered in the first block of the model, followed by gender in the second block and presence of ID in the third block. The first block, with presence of ASD as a predictor, was not significant,  $F(1, 45) = 3.32, p = .08$ . The addition of gender in the second block of the model did not lead to a significant change in the model ( $p = .21$ ). Similarly, the addition of presence of ID in the third block of the model did not lead to a significant change in the

model ( $p = .36$ ). Table 8 displays further details of the regression. These results suggest that the predictor variables of presence of ASD, gender, and presence of ID did not significantly predict comorbid psychopathology within the sample.

\*\*\*Insert Table 8 about here\*\*\*

### 3.8. Hierarchical Regression Analysis of AD/HD Symptoms

A hierarchical linear regression was conducted in order to examine if gender, presence of ASD, and presence of ID predicted AD/HD symptoms. Presence of ASD was entered in the first block of the model, followed by gender in the second block and presence of ID in the third block. The first block with presence of ASD as a predictor was not significant,  $F(1, 45) = .35, p = .56$ . The addition of gender as a predictor in the second block was significant,  $F(1, 45) = 3.13, p = .05, R^2 = .124$ , indicating that gender accounted for 12% of variance within AD/HD scores. The third block, with presence of ID as a predictor, was not significant,  $F(1, 45) = 2.09, p = .12$ . Table 9 displays further details of the regression. Whilst the regression analysis found that presence of ASD and ID did not significantly predict AD/HD symptoms, gender was found to be a significant predictor of AD/HD symptoms, with  $t$ -tests demonstrating that females exhibited higher levels of AD/HD symptoms than males.

\*\*\*Insert Table 9 about here\*\*\*

## 4. Discussion

The present research sought to examine the relationship between challenging behavior, comorbid psychopathology, and AD/HD in FRAX. A secondary aim of this study was to examine if such comorbid disorders were predicted by the individual factors of gender, presence of ASD, and presence of ID. Results demonstrated that challenging



behavior was a pervasive comorbid issue within the sample. Analysis of the data revealed that 80% of the sample engaged in SIB, 85% of the sample engaged in aggression, and 100% of the sample engaged in stereotypy. Seventy-two percent of the sample engaged in all three topographies of challenging behavior. Twenty-one percent of the sample engaged in two topographies of challenging behavior, and six percent of the sample engaged in one topography of challenging behavior. The rates of stereotypy reported in the present study are in keeping with those reported in previous research (e.g. Hagerman et al., 1986). However, it is of note that the rates of SIB and aggression reported in this study are far higher than rates cited in previous research (e.g. Bailey et al., 2008; Symons et al., 2010). These differing results may be explained by the age range of the individuals assessed by each respective study. Previous studies examined the prevalence of SIB and aggression in individuals whose ages ranged from infancy to over 30 whereas the present study assessed SIB and aggression in a sample aged between 2 and 17 years. These findings suggest that challenging behavior may be more prevalent in childhood and adolescence, which is a hypothesis that future research could examine.

Comorbid psychopathology was the second variable assessed. Results revealed that comorbid psychopathology was not a significant problem at a group level, although there was some variability in results at an individual level. Further analysis of the anxiety subscale within the ASD-CC yielded a 19% incidence of anxiety within the sample, a figure that is somewhat lower than figures found in previous research (e.g. Bailey et al., 2008; Cordiero et al., 2011). Lower rates of anxiety reported in this study may also have been a result of the different age ranges assessed. Cordiero et al. (2011) found that older age was associated with an increased prevalence of anxiety, suggesting that children and adolescents with FRAX may not exhibit higher rates of anxiety until they reach adulthood. This finding may account for

the lower rates of anxiety found in the present study, which assessed a younger cohort of participants.

AD/HD was the third variable assessed by the present study. Results indicated that 83% of the sample received an elevated *T*-score on the Conners assessment, indicating that problems with attention and hyperactivity were highly prevalent within the sample. The rates of AD/HD symptoms within the sample are similar if not slightly higher than those reported by previous research (e.g. Bailey et al., 2008). An explanation for the concurrence of these results with previous findings, despite the different age ranges assessed, may be due to the fact that symptoms of AD/HD are found to decrease as individuals with FRAX grow older (Tranfaglia, 2011).

The interaction between comorbid disorders such as challenging behavior and comorbid psychopathology was examined using correlational analysis. This analysis revealed a large positive correlation between challenging behavior and comorbid psychopathology ( $r = .59$ ), with high levels of challenging behavior associated with high levels of comorbid psychopathology. Furthermore, anxiety was found to have a medium positive correlation with challenging behavior ( $r = .34$ ). This finding supports the proposal by Boyle and Kaufmann (2010) that symptoms of comorbid psychopathology such as anxiety may manifest themselves as challenging behavior in FRAX. Despite the correlation found between challenging behavior and comorbid psychopathology, correlations were not found between comorbid psychopathology (as well as anxiety) and AD/HD symptoms, or challenging behavior and AD/HD symptoms.

Further analysis of the significant correlation between challenging behavior and psychopathology was conducted in order to examine if specific topographies of challenging behavior such as stereotypy correlated with comorbid psychopathology. Stereotypy was

found to have a large positive correlation with comorbid psychopathology in general ( $r = .60$ ), and a medium positive correlation with anxiety specifically ( $r = .48$ ). SIB and aggression were found to have a medium positive correlation with psychopathology in general ( $r = .44$  and  $r = .33$  respectively), but were not found to correlate with anxiety. These findings suggest that stereotypy was most strongly associated with comorbid psychopathology. Such an association may have clinical significance as it suggests that challenging behavior, but more specifically stereotypy, may be an indicator of comorbid psychopathology in FRAX. However, due to the small sample size assessed, this hypothesis should be interpreted with caution.

In order to examine if the individual factors of presence of ASD, gender, and presence of ID were associated with comorbid disorders, independent samples  $t$ -tests and hierarchical regressions were conducted. The independent samples  $t$ -tests revealed that those with ASD exhibited higher rates of challenging behavior compared to those without ASD ( $p = .04$ ). Additionally, females were found to exhibit higher rates of AD/HD symptoms than males ( $p = .02$ ). Whilst additional significant differences in the expression of comorbid disorders in relation to individual factors were not revealed, analysis of the effect size values revealed some interesting results. A moderate to large effect size value between ID and challenging behavior ( $d = 0.74$ ) and a small to moderate effect size between ASD and comorbid psychopathology ( $d = 0.52$ ) was reported. Furthermore, a small effect size between gender and psychopathology ( $d = 0.23$ ) and ID and comorbid psychopathology ( $d = 0.42$ ) was revealed. This finding indicates that a larger sample size may have revealed significant differences between such individual factors and comorbid disorders.

Hierarchical regression analyses were conducted in order to examine if individual factors predicted comorbid disorders. The regressions revealed that gender and ID did not predict challenging behavior. Gender, ASD, and ID did not predict psychopathology and

ASD and ID did not predict AD/HD symptoms. However, results revealed that ASD significantly predicted challenging behavior ( $p = .05$ ), whilst gender significantly predicted AD/HD symptoms ( $p = .05$ ).

The fact that ASD predicted challenging behavior corresponds to previous research which has reported a worsening of symptoms in those with comorbid FRAX and ASD (e.g. Hagerman et al., 1986; Hernandez et al., 2009; Turk & Graham, 1997). The clinical significance of this result is also of importance, as it suggests that such individuals may require more support. However, the finding that gender predicted AD/HD, with females exhibiting higher rates of AD/HD symptoms than males, needs careful interpretation due to the small sample of females assessed ( $n = 12$ ). This finding could be further investigated in future research.

The absence of additional significant relationships between individual factors and comorbid conditions in the regression may be a product of the central limitation of the present research. With so many individual factors to assess, the sample size of 47 participants may have been too small to be sensitive to such individual differences. Another reason that results may have not revealed significant differences between participants may be due to that fact that the majority of participants scored very highly on the BPI-S and AD/HD scales, resulting in little variance between individuals. A larger sample size may have revealed more variance in such scores. Further research utilising a larger sample size would also facilitate an assessment of the impact that FMR1 mutation status has on the expression of such symptoms. Severity of ASD and ID could also be examined as variables, rather than just assessing the presence or absence of ASD and ID as done in this study. Such a study would further reveal how individual factors impact upon the expression of comorbid disorders in FRAX.

The findings from the present study have several important implications. The high prevalence of comorbid disorders in FRAX strongly indicates that treatment should be a primary concern of future research. At present, the first choice in the treatment of FRAX appears to be medication (Hall, 2009). Several studies have indicated that a large number of individuals with FRAX are prescribed psychotropic medications (e.g. Berry-Kravis & Potanus, 2004; Valdovinos, Parsa, & Alexander, 2009). However, the evidence for the prescription of such treatments over other options has not been widely researched (Hall, 2009). Indeed few studies have evidenced the efficacy of other treatments such as behavioral interventions in the treatment of FRAX (Reiss & Hall, 2007).

Behavioral interventions have been found to be effective in the treatment of ASD. Studies have shown improvements in the areas of intellectual and adaptive functioning, communication, and social skills, as well as noting decreases in challenging behavior (e.g. Birchbauer & Leach, 1993; Eldevik et al., 2009; Lovaas, 1987; Sallows & Graupner, 2005). The similarity in the presentation of ASD and FRAX, and indeed the high comorbidity of ASD in FRAX, suggests that similar interventions could be a beneficial treatment option. However, whilst a number of studies have investigated the application of behavioral interventions for FRAX (e.g. Hall, DeBernadis, & Reiss, 2006; Hall, Maynes, & Reiss, 2009; Weiskop, Richdale, & Matthews, 2005) this research base is very limited and warrants further attention.

The present study has successfully demonstrated that individuals with FRAX exhibit a wide array of comorbid issues such as challenging behavior, comorbid psychopathology, and AD/HD symptoms. This study has also revealed that challenging behavior and comorbid psychopathology are correlated, particularly in the case of stereotypy, which also correlated with anxiety. Furthermore, analysis of the impact of individual factors on the expression of comorbid disorders found that presence of ASD predicted challenging behavior and being

female predicted AD/HD symptoms. In their entirety, these findings provide a wider understanding of the 'spectrum of involvement' in FRAX.

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Table 1.  
*Prevalence of Challenging Behavior*

Challenging behavior	<i>n</i>	%
SIB	38	80.9%
Aggression	40	85.1%
Stereotypy	47	100%
One topography	3	6.4%
Two topographies	10	21.3%
Three topographies	34	72.3%

Table 2.  
*ASD-CC Subscale Means, Standard Deviations, and Levels of Impairment*

Factor	<i>M</i>	<i>SD</i>	Level of impairment
Tantrum behavior	8.87	4.03	No/minimal
Repetitive behavior	6.26	3.47	No/minimal
Worry/depressed	3.06	2.56	No/minimal
Avoidant behavior	5.51	3.08	No/minimal
Under-eating	.30	.88	No/minimal
Conduct	1.53	1.47	No/minimal
Over-eating	2.34	1.52	No/minimal

Table 3.  
*ASD-CC Levels of Impairment across Participants*

Comorbid issues	No/minimal impairment		Moderate impairment		Severe Impairment	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Tantrum behavior	36	76.6%	6	12.8%	5	10.6%
Repetitive behavior	39	83%	6	12.8%	2	4.3%
Worry/depressed	39	83%	7	14.9%	1	2.1%
Avoidant behavior	31	66%	9	19.1%	7	14.9%
Under-eating	43	91.5%	3	6.4%	1	2.1%
Conduct	37	78.7%	6	12.8%	4	8.5%
Over-eating	28	59.6%	13	27.7%	6	12.8%

Table 4.  
*T-test for Differences in Challenging Behavior between ASD, Gender, and ID*

		<i>n</i>	<i>M</i>	<i>SD</i>	<i>t</i>	df	<i>p</i>	Cohen's <i>d</i>
ASD								
	Yes	20	40.70	20.80	2.07	45	.04	0.61**
	No	27	28.67	18.89				
Gender								
	Male	35	34.94	19.51	.66	45	.51	0.12
	Female	12	30.42	25.43				
ID								
	Yes	42	34.94	19.51	1.33	45	.19	0.74**
	No	5	22.40	25.43				

*Note.* \*\* = medium effect size



Table 5.

*T-test for Differences in Psychopathology between ASD, Gender, and ID*

	<i>n</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>df</i>	<i>p</i>	Cohen's <i>d</i>
ASD							
Yes	20	31.05	12.64	1.82	45	.08	0.52**
No	27	29.93	10.38				
Gender							
Male	35	28.20	11.89	.67	45	.51	0.23*
Female	12	25.58	11.30				
ID							
Yes	42	28.05	11.97	.88	45	.39	0.42*
No	5	23.20	8.69				

*Note.* \* = small effect size, \*\* = medium effect size

Table 6.

*T-test for Differences in AD/HD Symptoms between ASD, Gender, and ID*

	<i>n</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>df</i>	<i>p</i>	Cohen's <i>d</i>
ASD							
Yes	20	77.60	8.12	.59	45	.56	0.17
No	27	79.64	8.93				
Gender							
Male	35	76.69	8.29	2.49	45	.02	0.86***
Female	12	83.42	7.42				
ID							
Yes	42	78.48	8.00	.17	45	.87	0.06
No	5	77.80	13.41				

*Note.* \*\*\* = large effect size

Table 7.  
*Summary of Hierarchical Multiple Regression of Challenging Behavior*

	<i>B</i>	<i>SE B</i>	$\beta$	$\Delta R^2$
Block 1				.087
Constant	52.733	9.602		
Presence of ASD	-12.033	5.818	-.295*	
Block 2				.000
Constant	51.902	10.944		
Presence of ASD	-12.462	6.434	-.305	
Gender	1.201	7.296	.026	
Block 3				.013
Constant	58.186	13.667		
Presence of ASD	-11.027	6.725	-.270	
Gender	1.163	7.329	.025	
Presence of ID	-7.680	9.924	-.117	

Note. \*  $p < .05$ .

Table 8.  
*Summary of Hierarchical Multiple Regression of Comorbid Psychopathology*

	<i>B</i>	<i>SEB</i>	$\beta$	$\Delta R^2$
Block 1				.069
Constant	37.174	5.546		
Presence of ASD	-6.124	3.361	-.262	
Block 2				.000
Constant	37.010	6.323		
Presence of ASD	-6.209	3.717	-.266	
Gender	.236	4.215	.009	
Block 3				.003
Constant	38.742	7.939		
Presence of ASD	-5.813	3.906	-.249	
Gender	.226	4.257	.009	
Presence of ID	-2.116	5.764	-.056	

Table 9.  
*Summary of Hierarchical Multiple Regression of AD/HD Symptoms*

	<i>B</i>	<i>SE B</i>	$\beta$	$\Delta R^2$
Block 1				.008
Constant	76.063	4.183		
Presence of ASD	1.487	2.535	.087	
Block 2				.116
Constant	71.051	4.480		
Presence of ASD	-1.099	2.634	-.064	
Gender	7.236	2.986	.374*	
Block 3				.003
Constant	72.240	5.625		
Presence of ASD	-.828	2.768	-.048	
Gender	7.229	3.017	.374	
Presence of ID	-1.452	4.084	-.053	

Note. \*  $p < .05$ .