Social Behavioral Moderators of Executive Function Tasks in Fragile X Syndrome

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ABSTRACT

KYLEE MILLER: Social Behavioral Moderators of Executive Function Tasks in Fragile X Syndrome
(Under the direction of Dr. Stephen Hooper)

Fragile X syndrome (FXS) is the most commonly inherited form of intellectual disability, and is associated with a myriad of neuropsychological deficits, including executive dysfunction. Psychiatric symptoms have been addressed in the literature with conflicting findings. To date, investigations into the relationship between executive dysfunction and psychiatric functioning are limited, and warrant particular examination in the pediatric population. Here we will investigate measures of mood and anxiety in fifty-four boys with FXS who range in age from 7-13 years (M=10.1; SD=1.7). All boys were diagnosed with full mutation Fragile X on the basis of DNA analyses. It was hypothesized that the presence of severe behavior problems (Internalizing, Externalizing, Total Score on the CBCL) and presence of psychiatric diagnoses, could moderate the effects on selected executive functions in boys with FXS. It was expected ANOVAs with Internalizing, Externalizing, Total Score (dichotomized by one SD unit) and CBCL diagnosis would interact with executive functioning to produce more impaired performance for boys with FXS. No relationships were found between internalizing problems, specific DSM-oriented diagnoses, or the aggregate number of diagnoses endorsed on the CBCL and executive functioning in boys with FXS. These findings suggest that psychiatric

symptoms and disorders, variously defined, do not affect EF performance in boys with FXS to a greater degree than in age-matched typicals.

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CHAPTER 1

BACKGROUND

Prevalence

Fragile X Syndrome (FXS) is the most common heritable cause of intellectual disability (ID) (Hagerman, Rivera, & Hagerman, 2008). It is caused by a mutation of the X-linked FMR1 gene which creates a lack of the protein FMRP (Pieretti et al., 1991). Both males and females are affected by this neurodevelopmental disorder. However, as it is X-linked, males tend to be more severely affected, and prevalence studies suggest a higher frequency of FXS in males (Abrams & Reiss, 1995; Sobesky et al., 1996). Population-based studies have shown that approximately 1 in 4,000 males will inherit the full mutation (>200-230 repeats), and 1 in 2,000 females will have at least one x chromosome carrying the full mutation (Beckett, Qilu, & Long, 2005; Crawford, Acuna, & Sherman, 2001; Crawford et al., 1999; Turner, Webb, Wake, & Robinson, 1996). Fewer studies have been performed estimating the prevalence of premutation among males, and available reports have varied based on the cut-point for defining premutation, but were estimated at 1 in 379 by Rousseau (1994). Slightly more studies have been conducted on the prevalence of the premutation in females. Using the lower cut-off of 55 repeats for premutation, Beckett (2005) estimated approximately 1 in 100 women in the general population have Fragile X premutation.

Genetics

Fragile X syndrome is linked with a repeat of a trinucleotide repeat expansion (CGG) gene sequence on the X chromosome; this results in the gene's inability to express the protein coded by the fragile x mental retardation gene (FMR1) (Tsiouris & Brown, 2004). In typical individuals, the CGG repeats about 10-55 times. In people who are carriers of Fragile X syndrome, it is considered a premutation when this repeat occurs between 55-200 times, and full mutation when it is repeated more than 200 times (Brown, 2002). Women who are premutation carriers of the gene are often less affected by FXS and may show subtle deficits; however, if they pass this along to their children, the repeat may expand. The length of the repeat, thus the likelihood of getting a full mutation, is related to the size of the premutation; with 59-69 repeats at 30% risk, 70-79 repeats increasing the risk to ~80%, 80-89 repeats at nearly 90% increased risk, and repeats greater than 90 carrying nearly 100% risk of expansion to full mutation in the next generation (Nolin et al., 1996). Of the males who have full mutation, between 20-40% have cells that also show premutation – referred to as mosaicism. Only 10% of females have mosaic FXS (Tsiouris & Brown, 2004). Being an X-linked dominant trait, if a woman carries a premutation, both her female and male children are at risk of inheriting the syndrome or of being carriers themselves. As Tsiouris & Brown (2004) outline, with each pregnancy the premutation-carrier mother has a 50% increased chance of passing on the gene. If a male has a premutation it is referred to as "non-penetrant" (p. 689), and does not show the cognitive or physical characteristics of FXS, nor does the chromosome show up in his blood; he will pass this onto all of his daughters, although it will not

expand (i.e., stays in permutation form), though his grandchildren are at risk (Tsiouris & Brown, 2004).

Diagnosis for pre- and full-mutation FXS is done through DNA testing, generally with two separate tests. One is the polymerase chain reaction (PCR), which clarifies the number of CGG repeats, and the other is the Southern Blot test to tell whether or not the gene is methylated, or turned off. In a prenatal screening study Tassone and colleagues (2008)described two forms of prenatal screening used in children with Fragile X: at 10 weeks gestation chorionic villus sampling may be used, or at 16 weeks amniocentesis may be done, both of which are highly reliable (Brown & Houck, 1993). Additional methods for genetic screening have been suggested (Bailey, 2004; Bailey, Roberts, Mirrett, & Hatton, 2001; Pembrey, Barnicoat, Carmichael, Bobrow, & Turner, 2001). They include genetic counseling of women prior to conception to assist in making appropriate reproductive choices for themselves; and screening of pregnant women to give them prenatal options. These options, however, are costly (Bailey, 2004) and screening of newborns at the first sign of developmental delay may be more pragmatic from a cost perspective. Most recently, a model for newborn screening using an improved PCR was developed and tested as a pilot in Spain and Guatemala (Tassone, Hagerman, & Hagerman, 2008). While this method appears promising, its use on a larger scale has yet to be tested.

Physical Characteristics

Hagerman (2002) described the phenotypic characteristics of males with Fragile X syndrome as being less definite and identifiable than other developmental disabilities, though there are some physical features characteristic of FXS. These include: a narrow face, short distance between the eyes, exaggerated convex palate in the roof of the mouth, and large ears. Female carriers of FXS are generally without physical identifiers of the syndrome; however, some do have the same distinct facial features as those seen in affected males. Macroorchidism, large testes, is also common and most noticeable after puberty. Additionally, it is estimated that between 15-20% of males with Fragile X will develop seizures (Hagerman, 2002).

Cognitive Characteristics

In the past decade, research on FXS has been directed toward the developmental trajectory of males, specifically cognitive and social functioning (Mazzocco, 2000). Within the realm of cognitive functioning, evidence is mounting for deficits of executive functioning in children with FXS (Hooper et al., 2008). This review briefly addressed findings on female cognitive function for the purpose of comparison, but focus on the male cognitive profiles of FXS. Compared to males, females with FXS have more variability in their IQ, and these cognitive deficits are related to the percentage of active X chromosome cells on the normal X chromosome –called the X activation ratio (Abrams et al., 1994; Riddle et al., 1998).

Cognitive Deficits in Females

Studying females whose cognitive functioning provides researchers insight into genetic forms of ID, as it is generally one SD below the mean and more easily assessed than their male counterparts (Bennetto, Taylor, Pennington, Porter, & Hagerman, 2001). For women with the full mutation, some reports purport that there is little scatter between performance and verbal IQ (Bennetto et al., 2001), while other studies suggest that the Performance IQ is sensitive to FMRP levels, and that females with Fragile X have a lower Performance IQ than Verbal IQ (Abrams et al., 1994; Riddle et al., 1998). In terms of subtests, several researchers have identified specific areas of weakness in working memory, quantitative skills, and visuomotor tasks (Brainard, Schreiner, & Hagerman, 1991; Franke et al., 1999; Mazzocco, Pennington, & Hagerman, 1993).

Another widely studied deficit in females with FXS is executive function (EF) disorder (Cornish et al. 2005, 2007; Mazzocco, Hagerman, Cronister-Silverman, & Pennington, 1992; Sobesky, Pennington, Porter, Hull, & Hagerman, 1994). Executive functions are influential factors in other cognitive abilities that guide top-down cognitive processes to help us carryout goal-directed behavior (Miller & Cohen, 2001; Posner & Petersen, 1990; Posner & Rothbart, 2007). Specifically, EF includes inhibition, working memory, processing speed, set-shifting, and planning (Anderson, 2002; Hooper et al., 2008; Miyake & Friedman, 2000; Pennington, Krasnegor, Lyon, & Goldman-Rakic, 1997; Zelazo, Muller, Frye, & Marcovitch, 2003).

Although females with full mutation may have more severe deficits, those with premutation Fragile X have fewer and less severe problems with executive function, (Hagerman, 2002; Sobesky et al., 1996; Tsiouris & Brown, 2004). Females have been noted to perform poorly in the areas of social interaction, organization, impulsivity, and attention (Bennetto et al., 2001; Mazzocco et al., 1992; Mazzocco et al., 1993; Sobesky et al., 1994). When covaried with effects of IQ, these EF deficits remain statistically significant (Mazzocco et al., 1993; Sobesky et al., 1994). Several studies have found that women with FXS have intact functioning of short and long term memory (Hinton, Halperin, Dobkin, & Ding, 1995; Mazzocco et al., 1992; Mazzocco et al., 1993; Thompson et al., 1994); with the exception of short term auditory memory which appears to be a deficit (Brainard et al., 1991; Freund & Reiss, 1991; Grigsby, Kemper, & Hagerman, 1992; Kemper, Hangerman, Ahmad, & Mariner, 1986). A study by Bennetto (2001) elucidated the cognitive profile of women with FXS, by using mental age (MA) matched comparisons in women without Fragile X, as well as comparing women with full mutation to premutation FXS. This study supported the aforementioned results of relative strength in visual discrimination and long-term memory as assessed by Picture Completion (WAIS-R, Wechsler, 1981), as well as EF deficits. Of note, when IQ was controlled, females with FXS had noted deficits only with executive function tasks. With a profile of executive function deficits and relatively normal verbal skills, it appears that females with all forms of FXS have greater deficits in fluid intelligence compared to crystallized intelligence.

Cognitive Deficits in Males

While many females with full mutation Fragile X express a great deal of variation in their cognitive abilities males, on the whole, tend to exhibit mild to moderate ID (Cronister, Hagerman, Wittenberger, & Amiri, 1991; Hagerman, 2002; Hooper et al., 2008; Hooper, Hatton, Baranek, Roberts, & Bailey, 2000). In terms of general cognitive functioning, Van der Molen and colleagues (2010) examined the performance of 43 Dutch males with full mutation FXS, ages 18-48 (mean age = 28.7). Assessing IQ, nonverbal measures of reasoning, verbal performance, and memory, they found the men's performance clustered around level of adaptive functioning (high, intermediate, and average), with weaknesses noted in abstract reasoning and abstract performance abilities, and strengths in concrete reasoning and concrete performance abilities. Furthermore, they found that this profile was positively correlated to the males' level of functioning. That is to say, the men with FXS had more pronounced weaknesses in abstract information processing, and noted strengths in concrete information processing, when controlling for mental age peers (p. 435).

Tantamount to this proposed profile of cognitive abilities in determining the functioning of males with FXS, is executive control. A number of investigators have demonstrated that males with FXS show difficulty with response inhibition (Cornish, Scerif, & Karmiloff-Smith, 2007; Hooper et al., 2008), set-shifting (Cornish, Munir, & Cross, 2001; Hooper et al., 2008; Woodcock, Oliver, & Humphreys, 2009), and problem solving skills (Hooper et al., 2008).

From a developmental perspective, Hooper et al. (2008) explored executive functioning of boys ages 7-13 years. A group of boys with FXS was compared to typically developing mental age (MA) matched peers. All boys had MAs of 48 months or older and all executive function tasks (measures of working memory, inhibition, set-shifting, and planning) showed significant group differences, with the exception of the processing speed tasks. MA affected the performance of boys on all working memory, set-shifting, and planning tasks, as well as one of the two inhibition tasks. Above-and-beyond the effects of MA, Hooper (2008) found that boys with FXS had difficulty with set-shifting and working memory tasks. These results are similar to other EF research in boys with full mutation FXS (Loesch et al., 2003; Munir, Cornish, & Wilding, 2000); which found that 57% of boys were unable to complete the Wisconsin Card Sorting Task (WCST), and 37% were unable to finish the Rey-Osterrieth Complex Figure Test (ROCFT) (Loesch et al., 2003). These tasks were chosen for their low basals and use with children with MAs of at least four-years-old.

In studies of adult males with FXS (Van der Molen et al., 2010), the aforementioned findings of EF deficits were supported, but unlike the developmental literature (Hooper et al., 2008; Kogan et al., 2009; Loesch et al., 2003; Woodcock et al., 2009), set-shifting and planning deficits were found only in Verbal Memory MA-matched paradigms, but not in non-verbal measures with MA-matches. Rates of failure of the adult participants to complete the ROCFT were similar to those of children (see Hooper et al., 2008), and has been interpreted by many researchers as executive dysfunction (Kogan et al., 2009; Loesch et al., 2003; Munir et al., 2000;

Van der Molen et al., 2010). It appears that weaknesses in executive functioning dictate overall cognitive functioning, and further studies are necessary to parse out the effects that executive functions have on other psychological processes.

Social Behavioral Functioning in Fragile X Syndrome

Numerous studies have published reports on neurocognitive and psychiatric phenotypes of both pre-mutation and full-mutation carriers of FXS with varying results (Baumgardner, Reiss, et al., 1995; Bourgeois et al., 2009; Bourgeois et al., 2007; K. Cornish et al., 2005; Hunter et al., 2008; Hunter, Rohr, & Sherman, 2010; Kau, Reider, Payne, Meyer, & Freund, 2000; Reiss & Dant, 2003; Rodriguez-Revenga, Madrigal, Alegret, Santos, & Mila, 2008; Sullivan, Hooper, & Hatton, 2006).

Thompson et al. (1994) reported findings on a small group of premutation carriers (n=12) that showed them to have an increased rate of depression (75%) compared to the general population. Similarly, in a group of premutation carrier-mothers of children with FXS, increased rates of depression and anxiety were reported compared to non-carrier mothers of children with Autism Spectrum Disorder (ASD) (Franke, 1998). These findings suggest that the increased rates of depression were not related to the stress of caring for a child with special needs (Hunter, Abramowitz, Rusin, & Sherman, 2009). While there are studies reporting mental disorders at a higher rate than in either the general population or other disability groups, they are limited in scope. The majority of studies looking at social-behavioral functioning have been conducted on female premutation carriers, or older men in the context of fragile X-associated tremor ataxia syndrome (FXTAS), which

mainly affects men over the age of 50 (Bacalman et al., 2006; Bourgeois et al., 2007; Cornish et al., 2005; Hessl et al., 2007; Hunter et al., 2008; Hunter et al., 2010; Jacquemont, Hagerman, Hagerman, & Leehey, 2007; Rodriguez-Revenga et al., 2008). Cordeiro, L., Ballinger, E., Hangerman, R., and Hessl, D. (2011) found that 86 percent of males aged 5 to 33 years met criteria for anxiety disorder, with Social and Specific Phobias being the most common. It was found that 75% of participants with FXS met diagnostic criteria for one or more anxiety disorders; and many displayed anxious symptomology but did not meet criteria. In addition, they reported that Social Phobia occurred at a higher rate in persons over 18-years-old; and those with comorbid FXS and ID were more likely to meet criteria for any of the anxiety disorders except: Separation Anxiety, Social Phobia (unadjusted), GAD, and PTSD.

Several mouse studies have shown that when the FMR1 gene is removed, mice exhibit decreased rates of anxiety (Eadie et al., 2009; Mineur, Huynh, & Crusio, 2006; Qin, Kang, & Smith, 2002, 2005; Restivo et al., 2005) the mice were better able to complete a spatial navigation task commonly used to assess learning and memory in rats than those with anxious symptomology (D'Hooge et al., 1997; Eadie et al., 2009; Paradee et al., 1999; Qin et al., 2002). In rodent neurogenesis experiments, Eadie (2009) indicated that the loss of the FMR1 gene may alter anxiety-related behaviors in mice (e.g., motor activity, tendency to remain near maze walls (thigmotaxis), and the number of defecations (fecal boli). These findings are consistent with the literature on the hippocampal role in behaviors related to anxiety and spatial learning/memory (Bannerman et al., 2004). In addition to the

hippocampus' role in emotion regulation, the frontal cortex has been well associated with symptoms of depression (Herrington et al., 2010; Miller & Cummings, 2007). As such, the psychiatric functioning of individuals with FXS is of interest, if as of yet unclear.

Psychiatric Comorbidity in Females

In females with premutation Fragile X, nearly 50% carry a diagnosis of an anxiety or affective disorder, such as social phobia (Bourgeois et al., 2009; K. Cornish et al., 2005; Hunter et al., 2008; Kau et al., 2000; Sobesky & Hull, 1994; Sobesky et al., 1994; Tsiouris & Brown, 2004). These psychiatric diagnoses typically present during or after adolescence (Bourgeois et al., 2009). Research shows that there is a correlation between severity of psychiatric symptoms and the type of mutation on the FMR1 gene (Franke et al., 1998). Studies examining the psychiatric status of premutation carriers of FXS were initially done on females, as they have only one X chromosome affected by premutation X, and thus a higher chance at a buffer from extreme social-behavioral effects (Hessl et al., 2005). Several studies have been published regarding neurocognitive and psychiatric phenotypes of female FXS carriers. Franke et al. (1998) reported lifetime comorbid psychiatric diagnosis of unipolar affective disorder at 21.3%, major depression of 19.7%, and bipolar disorder of 11.5%, in premutation mothers of children with FXS. In a study comparing 93 females with FXS premutation to 2,159 female controls from the National Comorbidity Survey Replication (NCS-R) dataset, the Structured Clinical Interview for the DSM-IV (SCID-I) was administered to assess for lifetime and current history of mood and anxiety disorders (Roberts et al., 2009). This study

found that 19.7% of women with premutation who had children with Fragile X had a lifetime diagnosis of Major Depression significantly higher than the mothers with either full mutation (15.4%), or those with no mutation (5.6-9.5%). Concerning personality disorders, 23.1% of women with full mutation were diagnosed with Schizotypal, Schizoid, and Avoidant type, while only 4.9%, 1.6% and 8.2% of women with premutation were diagnosed with these respective disorders. Of the women in the control condition, only 2.45% were diagnosed with Avoidant personality disorder.

Psychiatric Comorbidity in Males

It is important to examine social-behavioral correlates of FXS in males separately due to the X-linked nature of the syndrome. The comorbidity between FXS and ASD is well established (Bailey et al., 2001; Rogers, Wehner, & Hagerman, 2001), but the implications of decreased cognitive functioning (Lewis et al., 2006; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004), and increased problem behaviors (Kau et al., 2000) have been challenged by others who state that boys with FXS have a relatively even behavioral development compared to those with Autism Spectrum Disorder (ASD) (Reiss & Dant, 2003). Specifically, withdrawal from social situations (Freund, Peebles, Aylward, & Reiss, 1995) and increased avoidance of social encounters (Kau et al., 2000) have been noted in boys with FXS, when matched on MA. In females this avoidance and difficulty relating to peers has been postulated as a direct correlate of reduced FMRP resulting in depressed mood as cognizance of social and cognitive differences increase (Fopma-Loy, 2000; Hoglund, Lalonde, & Leadbeater, 2008). It is unknown if these hypotheses extend to

males with FXS as well, or how they affect other features (e.g., neuropsychiatric symptoms, adaptive behavior).

Data from a developmental perspective appear to paint a somewhat different picture than the low endorsement rates of psychopathology in adult males. In a study comparing children with FXS to those with Developmental Delay, and matched for IQ, both groups had elevated rates of inattention and hyperactivity compared to the general population, but were not considered clinically significant compared to those typically developing (Kay et al., 2000). Boys with FXS did not differ significantly on ratings of attention or hyperactivity when compared to age- and IQ-matched peers with developmental disabilities as measured by the Achenbach Child Behavior Checklist (CBCL; Achenbach, 1991; Kau et al., 2000). No differences were found between the two groups in ratings of somatic complaints, anxiety, or depression (2000). In another study, boys with FXS were rated in the Borderline or Clinical range on the Total Problems behavior index of the CBCL, as well as the attention, thought problems, and social problems subscales. Of these boys, those with autistic behaviors were rated low on adaptability; and both low adaptability and autistic characteristics predicted thought problems (Hatton et al., 2003).

Von Gontard (2002) found that boys with FXS had scores on the CBCL placing them in the Borderline or Clinical range for social-behavioral problems, when compared to age-matched young males with an average IQ and who had Spinal Muscular Atrophy (SMA). Clinically significant scores were endorsed by the FXS group in both internalizing symptoms (63.3%) and externalizing symptoms (67.3%). Other psychiatric diagnoses met by the boys with FXS, as measured by the Kinder-

DIPS (Schneider, Unnewehr, & Margrag, 2009), were ADHD (73.5%) and Oppositional Defiant Disorder (28.6%) (von Gontard et al., 2002). This group found a significant correlation between the externalizing behaviors endorsed on the CBCL and high rates of endorsement on a measure of parent stress. As psychiatric comorbidity is elevated at a rate of as much as six times that of the general population of children with ID (von Gontard et al., 2002), the rates reported by this group are much higher, and warrant further investigation. Similar elevated ratings on the CBCL were found in a study by Hatton and colleagues (2002) on boys between 8- and 12-years-old with FXS. Specifically, 27 percent of the boys scored within the Borderline or Clinical range on internalizing symptoms and 29 percent Borderline-to-Clinical range on externalizing symptoms. Further examination of the reliability of the CBCL for use with children with FXS was done by Sullivan (2006). In a sample with 89% males, children with FXS were rated as having behavioral and/or emotional problems on at least one subscale. The lowest internal consistency was found on the Major Depressive Disorders (alpha = 0.39) and Dysthymic Disorder (alpha = 0.46) subscales on the parent form. Other low alphas were found on parents' subscale rating of Generalized Anxiety, DSM Anxiety Problems, Social Problems, Schizophrenia, and DSM Affective Problems. This suggests that the aforementioned items on the CBCL subscales do not measure the intended construct for children with FXS, as they did on the norming sample. Children rated by their parents as having high levels of autistic behaviors were also rated as having additional behavior and/or emotional problems, in particular being withdrawn, having somatic complaints, and feeling anxious or depressed.

In Sullivan's (2006) analysis of social emotional problems in children with fragile X; autistic behaviors, anxiety, and attention problems were the most frequently parent-endorsed behaviors on the CBCL. The children's scores on the CBCL DSM-IV-oriented Anxiety subscale and the CARS also were elevated (Sullivan, 2006). The relationship between these behaviors has been a topic of great debate. Some believe that autistic behaviors are related to anxiety (Cohen, 1995; Belser & Sudhalter, 2001); others have postulated that in children with FXS, anxiety explains some autistic behaviors (Mazzocco, 2000); while there are those that believe labeling autistic behaviors as autism is most appropriate (Bailey et al., 2004).

With evidence mounting that young boys with FXS exhibit increased social behavioral problems compared to adult males and females with FXS, further investigation into these symptoms and their correlates is warranted, particularly as they may affect other areas of functioning. In particular, despite anecdotal reports that psychiatric status may affect the cognitive functioning of boys with FXS compared to typically developing peers, there are no empirical data to support this assumption.

CURRENT STUDY

If rates of poor social behavioral functioning in boys with FXS are high enough or severe enough, they could serve as moderators of EF outcomes; however, despite anecdotal associations, these issues have not been addressed in the empirical literature. It is clear that the EF deficits in boys with FXS are both profound and specific, as they relate to working memory, set-sifting, inhibition, and

planning, and are highly correlated with MA. We have also seen the effect of MA on social-behavioral comorbid disorders with FXS, and the significant rate of endorsement of both internalizing and externalizing disorders in the pediatric populations as compared to typically developing peers. As these neuro- and psychopathological manifestations in boys with FXS appear to be above-and-beyond what is expected for children with developmental delay, further exploration into their interrelationship is warranted. On this point, the present study will look at social-behavioral problems, including autistic behaviors, as moderators of EF tasks in boys with FXS and a mental-age matched sample of typically developing boys.

Research Questions

The goals of the proposed research are to: (1) determine if social behavioral problems, as defined by the CBCL (Internalizing, Externalizing, and Total Score), moderate EF in boys with FXS; (2) explore the role of specific diagnoses (i.e., Anxiety Problems, Affective Problems, ADHD, ODD), as defined by the DSM-oriented scales on the CBCL as moderators of EF in boys with FXS; and (3) determine if the aggregate number of DSM-oriented diagnoses moderate EF tasks in boys with FXS.

Based on the available literature, it is hypothesized that internalizing problems will moderate executive functioning in males with FXS more than in mental-age matched typically developing boys; that the specific diagnoses of Anxiety Problems and Affective Problems will moderate EF in boys with FXS more than in mental-age matched typically developing boys; and that having more diagnoses will affect EF in boys with FXS more than in mental-age matched typically developing boys.

CHAPTER 2

Methods

Participants

This study used 56 boys with full mutation FXS, ranging in age from 7-to-13 years of age (M = 10.1; SD = 1.7), who participated in a prospective study investigating attention, memory, and EF. The majority of the children were Caucasian (83.3%), 13% were African American, and 3.7% were Latino or Asian. Mothers' education level ranged from 38.9% having completed high school, to 37% completing some secondary education/training; 14.8% receiving a college degree, and 9.3% having a graduate degree. Over half (64.2%) of the children with FXS were receiving psychiatric pharmacological treatment. Most common were stimulants at 21.9%, followed by sympathalytics (9.9%), antipsychotics (9.3%), SSRI (6.0%), anticonvulsants (4.6%), SNRI (4.0%), anxiolytics (1.3%), and antidepressants (1.3%). The mean MA in the group with FXS was 5.3 years (SD = 0.62).

The control sample consisted of 40 typically developing boys ranging in age from 4-to-8-years-old. Of the controls, 83.3% were Caucasian, 14.6% African-American, and 2.1% were Latino. The typically developing boys scored in the Average range (i.e., between 80 and 120) on the *Brief IQ Screener* of the Leiter International Performance Scale—Revised (LEITER-R; Roid & Miller, 1997). Attempts were made to match the two groups of boys both on MA and ethnicity,

however, six boys had no MA match and seven had more than a six-month disparity. The mean MA of the control group was 5.3 years (SD = 0.62). None of the boys in the control group were medicated during the assessment periods.

A description of the sample on key sociodemographic variables can be seen in Table 1.

Measures

All participants were part of a larger study in which they completed an assessment battery of neuropsychological functioning (Hooper, 2008). To control for potential covariates in the current study, the two groups were matched on mental age and maternal education, and each participant was also rated on autistic behavior as observed during the assessment period.

Intelligence Quotient

To measure mental age (MA) in this study, the *Brief IQ Screener* from the Leiter International Performance Scale—Revised (LEITER-R, Roid & Miller, 1997) was used as a measure of nonverbal intelligence. The Screener generates an IQ and corresponding age equivalent, from which the MA was calculated based on a growth curve analysis. The Brief IQ Screener is appropriate for use for individuals between 2 and 20-years of age. The *Leiter-R Brief IQ Screener* appears to be psychometrically sound, with reliability estimates ranging from alphas of 0.88 to 0.90. Concurrent validity tests between the Leiter-R (Brief and Full Scale IQ) and the Wechsler Intelligence Scale for Children (WISC-III) (Performance and Full Scale IQ) on children ages 6 to 16, report correlations of .85 and .86 (Roid, Pomplun, Martin, Naglieri, & Goldstein, 2009). In middle school students, comparison of the

Universal Nonverbal Intelligence Test (UNIT) and the Leiter-R have yielded a statistically significant correlation coefficient of 0.72 ($p < 0.001$) (Hooper, V., 2003).

Executive Functioning

Measures of EF were selected based on the empirical model of the dimensions of executive functions (Pennington et al., 1997) as well as the literature on executive functioning within the Fragile X population –inhibition, set-shifting/cognitive flexibility, and working memory (Hooper, 2008). For these analyses, one representative task was selected from each "executive" domain previously showing significant differences between the MA matched control group and the FXS group (Hooper et al., 2008). These tasks included measures of inhibition, working memory, set-shifting/cognitive flexibility, and planning.

Inhibition. As a measure of inhibition, the Day/Night Task (Diamond & Taylor, 1996) was used. The Day/Night Task is a widely used measure of interference control in children. Psychometric properties have not been widely tested (Montgomery & Koeltzow, 2010); but evidence exists for good internal reliability (Chasiotis, Kiessling, Winter, & Hofer, 2006; Rhoades, Greenberg, & Domitrovich, 2009; von Stauffenberg & Campbell, 2007), as well as test-retest reliability (Thorell & Wahlstedt, 2006). Administration procedures outlined by Gerstadt (1994) were used in the current study. Children were instructed to say the word "day" when viewing a card depicting a nighttime sky, and to say "night" when shown a picture of the daytime sky. Like adult Stroop tasks, the children had to (a) maintain task instructions over a series of trials, (b) suppress a dominant response to a perceptual stimulus, and (c) select and execute a competing, conflicting subdominant response.

Working memory. The Memory for Words subtest from The Woodcock-Johnson Tests of Cognitive Abilities, Third Edition (Woodcock, McGrew, & Mather, 2001) was used to measure working memory. Memory for Words requires the children to repeat a series of unrelated words in the same order in which they were presented. The items progressively increase in length, beginning with a single word and ending with a seven word sequence. The task was discontinued when the highest three items in a section were missed. The total correct raw score was used as a measure of working memory, and any child who received a raw score of 0 was not included in the analyses. Memory for Words has a median reliability coefficient of 0.80 (SEM = 6.63) (Flanagan & Harrison, 2005).

Cognitive flexibility/set-shifting. The Contingency Naming Task (CNT; Anderson, Anderson, Northam, & Taylor, 2000), a Stroop-like task, was used to assess cognitive flexibility/set-shifting. There are four subtests for the CNT and all were administered as appropriate to the sample. The CNT consists of a sheet of paper on which a series of shapes imbedded within shapes of varying colors is presented to the child. They are required to either name the shape or the color according to a predetermined rule (e.g., If the inside shape matches the outside shape, name the color; otherwise, name the outside shape*).* Subtests 1 and 2 were not used in the data analyses, as they do not tap set-shifting/cognitive flexibility skills, and subtest 4 was omitted from analyses as many of the boys were unable to complete it due to increased complexity and working memory demands. The total number of errors from Subtest 3 was used as the dependent variable for this measure. Additionally, any child who did not receive a score of at least two correct

responses on the 27 possible trials for Subtest 3 was excluded from analyses. The CNT's reliability and validity in school-aged children is established (Lee et al., 2003).

Planning. The Tower Task from the NEPSY (Korkman, Kirk, & Kemp, 1998) was used as the measure of planning. The Tower task requires the child to rearrange wooden discs on a set of three pegs from their original pattern to one illustrated on a picture board, all done in a prescribed number of moves without violating set rules (e.g., only moving one disc at a time between pegs). The trials become increasingly more complex, and only those completed within the allotted time were counted as correct and given a point. The Tower Task has been used as an effective measure of planning in studies of children with autism (Joseph, McGrath, & Tager-Flusberg, 2005). The total raw score, out of a possible 20, was used as a measure of planning and problem solving efficiency, and any child who earned a score of 0 was not included in the analyses. The Tower task was designed for children ages 5 to 12, and although there were children chronologically a few months younger than 5 years, no floor effects were observed.

Measures of maladaptive behavior and emotional problems

The Child Behavior Checklist (CBCL, Achenbach, 2001) was used to assess clinically relevant social-behavioral problems. The parent-report questionnaire was used to rate the child on various behavioral and emotional problems. The CBCL has been one of the most widely-used standardized measures in child psychology for evaluating maladaptive behavioral and emotional problems in children aged 2 to 18. The CBCL has a test-retest reliability of 0.84 to 0.97 (Achenbach, 1991). The parent version of the scale assesses internalizing (i.e., anxious, depressive, and over-

controlled) and externalizing (i.e., aggressive, hyperactive, noncompliant, and under-controlled) behaviors. Concurrent validity with the individual diagnoses targeted by that scale (e.g., Anxiety and SAD, GAD, SPEC) has been documented with the following results in the DSM-oriented scales: Anxiety Problems ($p < 0.001$), Affective Problems ($p < 0.001$), ADHD ($p < 0.001$), and Oppositional Problems ($p < 0.001$) (Ebesutani et al., 2010). For this investigation, the three composite scores of Internalizing, Externalizing, Total Behavior Problem were used, along with the DSM-IV-Oriented Scales of Anxiety Problems, Affective Problems, ADHD, ODD scores – keeping in mind the low reliability in this population (Sullivan, 2006). A cut-point using the T-values of > 60 were used, representing those children at less one standard deviation from the mean (i.e., < 16th percentile).

Autistic Behaviors

The Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980) was used to assess behavior in 14 domains generally affected by autism. This was used with the aim of differentiating autism from executive dysfunction and other psychiatric symptoms. The 15 items in the scale were rated by two trained researchers on a scale of 1 to 4; 1 indicating appropriate for age level, and 4 indicating severe deviance from normal behavior for age level. For this research the total CARS score was used as a continuous independent variable of autistic behavior, and children were not categorized into diagnostic groups. The CARS has high internal consistency, alpha = .94 in a large sample (n = 537) (Schopler, Reichler, & Renner, 1988). The CARS has also demonstrated utility in preschool and school-aged children (Schopler et al., 1988); as well as children with

developmental disabilities including FXS (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Bailey Jr, Hatton, Skinner, & Mesibov, 2001; Hatton et al., 2006; Hatton et al., 2003; Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005).

Data Analyses

Preliminary data analyses included the generation of descriptive statistics for the FXS and MA-matched typically developing children who completed the selected EF tasks. Variables showing a group difference were considered as potential covariates in subsequent analyses as long as they correlate with the dependent measures.

To answer the first, second, and third research questions, a correlation matrix was calculated to examine the relationships between the CBCL Internalizing, Externalizing, and Total Problem scales, the DSM-IV oriented scales, and the total number of DSM-IV oriented scales with the four executive function tasks. This correlation matrix was used to inform selection of the scales to be used in the univariate analysis of variance (ANOVA). Only those relationships found significant in the correlations were used in the ANOVA. Following examination of the correlation matrix, multiple univariate ANOVAs for each dependent variable were conducted and controlled for Type I error using a $p < .01$ level of significance. Of particular interest to this study are the interactions between group (FXS vs. Typicals) and the designated social-behavioral variables (Internalizing, Externalizing, Total Problems; Anxiety Problems, Affective Problems, ADHD, ODD; Total Number of DSM Diagnoses) for each of the four executive function tasks. A significant group by disorder interaction will reflect that one group is being affected to a significantly

greater degree than the other. The one standard deviation cut-point, previously described, was used to distinguish psychiatric variables on the CBCL and capture the moderator variables.

Overall, the boys with FXS were able to complete nearly half of all the EF tasks, with the exception of the set-shifting task *Contingency Naming*, which only 14 (25.9%) were able to complete. Follows are the completion rates for the other EF tasks: Inhibition (*Day-Night Total*) 42 (77.8%); Working Memory (*Memory for Words* –WJ-III) 51 (94.4%); and Planning (*Tower Task* –NEPSY) 35 (64.8%). The task completion rates for the Typically developing boys were between 92 and 96 percent for each of the tasks, with the exception of the *Contingency Naming* task of which 31 (64.6%) boys completed. Of the boys with FXS who scored over 30 on the CARS scale, many were able to complete the EF tasks. Specifically, 3 could not complete the working memory task and had high CARS scores between 36 and 47; similar to the composition of boys who were unable to complete the set-shifting task (mean CARS score=29.2).

Chapter 3

Results

Demographics

Data from the Attention, Memory, and Executive Functions in Males with FXS data set were analyzed using SPSS 17.0 for Windows. The data contained boys with FXS (N = 56) and a typically developing group of boys (N = 40). The sample size was large enough to generate adequate power for the proposed predictor model. No missing data were revealed through an exploration in any of the moderator variables (i.e., CBCL scales) or the targeted dependent variables (i.e., EF tasks). While the groups differed significantly in chronological age (FXS =10.1 years-old; Typically Developing = 5.2 years-old), as a result of the study's mental-age matching procedures, the distribution of the mental ages was even (FXS = 5.24 years, Typical = 5.32 years). No significant differences were found in level of maternal education between the groups (the mean for both groups completed college).

Psychiatric Moderators of Day/Night Task (Inhibition)

Of the boys with FXS, 42 (77.8%) were able to complete the inhibition task with a mean score of 9.24 (SD=5.09), compared to the typically developing cohort which had a mean of 13.07 (SD=2.96). Examination of the correlation matrix between the psychiatric variables and the Day/Night Task revealed several significant correlations. The Day/Night Task was significantly correlated with CBCL Anxiety Problems, Affective

Problems, ADHD, and the Total Number of Diagnoses. All of the correlations were of moderate strength. These variables were used in the ANOVA to examine potential moderating effects on the executive function of inhibition. The CBCL variables of Internalizing Problems, Externalizing Problems, Total Problems, and Oppositional Defiant Disorder did not significantly correlate with the Day/Night Task. These relationships can be seen in Table 2.

A single ANOVA was conducted to examine the moderating effects of the CBCL variables on the Day/Night Task. When the moderators of Anxiety Problems, Affective Problems, ADHD, and Total Number of DSM Diagnoses were entered into the model, none of these variables significantly interacted with the group variable. The results indicated that these specific psychiatric variables did not affect the performance of boys with Fragile X on the Day/Night Task significantly more than their typically developing MA-matched peers. These findings can be seen in Table 3.

Psychiatric Moderators of Woodcock-Johnson Memory for Words Task (Working Memory)

Fifty-one (94.4%) of the boys with FXS completed the working memory task with a mean score of 5.84 (SD=2.94), compared to the mean score of 12.78 (SD=2.37) in their typically developing peers. Examination of the correlation matrix between the psychiatric variables and the Woodcock-Johnson Memory for Words task revealed several significant correlations. The Day/Night Task was significantly correlated with CBCL Internalizing Problems, Total Problems, Anxiety Problems, Affective Problems, ADHD, and the Total Number of Diagnoses. Nearly all of the correlations were of moderate strength, with the relationship with Anxiety Problems and ADHD being strong.

These variables were used in the ANOVA to examine potential moderating effects on the executive function of working memory. The CBCL variables of Externalizing Problems and Oppositional Defiant Disorder did not significantly correlate with the Memory for Words Task. These relationships can be seen in Table 2.

A single ANOVA was conducted to examine the moderating effects of these CBCL variables on the Memory for Words Task. When the moderators of Internalizing Problems, Total Problems, Anxiety Problems, Affective Problems, ADHD, and Total Number of DSM Diagnoses were entered into the model, none of these variables significantly interacted with the group variable. The results indicated that these specific psychiatric variables did not affect the performance of boys with FXS on the Woodcock-Johnson Memory for Words Task significantly more than their typically developing peers. These findings can be seen in Table 4.

Psychiatric Moderators of Contingency Naming Test Subtest 3 Total Errors (Set-Shifting)

Fourteen (25.9%) boys in the FXS group completed the set-shifting task with a mean Total Errors score of 12.5 (SD=5.50), compared to the typically developing boys' mean Total Errors score of 3.68 (SD=5.07). Examination of the correlation matrix between the psychiatric variables and the Contingency Naming Test Subtest 3 Total Errors revealed several significant correlations. Subtest 3 Total Errors was significantly correlated with CBCL Total Problems, Anxiety Problems, Affective Problems, ADHD, and the Total Number of Diagnoses. Nearly all of the correlations were moderately strong, with ADHD being the strongest. These variables were used in the ANOVA to examine potential moderating effects on the executive function of set-shifting. The

CBCL variables of Internalizing Problems, Externalizing Problems, and Oppositional Defiant Disorder did not significantly correlate with the Total Errors on Subtest 3 of the Contingency Naming Test. These relationships can be seen in Table 2.

A single ANOVA was conducted to examine the moderating effects of these CBCL variables on Subtest 3 Total Errors of the Contingency Naming Test. When the moderators of Total Problems, Anxiety Problems, Affective Problems, ADHD, and Total Number of DSM Diagnoses were entered into the model, none of these variables significantly interacted with the group variable. The results indicated that these specific psychiatric variables did not affect the performance of boys with FXS on the Contingency Naming Test significantly more than their typically developing peers. These findings can be seen in Table 5.

Psychiatric Moderators of NEPSY Tower (Planning/Problem Solving)

Thirty-five (64.81%) of the boys with FXS completed the planning task yielding a mean score of 3.89 (SD=2.47), compared to a mean of 8.61 (SD=3.43) for the typically developing boys. Examination of the correlation matrix between the psychiatric variables and the NEPSY Tower Task revealed several significant correlations with the CBCL DSM-Oriented Scales. Specifically, the Tower Task was significantly correlated with CBCL Anxiety Problems, Affective Problems, ADHD, and the Total Number of Diagnoses. All of the correlations were of moderate strength. These variables were used in the ANOVA to examine potential moderating effects on the executive function of planning/problem solving. The CBCL variables of Internalizing Problems, Externalizing Problems, and Total Problems did not significantly correlate with the NEPSY Tower Task. These relationships can be seen in Table 2.

A single ANOVA was conducted to examine the moderating effects of these CBCL variables on Tower Task. When the moderators of Anxiety Problems, Affective Problems, ADHD, and Total Number of DSM Diagnoses were entered into the model, none of these variables significantly interacted with the group variable. The results indicated that these specific psychiatric variables did not affect the performance of boys with FXS on the NEPSY Tower Task significantly more than their typically developing peers. These findings can be seen in Table 6.

Chapter 4

Discussion

The primary purpose of this paper was to explore the potential moderating effects of social-behavioral problems on the executive functioning in boys with FXS. This was accomplished using measures conceptualized from a multidimensional model of EF, where differences have been noted between boys with FXS and mental-age matched typical boys (Hooper et al., 2008), and the CBCL as a measure of social-behavioral functioning using a dimensional diagnostic parent rating scale with associated DSM-IV scales. Using the same sample from the Hooper et al. (2008) study, none of the measured symptoms had significant interactions with working memory and planning. These findings showed that, in general, social-behavioral difficulties do not appear to affect executive function performance any more than what might be seen in a typically developing population; i.e., the effects were not disproportionately more in the sample of boys with FXS. This was true whether the CBCL summary scores were used, the DSM-IV-Oriented Scales, or the Total Number of DSM-IV diagnoses were used.

Question 1

Question one related to whether social behavioral-problems, as defined by the CBCL (Internalizing, Externalizing, and Total Score), moderated EF in boys with FXS. It was hypothesized that internalizing problems would moderate the executive functioning in males with FXS more than in mental-age matched typically developing

boys. Based on the correlation matrix with each of the four executive function tasks, Internalizing Problems correlated only with Woodcock-Johnson Memory for Words (working memory), Total Problems with both Woodcock-Johnson Memory for Words and Subtest 3 Errors on the Contingency Naming Test (set-shifting), and the Externalizing Problems scale did not correlate with any of the executive function tasks. Despite these significant correlations with the dependent measures, none of the targeted interactions were significant. This indicated that elevated ratings on the CBCL summary scales did not significantly affect EF performance any more for the boys with FXS than the typically developing boys. These findings did not support the hypothesis that internalizing symptomology would affect executive functioning. This may be due in part to the low reliability of the CBCL for children with FXS and intellectual disability. Using appropriate diagnostic scales for this population, results would likely reflect findings by other researchers which signal elevated rates of anxiety, namely Specific and Social Phobias (Cordeiro et al., 2011; Freund et al., 1995; Kau et al., 2000).

Question 2

Research question two pertained to how specific diagnoses (i.e., Anxiety Problems, Affective Problems, ADHD, ODD), as defined by the DSM-oriented scales on the CBCL, might serve as specific moderators of EF in boys with FXS. Based on the available literature, it was hypothesized that the specific diagnoses of Anxiety Problems and Affective Problems would moderate the EF performance in boys with FXS more than in mental-age matched typically developing boys. Although the correlation matrix produced more significant correlations with the EF tasks than the

CBCL summary scales, it was interesting that none of the dependent measures correlated significantly with the Oppositional Defiant Disorder scale. Despite these significant correlations, none of the particular diagnoses of Anxiety, Affective, or ADHD on DSM-oriented scales on the CBCL were found to be moderators of EF in boys with FXS. Similar to Question 1, the aforementioned low internal consistency of the DSM-oriented Anxiety and Affective Problems scales on the CBCL in boys with FXS may be responsible, in part, for this lack of an interaction with the group variable. As previously discussed, the DSM-Oriented scales have been shown to be suspect measures of Anxiety and Affective problems in boys with FXS (Sullivan, 2006). Despite this potential measurement shortcoming, it does not appear that specific psychiatric diagnoses, as derived from parent report, disproportionately affect EF in boys with FXS when compared to typically developing boys. Further, as anxiety is not a singular phenomenon, perhaps the use of "state" versus "trait" measures of anxiety would produce a different result. Perhaps boys with FXS would show more disruption of their cognitive abilities than typically developing boys during moments of emotional disequilibrium. As such, measures of state anxiety (e.g., physiological responses) may prove more fruitful as potential moderators of cognitive functions.

Question 3

Similar to research questions one and two, the aggregate number of DSM-oriented diagnoses on the CBCL was not found to moderate EF tasks in boys with FXS, singularly or when combined with ASD symptoms. This outcome is expected given the results of the individual DSM-Oriented scales. It may be the case that

symptomology appropriately assessed for this population, and then inserted into a cumulative scale, would yield different results.

In addition, it is important to keep in mind the neurodevelopmental research which suggests that progressive improvement of executive functions occurs over time (Anderson, 2002; Levin et al., 1991; Welsh & Pennington, 1988), and that such skills may be entwined with other emerging abilities such as language (Halperin et al., 1989; Luria, 1973) and memory (Hale, Bronik, & Fry, 1997; Henry & Millar, 1993). It may be that moderating factors, such as social-behavioral functions, affect executive functions with increasing age and accompany slower rates of growth in the executive function domains. Examination of the mediation effect of various social-behavioral functions over time may prove useful.

Limitations and Future Directions

Low completion rates of the EF tasks by the boys with FXS who had high scores for ASD symptomology on the CARS replicates literature reporting dysfunction in these domains in children with comorbid ASD. Several researchers have also reported increased rates of social withdrawal and avoidance (Cordeiro et al., 2011; Freund et al., 1995; Kau et al., 2000; Sullivan, 2006) in boys with comorbid FXS and ASD. Future research on moderators of EF in children with FXS would benefit from assessment of ASD symptomology between groups to parse out this additional source of comorbidity.

Although the CBCL has been used successfully with FXS (Hatton et al., 2003) and other populations with intellectual disabilities (Pandolfi, V., Magyar, & Dill., 2009; Scholte, Van Berckelaer-Onnes, & Van der Ploeg, 2008), other social-emotional

assessment strategies may have yielded a different set of results, perhaps producing the expected group by social-behavioral interaction for each of the executive function tasks examined. Further assessment of Internalizing symptoms and other behaviors using questionnaires sensitive to children with FXS may help us better understand which mechanisms of the autonomic nervous system compete with attention resources, and in which states they are most likely to manifest. Specifically, physiological measures (e.g., heart rate, Galvanic skin response, etc.) may be of significant interest during the assessment process to determine if state-related anxiety affects performance in a disproportionate manner when compared to mental age matched controls.

Additionally, it has been postulated that executive dysfunction is linked to an increase in internalizing behavior problems in typically developing, school-aged children (Cassidy, 2011). Findings from the current study may not be unique to boys with FXS, but rather a developmental phenomenon that becomes more pronounced with age, and specific moderating effects of social-behavioral function may manifest at a later developmental time point in this population. Future studies should focus on boys with FXS at various ages, as well as state-versus-trait anxiety profiles; particularly if EF developmental trajectories begin to plateau with increasing age in the boys with FXS.

The relationship between parents' stress levels/behaviors and children's internalizing behaviors is well documented in children with developmental disabilities (e.g., Spratt et al., 2007). While it was out of scope of this project, it is important to keep in mind the ecological milieu of the study sample, and note that a child with

endorsed behavior and/or cognitive problems likely increases the parents' stress, which has been shown to exacerbate the child's internalizing symptoms.

Conclusions

In the current study, maladaptive behavioral and emotional problems did not negatively influence executive functioning boys with FXS. Specifically, there was no correlation found between internalizing problems, any specific DSM-oriented diagnoses, or the aggregate number of symptoms endorsed on the CBCL and executive functioning in this sample. While it is common perception among clinicians that boys with FXS exhibit symptoms of anxiety that affect their task performance above and beyond that of their mental-age matched peers, findings from the current study did not support these anecdotes. Future research should focus on symptom-specific assessment appropriate for children with ID to best target necessary interventions.

Table 1. Demographics x Group

	Fragile X (N = 56)	**Typically Developing (N = 40)**
Chronological Age	120.91 (20.93) N = 56	62.28 (9.53)
Mental Age	62.87 (8.65) N = 55	63.85 (9.40)
Ethnicity	White = 47 (84%) Minority = 9 (16%)	White = 34 (85%) Minority = 6 (15%)
Maternal Education	College N=53	College
Meet Cutoff for:		
Internalizing Problems	N = 18 (32.1%)	N = 3 (7.5%)
Externalizing Problems	N = 22 (39.3%)	N = 3 (7.5%)
Total Problems	N = 29 (51.8%)	N = 1 (2.5%)
Anxiety Problems	N = 27 (48.2%)	N = 4 (10%)
Affective Problems	N = 21 (37.5%)	N = 5 (12.5%)
ADHD	N = 21 (37.5%)	2 (5%)
ODD	N = 20 (35.7%)	2 (5%)
Total Number of Diagnoses	N = 36 (64.3%)	11 (27.5%)

Table 2. Correlations of Executive Function Tasks with CBCL Summary Scales, DSM-Oriented Scales, and Number of Diagnoses.

Fragile X Group	Day/Night Task (Inhibition)	WJ Memory for Words (Working Memory)	Contingency Naming Test Subtest #3 Errors (Set-Shifting)	NEPSY Tower (Planning)
Internalizing Problems	-.271	-.391**	.296	-.21
Externalizing Problems	-.047	-.159	.135	.032
Total Problems	-.304	-.479**	.412***	-.273
Anxiety Problems	-.420**	-.565***	.447**	-.418**
Affective Problems	-.363*	-.312*	.378*	-.353*
ADHD	-.398**	-.505***	.569***	-.407**
ODD	-.053	-.136	.055	.034
Total Number of Diagnoses (CBCL)	-.398**	-.469**	.414**	-.390**

* < .05
** <.01
*** <.00

Table 3. CBCL Moderators of Day/Night Task Performance (Inhibition).

Interactions	F	*p* Value
CBCL DSM Oriented Scales		
Group x Anxiety Problems	.372	.544
Group x Affective Problems	1.431	.236
Group x ADHD	.190	.664
CBCL Total Diagnoses		
Group x Total Number of Diagnoses[1]	.701	.500

df = 1, 69
[1]df = 2, 73

Table 4. CBCL and CARS Moderators of WJ Memory for Words Task (Working Memory).

Interactions	F	*P* Value
CBCL Summary Scales		
Group x Internalizing Problems	3.114	.081
Group x Total Problems	.794	.376
CBCL DSM Oriented Scales		
Group x Anxiety Problems	.108	.743
Group x Affective Problems	.079	.779
Group x ADHD	.019	.891

df = 1, 78
*p < .05

Table 5. CBCL Moderators of Contingency Naming Test Subtest 3 Total Errors (Set-Shifting).

Interactions	F	*p* Value
CBCL Summary Scales		
Group x Total Problems	1.222	.276
CBCL DSM Oriented Scales		
Group x Anxiety Problems	.931	.341
Group x Affective Problems	.031	.098
Group x ADHD	.264	.610
CBCL Total Diagnoses		
Group x Total Number of Diagnoses[1]	.241	.787

df = 1, 35
[1]df = 2, 33

Table 6. CBCL and CARS Moderators of NEPSY Tower (Planning).

Interactions	F	*p* Value
CBCL DSM Oriented Scales		
Group x Anxiety Problems	.345	.559
Group x Affective Problems	.170	.681
Group x ADHD	.933	.337
CBCL Total Diagnoses		
Group x Total Number of Diagnoses[1]	.862	.427

df = 1, 73
[1]df = 2, 74
* p < .001

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