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ADHD Symptoms, Social Problems, And Independence In Adolescent And Young Adult Males With FXS

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DEDICATION

This work is dedicated to my parents. I can never thank you enough for your unwavering love, support, and confidence while I pursued my goals.

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ABSTRACT

Adolescents and young adults with fragile X syndrome (FXS) typically report a range of comorbid, impairing conditions including cognitive deficits, autism, and attention deficit/hyperactivity disorder (ADHD). Similarly these individuals experience social problems and very low levels of proficiency in independent living, which makes it extremely important to better understand what contributes to these deficits and how to potentially intervene and improve outcomes. Despite this importance, very little attention has been paid to the developmental period of adolescence in the FXS population. In addition, no previous work has utilized specific narrow band measures to probe for ADHD symptoms and instead has relied on broad-band measures. The purpose of the current study was to investigate the prevalence of ADHD symptoms within a sample of adolescent and young adult males with FXS and the impact that ADHD symptoms have on socialization and independence when controlling for autism and IQ. Results suggested that ADHD was not related to any of the outcomes when controlling for autism and IQ. However, higher levels autism severity were related to lower levels of adolescent independence, reiterating previous research documenting the impairment autism has on independence in adolescents with FXS. Additionally, the results provided ADHD prevalence rates in adolescents and young adults with FXS through the employment of a narrow-band measure. Finally, the study developed an adolescent scale of independence to better capture levels of independence in comparison to measures created for adults. Implications of findings, limitations, and directions for future research are discussed.

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CHAPTER I

INTRODUCTION

Fragile X syndrome (FXS) is a single gene disorder associated with significant developmental concerns and high rates of comorbidity, with more than 95% of individuals diagnosed with FXS reporting at least one comorbid condition (Bailey, Raspa, Olmsted, & Holiday, 2008; Bailey, Raspa, Holiday, Bishop, & Olmsted 2009; Hartley et al., 2011). Investigations of comorbid conditions within FXS have shown that males display early emerging attention deficits and hyperactivity which persist and subsequently put them at risk for attention deficit hyperactivity disorder (ADHD; Bailey et al., 2008; Sullivan, Hatton, & Hammer, 2006). ADHD is a widely recognized developmental disorder characterized by impairing levels of inattention and/or hyperactivity and impulsivity (American Psychological Association, 2013). However, significant gaps exist in the current understanding of the presentation, developmental nature, and impact of ADHD in FXS and whether it is similar to, or unique from, individuals with *idiopathic ADHD* (ADHD not associated with FXS). Furthermore, information is scant concerning ADHD in FXS during adolescence and the transition to adulthood, when outcomes are particularly salient for long-term quality of life, limiting our understanding of the dynamic relationship between ADHD symptomology and adult outcomes. The purpose of the current study was to investigate the presence of ADHD symptoms in adolescent and young adult males with FXS and to examine the impact these symptoms have on socialization and independence in adulthood.

In order to fully understand the complexities of the emergence of ADHD in clinical populations such as FXS, a dynamic, developmental approach must be utilized. Dynamic systems theory is a theoretical framework that supports the examination of multiple mechanisms including biological, social, and cognitive facets using a developmental approach to examine mechanisms' change or stability over time. The dynamic system theory implements this developmental investigation of mechanisms by integrating the influence of previous experiences while dually recognizing that each mechanism also exerts influence on future outcomes (Smith & Thelen, 2003; Thelen, 1992, 2008; Thelen & Smith, 1998). As such, dynamic systems theory is well suited as a framework for the current study given that FXS is a single gene disorder associated with a cumulative impact of social and cognitive impairments. Other approaches, such as a strictly genetic approach, which only accounts for genetic influences in isolation, or a strictly behavioral approach that only accounts for observable, behavior-based relationships, cannot fully address the nature and impact of ADHD in FXS.

Fragile X Syndrome

FXS is a single gene disorder characterized by nearly universal cognitive impairments in males. FXS is caused by a trinucleotide (CGG) repeat expansion in the 5 untranslated region of the fragile X mental retardation 1 (*FMR*1) gene on the X chromosome (Sherman, 2002), that suppresses the production of the fragile X mental retardation protein (FMRP). FMRP is crucial for brain development, especially in the cognitive functions of learning and memory. FXS is the most common heritable form of intellectual disability (ID), affecting approximately one in 2,500 individuals across demographics (Hagerman, 2008). Since FXS is an X-linked genetic disorder, males are

most severely affected, while females may have varying degrees of impairments given that they have two X chromosomes with one randomly inactivating (Hagerman, 2008). Children with FXS exhibit a number of behavioral and cognitive concerns that distinguish the fragile X phenotype from those of other neurodevelopmental disorders, such as impaired memory, delayed social skills development, and diminished capacities for attention, learning and adaptive functioning.

Comorbidities in FXS. Co-occurring conditions are prevalent in FXS, with over 95% of males diagnosed with at least one comorbid condition (Bailey et al., 2008). Furthermore, males with FXS report an average of four comorbidities (Bailey, Raspa & Olmstead, 2010). While the impairment seen by FXS alone can be severe and result in a variety of negative outcomes, the addition of a comorbid disorder has the potential to increase the levels of impairment seen in these individuals. ID is the most common comorbid condition reported in FXS, with nearly 98% of males experiencing intellectual impairments (Bailey et al., 2008). Generally, males with FXS exhibit moderate to severe IDs, which lead to difficulties in language development, behavioral regulation, and the acquisition of mastery in adaptive and life skills (Hall, Burns, Lightbody, & Reiss, 2008). These deficits create many challenges related to daily functioning that compound other health and developmental considerations.

While ID is the hallmark feature of FXS, there are a number of behavioral concerns and comorbid conditions frequently associated with FXS, and one of the most prevalent is autism spectrum disorder (ASD; Bailey, Hatton, Skinner, & Mesibov, 2001; Hatton et al., 2006). Based on findings from studies employing diagnostic, ASD-specific measures, the prevalence of autism in males with FXS is approximately 65–75% (Klusek,

Martin, & Losh, 2014; McDuffie, Thurman, Hagerman, & Abbeduto, 2014; Thurman, McDuffie, Hagerman, & Abbeduto, 2014), with nearly 90% of males with FXS displaying at least one symptom of autistic behavior (Bailey et al., 2008; Kaufmann et al., 2004). Children with comorbid ASD and FXS often have significant cognitive deficits and exhibit impaired adaptive and social skills with severe problem behaviors, impeding their abilities to acquire appropriate levels of daily independent functioning (Bailey et al., 2001; Kau et al., 2004; Kaufmann et al., 2004; Rogers, Wehner, & Hagerman, 2001). Therefore, with nearly 90% of males reporting at least one autistic behavior, ASD needs to be addressed as a possible compounding factor when investigating other behavioral disorders or concerns in FXS, such as ADHD.

Identifying comorbidities in FXS. Given the significant rates of comorbidity within FXS, a major challenge is distinguishing individual disorders and understanding their unique impact on outcomes. In order to accomplish this, multiple methods are available to probe for symptoms. The most commonly used tools are broad-band rating scales (e.g., the Child Behavior Checklist, CBCL, Achenbach, 1991; Achenbach & Rescorla, 2001; the Child Behavior Questionnaire, CBQ, Rothbart, Ahadi, Hersey, & Fisher, 2001; the Behavior Assessment Scale for Children, BASC, Reynolds & Kamphaus, 2004), which survey for a wide variety of symptoms that could be indicative of a large array of disorders. These are useful in investigations aimed at identifying all possible symptoms or deficits a sample or population may experience. However, when a particular disorder of interest is identified, more disorder-specific or narrow-band measures are applicable (e.g., the Conners rating scales for ADHD; Conners, 2008). Narrow-band measures typically have higher specificity to accurately probe for

symptoms of a specific disorder and, ideally, will result in more true-positive diagnoses especially in populations where there may be competing symptoms, such as FXS (Herreais, Perrin, & Stein, 2001; Thapar & Thapar, 2003). In the FXS literature, the majority of information regarding ADHD comorbidity has come from utilizing broad-band measures to survey for symptoms. In comparison, investigations into the identification of ASD in FXS have successfully used autism-specific diagnostic measures (Klusek, Martin, & Losh, 2014; McDuffie, Thurman, Hagerman, & Abbeduto, 2014; Thurman, McDuffie, Hagerman, & Abbeduto, 2014). Using specific, narrow-band measures when investigating other disorders will likely lead to more accurate identifications of the presence of symptoms and can help identify developmental outcomes that are impacted by those symptoms.

ADHD in FXS

Attention deficit/hyperactivity disorder (ADHD) is a persistent pattern of inattention and/or hyperactivity/impulsivity that occurs across settings and across development (American Psychiatric Association, 2013). Inattention symptoms represent persistent trouble with sustaining focus on tasks or activities and symptoms of hyperactivity-impulsivity involve excessive movement and the inability to regulate behaviors (APA, 2013). Diagnoses for ADHD are given based on individuals meeting criteria from the Diagnostic and Statistical Manual, Fifth Edition (DSM-V; APA, 2013). The DSM-V states for a diagnosis of ADHD – Inattentive presentation, six symptoms of inattention and less than six symptoms of hyperactivity/impulsivity need to be present. Similarly, for ADHD Hyperactive/Impulsive presentation, six symptoms of hyperactivity/impulsivity and less than six symptoms of inattention need to be present.

Finally, ADHD Combined presentation is diagnosed when 6 or more symptoms of both inattention and hyperactivity/impulsivity are present. Additionally to symptom count, a diagnosis of ADHD requires significant impairment in academic, social or occupational functioning and these symptoms must be present across at least two settings for more than six months and have been present before the age of twelve.

Regarding symptoms at the core of ADHD (i.e., inattention, hyperactivity, impulsivity), findings from broad-band measures for behavioral concerns (e.g., CBCL, CBQ) and experimental measures of attention suggest that children with FXS are at a disproportionately high risk for developing ADHD (Bailey et al., 2008; Cornish, Scerif, & Karmiloff-Smith, 2007; Cornish et al., 2013; Cornish & Wilding, 2010; Sullivan et al., 2006). However, the use of ADHD-specific measures to probe for symptoms is lacking in the FXS literature, making it difficult to draw accurate conclusions about the unique effects of ADHD in FXS. While a number of studies measure ADHD symptoms (i.e., inattention, impulsivity, hyperactivity) as part of a larger project, only three studies explicitly focused on the prevalence of ADHD in FXS and none of them used measures specific to ADHD (Bailey et al., 2008; Farzin et al., 2006; Sullivan et al., 2006). A national parent report survey of 967 families with a male with FXS aged 6 through adulthood indicated problems with inattention (84%) and hyperactivity (66%; Bailey et al., 2008), while a small study of males with FXS across the lifespan suggested 93% were above clinical cutoffs for ADHD (Farzin et al., 2006). In another study incorporating broad-band measures of parent and teacher-report and symptom inventories and diagnostic checklists to capture ADHD symptomatology and areas of impairment in boys with FXS (mean age 10 years old), 31% met criteria for ADHD – Inattentive type, 7.4%

met criteria for ADHD – Hyperactive type, and 14.8% met criteria for ADHD- Combined type (Sullivan et al., 2006). These rates of elevated ADHD symptoms are commensurate or higher than those in populations of individuals with nonspecific ID (8-45%; Hastings et al., 2005) and individuals with other genetic disorders such as Williams Syndrome (60%; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006) and Down syndrome (6-44%; Ekstein, Glick, Weill, Kay, & Berger 2011). In sum, the use of broad measures of symptomatology and behavior suggest that features of ADHD appear to be salient and impairing in FXS. However, while prevalence rates have been reported using parental report or broad based screeners, further investigation with narrow-band measures is needed to draw conclusive relationships about the presentation, development, and impact of ADHD in FXS.

Etiology of ADHD in FXS. The underlying mechanisms of idiopathic ADHD are not clearly identified; however, the literature implies a strong genetic component with estimates that the heritability of ADHD lies between .60 and .80 (Barkley, 2006; Hankin, Abela, Auerback, McWhinnie, & Skitch, 2005; Hunter, Epstein, Tinker, Abramowitz, & Sherman, 2012). Multiple genes have been identified as risk factors for developing ADHD across populations, such as the dopamine transporter and receptor genes (i.e., DAT4; Hawi et al., 2003; Hunter et al., 2012). In FXS, the etiology of ADHD is also unclear given that atypical *FMR*1 gene function (associated with the suppression of FMRP production) is implied. The loss of FMRP causes the dysregulation of many genes, resulting in altered brain structure, neural connections, and structural pathways (Lo-Castro, Agati, & Curatolo, 2010). These alterations may lead to the enlargement of the amygdala, hippocampus, and thalamus, which are also implicated in idiopathic

ADHD. Despite these similarities, other research has shown that FMRP is not directly related to higher levels of ADHD symptoms in males with FXS (Farzin et al., 2006; Sullivan et al., 2006). One study examined the unique effect of *FMR*1 levels on ADHD symptoms as measured by an ADHD-specific rating scale (CAARS; Conners, 1999) and the impact of FMR1 in conjunction with polygenetic systems (e.g., familial pedigrees) in adult female carriers of fragile X (carrier individuals have a mutated form of the *FMR*1 gene, but do not have the full mutation, FXS). The study indicated that the *FMR*1 gene accounted for 5% of the variance seen in ADHD symptom severity, while polygenetic factors accounted for approximately 50% of the variance (Hunter et al., 2012). Therefore, while the *FMR*1 gene may play a role in the development of ADHD symptoms, multiple genes are clearly involved and the specific impact of *FMR*1 on the underpinnings of ADHD in FXS appears complex.

Presentation of core ADHD features in FXS. The core symptoms of idiopathic ADHD include impulsivity, impaired attention, and over-activity (American Psychological Association, 2013; Barkley, 2006; Faraone & Mick, 2010; Hankin, et al., 2005). Boys with FXS often report a similar constellation of core symptoms to those reported in boys with idiopathic ADHD, including attention problems, behavior concerns, trouble with social interactions, and poor adaptive functioning (Backes et al., 2000; Hatton et al., 2002; Kau et al., 2004, Sullivan et al., 2006). Parent and teacher ratings indicate that boys with FXS have significantly more behavior problems in the classroom than do non-FXS peers (i.e., inattention, peer issues, and restlessness), and these problems align with those experienced by children with idiopathic ADHD (Symons, Clark, Roberts, & Bailey, 2001; Turk, 1998). These concerns begin early in childhood

and are salient across both home and school settings, resulting in impaired functioning across a variety of adaptive skills and regulatory processes (Backes et al., 2000; Hatton et al., 2002; Kau et al., 2004, Grefer et al., 2016).

Presentation of associated ADHD features in FXS. Beyond the hallmark symptoms of ADHD, other associated features have been shown to influence the presentation of ADHD in FXS in a similar fashion to individuals with idiopathic ADHD, such as specific cognitive patterns and temperament characteristics. On average, individuals with idiopathic ADHD typically have lower global cognitive abilities than do their non-ADHD peers (Rommel et al., 2015) and experience delays or deficits in specific cognitive processes such as poor attentional control, slower processing speeds, delayed executive functioning, and impaired working memory (Calhoun & Mayes, 2005; Mayes & Calhoun, 2007; Wechsler, 2003; Willcutt et al., 2005). Likewise, individuals with FXS and elevated ADHD symptoms also exhibit deficits in sustained attention and executive functioning, which result in pervasive inhibitory control deficits that persist across development into early adulthood (Bailey et al., 2008; Cornish et al., 2013; Farzin et al., 2006; Hatton et al., 2002; Scerif et al., 2004; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012; Sullivan et al., 2006). Similarly, childhood temperament characteristics (e.g., social approach, activity level, impulsivity) have been associated with ADHD symptoms in both individuals with idiopathic ADHD (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Martel & Nigg, 2006) and individuals with FXS (Grefer et al., 2016). Grefer et al. (2016) found that the temperament domain of surgency, characterized by impulsivity, activity level, and approach, was indicative of elevated ratings of ADHD by parents of young boys with FXS during preschool ages (3–4 years

old) and at school entry (5–6 years old). These associated features provide some insight regarding the cognitive difficulties and individual differences that potentially influence the unique manifestation of ADHD in FXS.

Developmental Trajectory of ADHD in FXS. To date, the majority of ADHD-FXS literature has concentrated on children, so significant gaps still exist in literature regarding the development and presentation of ADHD symptoms in FXS in adolescence and adulthood. The development of core and associated symptoms of ADHD appears to follow similar trajectories in both FXS and idiopathic ADHD populations. The symptoms of impaired attention, increased impulsivity and reduced inhibition emerge early in childhood in males with FXS and idiopathic ADHD and persist through the lifespan (Barkley, 2006; Farzin et al., 2006; Frolli, Piscopo, & Conson, 2014; Hagerman & Hagerman, 2002; Sullivan et al., 2006). Hyperactivity is an elevated concern when boys are young, but the severity seemingly lessens with age, usually by adolescence or adulthood (Barkley, 2006; Hagerman & Hagerman, 2002). Also, in idiopathic ADHD, hyperactivity symptoms may not necessarily decrease with age, but transform and manifest differently in adulthood (e.g., restlessness in adulthood) compared to the observable over-activity seen in childhood (Volkow &Swanson, 2013). It also worth noting that Frolli et al. (2014) reported a decline in both hyperactivity and inattention in adolescents with FXS based on findings from broad-band surveys. The lack of ADHD-specific measures employed in the FXS population again makes the specific course and presentation of ADHD less definitive than in the idiopathic ADHD literature. Additionally, in individuals with idiopathic ADHD, symptoms of ADHD negatively impact achievement, levels of functioning, and social relationships for adolescents and

young adults (Kent et al., 2011; Loe & Feldman, 2007), which may lead to delinquency, drug use, poor relationships, and lower ratings of overall life satisfaction (Barkley, 2006; Flory & Lynam, 2003; Hoza, 2007; Molina et al., 2012; Sibley et al., 2012; Wehmeier, Schacht, & Barkley, 2010). To date, no studies have been conducted to investigate the direct impact that ADHD symptoms have on the lives and developmental outcomes (i.e., job performance, relationships, daily functioning) of adolescents and young adults with FXS. The investigation of the impact of ADHD symptoms in adolescents and young adults with FXS is warranted to further probe for any similarities or differences that may exist between these individuals and individuals with idiopathic ADHD.

ADHD in FXS: Compounding Conditions. As previously stated, males with FXS report an average of four comorbid conditions (Bailey, Raspa, & Olmstead, 2010). Given this, it is important to tease apart the impact of ADHD symptoms from those of other conditions, such as ID and ASD. While both individuals with idiopathic ADHD and individuals with FXS and elevated ADHD symptoms exhibit certain cognitive patterns of deficits, these patterns differ from an impairing ID. When identifying the effects of ADHD in conjunction with or separate from ID, studies from the FXS literature have shown that ADHD symptoms and IQ are not typically correlated and lower IQ does not result in more severe or persistent levels of ADHD symptoms in this population (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012; Scerif &5, 2013). So, while children with FXS experience the core symptoms associated with ADHD, these symptoms cannot be solely explained by their intellectual impairment.

Similarly, the co-occurrence of both ASD and ADHD is often prevalent in both FXS and non-FXS populations (Larson, Russ, Kahn, & Halfon, 2011; Rommelse et al.,

2011; Simonoff et al., 2008). These two disorders share common symptoms such as attention problems, inhibition, and impaired executive functioning and working memory (Bailey et al., 2001; Chantiluke et al., 2014; Cornish et al., 2012; Guy et al., 2012; Kau et al., 2004; Rommelse et al., 2011). While diagnosis-specific measures of ASD and ADHD have been employed in non-FXS populations, this has not been the case in FXS. Previous studies of males with FXS have used ASD-specific measures but are limited to experimental measures of attention or broad-band behavior measures to probe for symptoms of ADHD. Given the high prevalence of both ASD and ADHD symptoms in the FXS population, it is crucial to employ ADHD-specific, narrow-band measures to adequately tease apart and clarify the unique impact of ADHD symptoms on a variety of outcomes.

Adult Outcomes in FXS: Socialization

Children and adolescents with idiopathic ADHD show higher rates of peer rejection and fewer close relationships with more problematic social relationships with peers and family as compared to non-ADHD peers (Bagwell et al., 2001; Friedman et al., 2003; Hoza, 2007; Mariano & Harton, 2005; Sibley et al., 2012). As these individuals mature, they often report lower levels of relationship satisfaction and are more likely to associate with deviant peer groups (Barkley, 2006; Friedman et al., 2003; Hoza, 2007; Wehmeier et al., 2010). In comparison, individuals with ID and elevated ADHD symptoms have more instances of social isolation, problems making friends, and overall problems with social skills (Mayes, Calhoun, Mayes, & Molitoris, 2012). Of note, however, no studies have examined how the presence of ADHD directly affects social outcomes in individuals with ID. Social problems are a persistent concern for individuals

with FXS as well, and parents and teachers of boys with FXS endorse that children with FXS are observed to have fewer friendships and instances of social interaction (Bailey & Hatton, 2001; Hatton et al., 2002; Kau et al., 2004). These impairing socialization problems have the potential to hinder the acquisition of skills needed for daily living as well as impact the quality of life experienced by these individuals.

As expected, social problems in individuals with FXS are persistent across the lifespan as well. In a national study of adult males living with FXS, less than a third of the participants had developed friendships, less than 1% had a significant other or romantic relationship, and that most of their leisure time was spent in solitary activities (e.g., watching TV, listening to music; Hartley et al., 2011). Frolli et al. (2014) explicitly examined changes from childhood to adolescence in individuals with FXS, no changes concerning problems with peers, pro-social behaviors, emotional symptoms, or instances of behavioral problems with the onset of adolescence, were reported. Despite stagnant trends from childhood to adolescence, these individuals still consistently reported elevated levels of peer problems (Frolli et al., 2014). Additionally, adolescents with FXS exhibit social avoidance behaviors, impaired theory of mind abilities, and are frequently diagnosed with social anxiety (Cordeiro et al., 2011; Hall et al., 2009; Lewis et al., 2006).

Of particular interest to the current study, Chromik and colleagues (2015) investigated the influence of ADHD symptoms on various measures of socialization in adolescent and young adults with FXS, reporting that ADHD symptomatology resulted in an increase of social problems and a decrease in adaptive measures of socialization. Chromik's sample endorsed high levels of ADHD symptoms across two parent-report measures of ADHD and high levels of social problems on the CBCL Social Problems

scale, the same scale used in the current study. Chromik's study included IQ as a covariate in their analyses; however the study did not account for autism or any other possible confounding, comorbid condition that could affect the interpretation of the relationship between ADHD symptoms and social problems. Investigations have shown that individuals with FXS on average endorse at least 4 comorbidities (Bailey, Raspa & Olmstead, 2010) with significant rates of males also meeting criteria for ASD (70%; Klusek, Martin, & Losh, 2014; McDuffie et al., 2014; Thurman et al., 2014). In sum, while a few number of studies reported elevated social problems in an adolescent FXS population (Frolli et al., 2014; Hall et al., 2009; Lewis et al., 2006), Chromik and colleagues reported the only finding, to date, that ADHD symptoms directly resulted in the increase of social problems (Chromik et al., 2015). This study however, did not include other comorbidities in their investigation, a crucial component in teasing apart the unique contribution of ADHD from other comorbidities. Given that Chromik and colleagues were the first to investigate this relationship, more research is needed to replicate these findings or examine if the explicit investigation of other comorbid conditions may play a role in the influence and presentation of ADHD in this population.

Adult Outcomes in FXS: Independence

One of the crucial outcomes of adolescence and young adulthood is the development of independence. Independence includes proficiency in daily activities, employment, involvement in finances, personal hygiene, leisure activities, establishment of residence, and the development of romantic relationships and friendships (Bailey et al, 2009; Hartley et al., 2011; Luckasson et al., 2002; Seltzer & Krauss, 1989). At present, a limited number of descriptive studies have been conducted to investigate independence

and adulthood outcomes in FXS. Of those, very few have included examination of the relationship between comorbid conditions in FXS and outcomes in adulthood. Despite the ample knowledge of lower independence and poorer outcomes in idiopathic ADHD, no studies have been conducted to examine the impact of ADHD on independence in individuals with FXS. The common problems noted in achieving independence for individuals with idiopathic ADHD include poor job performance (e.g., higher high school dropout rates and lower rates of post-secondary education, lower ratings on job performance, lower salaries, lower job satisfaction, job loss), poorer and fewer social relationships, substance abuse, and lower ratings of overall effectiveness and efficiency in daily life (Barkley, 2006; Sibley et al., 2012; Turgay et al., 2012).

To date, Hartley et al. (2011) have conducted the most in-depth study of adult outcomes for individuals with FXS, in which they examined adult life in five domains: residential setting, employment, assistance needed with everyday life, friendships, and leisure activities. For males with FXS (N = 239; M = 31.46 years old, age range: 22.1 - 63.5 years old), approximately 70% co-resided with their parents, while 10% lived independently, and nearly 20% lived in a group home. Hartley et al. (2011) also reported that 95% of individuals needed assistance in everyday life. The majority (60%) of adult males with FXS were employed, with over 20% full-time and 40% part-time. With respect to friendships, 79% endorsed having at least one or more friendships. Hartley et al. (2011) reported that 87% partook in multiple activities, while 13% engaged in less than two leisure activities. Hartley et al. (2011) generated an overall independence score based on the five domains of adult independence outlined above (i.e., residence, employment, assistance, friendships, and leisure activities), which fell on a scale from 1

to 10. Within their sample of adult males with FXS, 19% had very low levels of independence (score 0-2) and nearly 72% had low (3-4) or moderate (5-6) levels of independence, while just over 8.5% had a high level of independence (7-8).

Bailey et al. (2009) asked families who had at least one child with FXS about functional skills and measures of independence. They obtained data on children with the full mutation (1,015 boys and 283 girls) whose ages ranged from infancy to 61. In males aged 16 and older, the majority of the participants reportedly mastered the most skills within the domains of personal care, with the exception of specific skills such as eating at a normal pace or brushing teeth, which were mastered by less than half of the sample. Also, specific communication skills, such as understanding others, using two- to three-word sentences, speaking at a normal volume, and recognizing letters and words by sight, were mastered. Bailey et al. (2009) also investigated the influence of comorbid conditions on skill mastery and found that as the number of comorbid conditions increased, the level of mastery decreased, although they did not investigate whether specific conditions affected skill mastery more so than others.

Finally, Hustyi, Hall, and Reiss (2014) also investigated independent living skills in adolescents and young adults with FXS, and how these skills are influenced by autism symptomatology. A sample of 70 individuals with FXS and 35 controls matched on IQ, with an average age of 20.57 years, were assessed for an autism spectrum disorder and independent living skills were evaluated with the Independent Living Scales (ILS; Loeb, 1996). The ILS is a task aimed to gauge the participants' proficiency in the domains of orientation and memory (ability to tell time, recall his/her phone number, etc.), money management, home and transportation management, health and safety, and social

adjustment (Hustyi et al., 2014; Loeb, 1996). Regarding autism classification, 23 males (65.7%) with FXS met criteria for an autism spectrum disorder on the ADOS. In Hustyi et al.'s (2014) study, 100% of the males with FXS scored in the non-independent range. Interestingly, however, when matched on age, IQ, and autism status, individuals with FXS were no more impaired than were their non-FXS controls with intellectual disabilities. This suggests that the presence of comorbid conditions, specifically autism, is more indicative of lower independence skills and delayed functional skills than FXS status alone. In order to increase knowledge about independence in FXS, further investigation is needed to examine how independence is affected by elevated ADHD symptoms, and specifically the impact ADHD has on independence in adolescents and young adults with FXS.

Current Study

The literature indicates that ADHD symptoms are present in children with FXS and these symptoms persist into adolescence and adulthood. Previous studies have relied on broad measures to probe for ADHD symptoms or experimental measures to describe features of ADHD, which limits the direct conclusions that can be drawn about the presentation and impact of ADHD symptomatology in FXS. Narrow-band, specific measures are crucial to identifying the unique ADHD symptom presentation and subsequent impact on developmental outcomes. Broad-band measures may pick up on symptoms associated with other comorbidities such as ID and ASD. Hence, specific measures for each condition are important in order to tease out the unique impact of ADHD symptoms while also controlling for any possible effects of other comorbidities (i.e., ID and ASD). A measure such as the Conners 3 (Conners, 2008) allows for a

specific and direct assessment and is sensitive for symptoms aligned with *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*; APA, 2004) criteria for an ADHD diagnosis. Additionally, while social problems and low adulthood independence have been observed in FXS, there is a substantial need for further description of how ADHD symptoms affect social behaviors and independence in adolescent and adult males in this population, especially since this is a major transition period for individuals. The purpose of this study was to fill these gaps through the examination of how social problems and levels of independence are affected when elevated symptoms of ADHD are present in adolescent and young adult males with FXS. Through the investigation of the following research questions, an increased understanding of the impact ADHD has on adolescent and young adult males with FXS has the potential to inform training programs and interventions to improve the quality of life experienced by these individuals. The study's research questions are as follows:

Research Question I: What is the relationship between ADHD symptoms and socialization in adolescent and young adult males with FXS, controlling for autism severity and cognitive ability (IQ)?

Hypothesis: Given the literature on problems socialization in idiopathic ADHD and problems in socialization in the FXS population, we hypothesize that elevated levels of ADHD will be related to higher levels of social problems.

Research Question II: How do ADHD symptoms affect independence for males with FXS, controlling for autism severity and cognitive ability (IQ)?

Hypothesis: Given the previous literature on independence for males with FXS, we hypothesize that individuals with elevated symptoms of ADHD will have

lower levels of independence across two scales, one measuring adult independence and one measuring adolescent independence.

CHAPTER II

METHOD

Participants

Participants for the current study were enrolled in an ongoing cross-site investigation targeting the longitudinal language and behavioral development of adolescent males with FXS or ASD. Inclusion criteria for the original longitudinal study required that the participant lived with his biological mother at the time of the first assessment session (T1) and a positive genetic test to confirm FXS status. The sample for the larger study includes 60 males with FXS and 25 males with ASD across two investigation sites -- the University of California, Davis M.I.N.D. Institute (UC Davis) and the University of South Carolina (USC). The sample for the current study consisted of males with FXS who were assessed at USC (N = 30) at the second assessment session (T2). As previously stated, males with FXS are more severely affected than their female counterparts who have varying degrees of impairment (Hagerman, 2008). The inclusion of only males with the full mutation better controls for confounding considerations that accompany the inclusion of permutation or carrier females, who report varied profiles in behaviors and outcomes due to varying levels of cognitive and biological impairment, rather than the presence of comorbid conditions (e.g., ADHD and ASD). The mean age for the participants at T2 was 18.74 years (SD= 2.30; range: 16.05-24.11). Concerning racial background, 80% of the sample identified as Caucasian (non-Hispanic), 7% Hispanic, 7% African-American, 3% Asian, and 3% biracial.

Of the available literature reporting racial distribution, the current study's representation resembles those in other studies, with 70-85% of the samples being Caucasian, 2-15% Hispanic, 2-12% African-American, 1-2% Asian, 1-5% Native American/Pacific Islander (Bailey et al., 2009; Sansone et al., 2011; Sullivan et al., 2006). The average household reported four residents and the average household income for the participants' families was $79,038 (range: $10,000–$150,000+). See Table 2.1 for demographics.

With respect to interventions and treatment, mothers indicated that at the time of assessment, 10% were not currently receiving any interventions, 60% received speech services, 30% occupational therapy, 10% physical therapy, 13% behavioral interventions, 7% other mental health services, and 53% were taking medication for a range of symptoms. Of particular interest to this study concerning medication, 37% of the sample was taking medication for attention problems and 23% was taking medication for hyperactivity. Refer to Table 2.2 for current interventions and Table 2.3 for target symptoms of medications.

Relationships between the treatments and the study's variables were examined. A significant relationship was found between medication status (i.e., those individuals taking medication for *any* symptom) and total ADHD symptoms (r= .540, *p*= .002). A significant relationship was also reported for medication status and ADHD hyperactivity symptoms (r= .584, *p*= .001). Medication status was not related to social problems or adult or adolescent independence. Interestingly, medication for ADHD symptoms (e.g., inattention, hyperactivity) was not related to the ADHD symptoms or social problems or adult or adolescent independence. Individual treatments (i.e. speech, physical therapy,

behavioral interventions) and the total amount of non-medication treatments was also not related to ADHD symptoms, social problems, or independence.

Procedure

Data were collected as part of an ongoing cross-site investigation targeting the longitudinal language and behavioral development of adolescent males with FXS or ASD. Given the longitudinal nature of the larger project, assessments occur annually for a total of four years. Every year, the participants with FXS are asked to complete multiple measures designed to capture their language and behavioral development. Measures from the larger investigation that are identified for this study included autism severity ratings, collected at time 1 (T1), and measures of social problems, independence in adulthood, cognitive ability/IQ, were collected at the second assessment session (T2), with a few collections occurring at the third assessment session (T3; n = 3) or fourth assessment session (T4; n = 1). Additionally, the current study asked mothers to complete an ADHD rating scale, the Conners 3 (Conners, 2008), regarding her son's possible ADHD symptoms at T2, with the exception of three participants who completed it at T3 and one at the T4. The variability in assessment time points was due to the late addition of the ADHD measure to the study protocol for T2, so those participants missed at T2 were assessed at T3 or T4. Finally, the data on ADHD symptoms were only collected at USC at T2 as part of a site-specific data collection expansion effort to investigate other behavioral and developmental concerns beyond the scope of the original study.

Measures

Primary Variables

As stated in the research questions, the primary independent variable was total ADHD symptoms. The primary dependent variables were social problems, adult independence, and adolescent independence.

Total ADHD symptoms. The total number of ADHD symptoms for each participant was measured utilizing the Conners 3rd Edition–Parent Short Form (Conners 3–P(S); Conners, 2008), completed by each participant's mother. The Conners 3 – P(S) is a 43-item rating scale that probes for symptoms on six different subscales associated with ADHD, as defined by *DSM-IV-TR* (4th ed., revised; *DSM-IV*; APA, 2000) criteria: inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and peer relations. Ratings are on a 4-point Likert scale: *not true at all* (0); *just a little true* (1); *pretty much true* (2); and *very much true* (3). For each scale, a raw score is generated, as well as a *t* score and percentile to indicate severity. The Conners 3 scales were normed on a large, representative sample reflecting the 2000 United States Census (Conners, 2008). Previous versions of the Conners scales have a history of robust reliability and validity. The internal consistency (Cronbach's alpha) of the Conners 3–P scales ranged from 0.85–0.94 (Gallant et al., 2008). The Conners 3 Parent rating scale yielded high rates of test-retest reliability (r = 0.85) and inter-rater reliability (r = 0.81). Further, the content scales reflected the expected trends in convergent and divergent validity as well as a discriminative validity value of 0.78 (Kao & Thomas, 2010). The Conners scales have previously been used in populations with nonspecific intellectual disability (Deb, Dhaliwal, & Roy, 2008; La Malfa, et al., 2008) and other genetic

disorders such as Down syndrome (Edgin et al, 2010) and Prader-Willi syndrome (Wigren & Hansen, 2005).

The current study used a total ADHD symptoms raw score, a combination of the raw scores of the inattention and hyperactivity/impulsivity scales on the Conners 3, to investigate trends of total ADHD symptoms endorsed in the sample. This scale consists of 11 items, where parents can rate each item from 0 – 3, indicating the presence of the symptoms and how much the item reflects the severity of the symptom in the child. This total is reflected in the Total ADHD symptoms raw score and this score is a measure of symptom presence and severity. It should be noted that this total symptom score is not necessarily equivalent to an ADHD diagnosis, as it does not account for other DSM-V criteria such as the number of settings where symptoms are present, areas of impairment, or presence of symptoms for 6 months or before the age of 12. See Tables 2.4 and 2.5 for descriptive statistics. The internal consistency for the ADHD symptoms raw score in the current study was strong ($\alpha = 0.93$). For additional descriptive considerations of the sample, *t* scores were examined and findings were as follows. *T* scores indicative of above-average parental concerns fall under the ranges of: 60–64 = high average; 65–69 = elevated; and 70+ = very elevated. Specifically for inattention, 5 participants from this sample fell in the high average range, 2 participants in the elevated range, and 14 in the very elevated range. Concerning hyperactivity/impulsivity, 2 participants fell in the high average range, 2 in the elevated range, and 10 in the very elevated range. Those who obtain elevated or elevated scores are above clinical cutoffs for inattentive, hyperactive/impulsive, or combined (inattention and hyperactivity/impulsivity) presentations of ADHD. In this sample, 12 participants with elevated to very elevated

symptoms of inattention and hyperactivity/impulsivity (combined presentation; 40%), 4 had elevated to very elevated symptoms of inattention only (13%), and 2 had elevated to very elevated symptoms of hyperactivity/impulsivity only (7%).

Social problems. The social problems subscale of the Child Behavior Checklist (CBCL/6-18; Achenbach, 1991; Achenbach & Rescorla, 2000) was used to measure social problems in this sample. The CBCL was completed by each participant's mother. The CBCL is a widely used, 118-item parent rating scale used to assess the internalizing and externalizing symptoms of children. Items are answered using a 3-point Likert scale of *not true* (0), *somewhat or sometimes true* (1), and *very true* (2). The CBCL consists of symptom-specific scales, composite scores (internalizing, externalizing, and total problems), and also scales based on criteria from the DSM-IV (APA, 2004). The social problems subscale consists of 11 items that probe for problems in socialization that affect children, adolescents and young adults such as: jealousy, loneliness, dependence, difficulty getting along with others, preference for younger friends, difficulty being liked, and a history of being teased. The social problems scale demonstrates strong construct and discriminative validity in previous research (Eiraldi et al., 2000; Ivanova et al., 2007).

The CBCL was normed on a large, representative sample of children and adolescents ranging from six to eighteen years of age and yielded high rates of reliability ($r = 0.95$; Nakamura, Ebesutani, Bernstein, & Chorpita, 2009). The test-retest reliability rate for the CBCL empirically based scales had a mean of 0.85 (range: $r = 0.79 – 0.89$; Eiraldi et al., 2000). The internal consistency for the CBCL (Cronbach's alpha) was 0.80 (range: $\alpha = 0.76–0.85$; Eiraldi et al., 2000). This version of the CBCL has also

successfully been used in populations with FXS (Bargagna, Canepa, & Tinelli, 2002; Farzin et al., 2006; Hatton et al., 2002; Hatton et al., 2006) and in adolescent and young adult populations of FXS, specifically through the age of 25 (Chromik, et al., 2015; Hoeft et al, 2007; Smith et al., 2012). Of particular interest to the current study, the social problems subscale on the CBCL has been used in adolescent and young adults with FXS and shown to be a valid measure of this population's social problems (Chromik, et al., 2015).

This study utilized the social problems subscale raw score to examine the total number of social problems endorsed in the sample. One participant did not have a CBCL social problems score due to errors in data collection. The internal consistency for the social problems scale in this sample was $\alpha = 0.51$. See Table 2.4 for descriptive information. The average number of social problems endorsed was 2.57 (SD = 1.55). At an item level, 22 participants endorsed speech problems, 15 dependence, 12 clumsiness, 11 a preference for younger individuals, 5 teased, 4 jealousy, 3 not liked, 2 lonely, 2, not getting along with others, 1 for accidents, and 0 for believing others are out to get them. For additional descriptive considerations of the sample, *t* scores were examined and findings were as follows. *T* scores between 67-70 indicate a child is at-risk for experiencing social problems while *t* scores above 70 are clinically significant. In this sample, no participants had social problems *t* scores falling in the clinically significant range. Nine participants (30%) had social problems *t* scores in the at-risk range.

Independence in adulthood. Adult independence scores were obtained from a parent report survey, the Current Life Questionnaire (CLQ; Hartley et al., 2011). The CLQ was completed by each participant's mother. Hartley et al. (2011) developed the

questionnaire and scoring based on questions selected from a national survey of individuals with FXS created by Bailey, Raspa, and Olmsted (2010). The complete survey consists of 16 items indicating levels of independence across multiple facets of daily functioning and has been used to survey adults older than 21 years of age (range: 22 to 64 years).

The adult independence composite score, as defined by Hartley and colleagues (2011), is compiled from the ratings on five specific items on the CLQ in order to provide an efficient rating of adult independence. The items were coded on 3-point scale, on which a higher score indicates a higher level of independence in the given domain. The five domain items that are used to calculate the adult independence composite score are: residence (2 = *independent living,* 1 = *co-reside with parents,* 0 = *in a group home*); the amount of assistance needed in everyday life (2 = *no assistance,* 1 = *minimal assistance,* 0 = *moderate or considerable amount of assistance*); employment (2 = *full-time,* 1 = *part-time,* 0 = *no job*); the number of friendships (2 = *three or more friends,* 1 = *one to two friends,* 0 = *no friends*); and the number of leisure activities (2 = *six or more activities,* 1 = *three to five activities,* 0 = *two or fewer activities*). When indicating the number of leisure activities, mothers also specify the type of activities, which include visiting family; reading, writing, or going to the library; housework, such as cooking or gardening; painting, drawing, or other art activities; playing on the computer or surfing the Internet; watching TV or playing video games; and listening to music. The composite score of adult independence can range from 0 –10. Scores from 0–2 indicate very low independence, 3–4 is low independence, 5–6 is moderate independence, 7–8 is high independence, and 9–10 is very high independence. This adult independence composite

score was used to measure adult independence in our sample. The internal consistency for the adult independence scale in this sample was adequate, $\alpha = 0.61$. This score was expected due to the heterogeneity of items in this scale. See Tables 2.4 and 2.6 for descriptive statistics.

Independence in adolescence. The current study also generated and used an adapted eight-item adolescent independence score from items on the CLQ to examine domains of independence emerging in adolescence. The items from the adult independence composite score on the CLQ that were also included in the adolescent independence composite scale were: the amount of assistance needed in everyday life, the number of friendships, and the number of leisure activities. Due to the residential requirement in the inclusion criteria at T1 of the larger study (participants must be residing with biological mothers at T1) and the targeted adolescent and young adult age range of the sample (*M*= 18.74, age range: 16-24; 90% participants are in school or training programs but not employed), the items of residence and employment were not included in the adolescent independence composite score. Items from the CLQ that were not included in the scale for the original adult independence composite score but were then included in the adolescent independence score were: managing finances, having a romantic relationship, having a driver's license or permit, participating in activities with people who do not have a disability and having friendship with people who do not have a disability. These items have either a score of 1 (*yes*) or 0 (*no*). Similar items have been used in previous studies to capture independent functioning in across populations of adolescents (Conti-Ramsden & Durkin, 2008; Hume et al., 2014; Smith et al., 2013; Van Petegem et al., 2012; Wallace et al., 2000). The only other items on the CLQ that were

not included related to employment or other adult services that our sample was not reporting (e.g., type of employment, work benefits, working with a job coach, and using other community post-21 services). The new eight-item adolescent independence composite scale yields scores ranging from 0 - 11. Scores from 0–2 indicate very low independence, 3–4 is low independence, 5–6 is moderate independence, 7–8 is high independence, and 9–11 is very high independence. Refer to Tables 2.4 and 2.7.

Covariates

Cognitive ability (IQ). The Leiter International Performance Scale–Revised (Leiter-R) is a non-verbal measure of intelligence for individuals from ages 2 to 20 and 11 months. The Leiter-R was administered by trained research staff to each participant. It consists of 20 subtests that load on to four domains of intelligence: reasoning, visualization, memory, and attention. The distribution of intelligence scores follows a bell curve with mean equal to 100 and standard deviation equal to 15; thus, average cognitive abilities range from 85–115. There was high internal consistency (Cronbach's alpha; Roid & Miller, 1997) across norming groups for Overall IQ ($\alpha = 0.88–0.93$), Reasoning and Visualization ($\alpha = 0.75–0.90$), and Memory and Attention ($\alpha = 0.67–0.85$). The Leiter-R is intended for use with individuals with limited verbal abilities (Roid & Miller, 1997). Tasks include activities such as picture completion and sequential ordering. It has also been used consistently in FXS populations with reliable results (Bailey et al., 2001; Hatton et al., 2006). This study used the Overall (Brief) Intelligence Quotient (IQ) standard score as a measure of cognitive ability (IQ). See Table 2.4.

Autism symptom severity. Scores of autism severity were derived from the comparison score on the Autism Diagnostic Observation Schedule, Second Edition

(ADOS-2; Lord et al., 2012). The ADOS-2 was the only measure completed at the first assessment time point (T1) and was only administered at T1, due to the larger study's protocol. It was administered and scored by trained research staff at USC. The ADOS-2 is a semi-structured, standardized assessment that probes for ASD symptoms across the domains of communication, social interaction, and restricted and repetitive behaviors, and is considered a "gold standard" for assessing for autism symptoms. The ADOS-2 has four available modules based on chronological age and language abilities. Modules 2 and 3 were used in the original longitudinal study. Items on these two modules fall on either the Social Affect (SA) scale or the Repetitive and Restrictive Behavior (RRB) scale, both of which are combined for the Overall Total scale. For modules 1–3, as reported in the ADOS-2 manual, internal consistency was adequate for SA (SA $\alpha = 0.87–0.92$), but low for RRB (RRB $\alpha = 0.51–0.66$). The low internal consistency was expected for RRB given the heterogeneity of the items on this scale. The ADOS-2 Overall Total scale yields high inter-rater reliability (Module 2: $r = 0.96$; Module 3: $r = 0.94$) and high test-retest reliability (Module 2 = 0.83; Module 3 = 0.87). The ADOS modules have been used in FXS research (Farzin et al., 2006; Hazlett et al., 2009; Hustyi et al., 2014; Klusek, Martin, & Losh, 2014).

Comparison scores on the ADOS-2 were developed from calculations previously used to generate calibrated severity scores (Gotham et al., 2009) for earlier editions of the ADOS. Comparison scores do not measure functional impairment, but rather provide an index of severity for autism symptoms relative to age and language level (Gotham, Pickles, & Lord, 2012; Lord et al., 2012). Comparison scores ideally are more informative indicators of the impact of ASD symptoms than using cut-off scores which

only provide simple, dichotomous "autism"/ "no autism" categorical levels. Concerning comparison scores (autism symptom severity), 47% of the sample had moderate severity and 27% had high severity, while 10% had low severity and 16% of the sample had minimal to no symptoms. Total Scores were also examined prior to analyses, and 73% were above the cut-off for autism or autism spectrum (N = 22). Given the impact of ASD in FXS and the ASD-ADHD symptom overlap in the literature, ASD severity scores were used as a covariate variable to account for the impact of ASD symptom severity in the sample. See Table 2.4 for descriptive statistics.

Statistical Procedures

For descriptive statistics for the primary and covariate variables, see Table 2.4. To address the research questions, three multiple regression analyses were proposed to examine the possible relationship between ADHD symptoms and a dependent variable of interest (social problems, adult independence, or adolescent independence), while accounting for the identified covariates, IQ and autism severity. All analyses were performed using the IBM SPSS 23 software or GPower 3.1 software. Finally, a sensitivity power analysis was performed before the primary data analysis to investigate the expected effect size for the study, given the sample size (N = 30). Under conditions using common alpha ($\alpha = .05$) and power (power = .80) standards (Cohen, 1969, 1988), a sample size of 30 has an expected effect size in the regression models of 0.22 (GPower 3.1 Software).

Prior to the primary regression analyses, assumptions for normality, linearity, and homoscedasticity of residuals were examined. The presence of univariate outliers was examined for each variable through examination of boxplots and standard scores,

specifically z-scores. Normality and homoscedasticity were assessed through the visual examination of histograms. Linearity was assessed through the visual examination of bivariate scatterplots. Appropriate transformation methods were performed for those variables that violated assumptions (ADHD, IQ, autism severity). Box-Cox transformations were used, given these transformation identify the appropriate lambda (λ) value for each variable and then raise all data to the power indicated by that lambda value (equation: $Y' = Y^{\lambda} - 1/\lambda$; Box & Cox, 1964). Box-Cox transformations are also commonly used in social science research (Osborne, 2010). Finally, Pearson correlations were conducted to determine if correlational relationships were present between ADHD symptoms, the covariates (IQ and autism severity), and the dependent variables (social problems, adult independence, and adolescent independence).

Following the examination of these assumptions, three regression analyses were conducted and examined. For each model, the ADHD variable was included, along with IQ and autism severity as covariates, for each respective dependent variable (social problems, adult independence, adolescent independence). Following any significant findings, a Bonferroni correction was applied to the model in order to adjust for multiple comparisons with a significance value of $p = .016$. The Bonferroni correction was applied to reduce the likelihood of a Type I error resulting from the analysis of three separate regression models. Significant findings before and after the Bonferroni correction were discussed.

Table 2.1 Descriptive Statistics of Participant Characteristics

Participant Characteristics	**N**	**%**
Race/ethnicity		
Caucasian (non-Hispanic)	24	80
Hispanic	2	7
African American	2	7
Asian	1	3
Biracial	1	3
Household Size		
2	1	3
3	7	23
4	11	37
5+	11	37
Household Income		
10,001 – 50,000	9	30
50,001 – 100,000	8	27
100,001 – 150,000	7	23
150,001 +	6	20

Table 2.2 Current Interventions Services

Intervention	**N**	**%**
Medication	16	53
Speech Services	18	60
Occupational Therapy	9	30
Physical Therapy	3	10
Behavioral Services	4	13
Mental Health Services	2	7
No Services	3	10

Table 2.3 Breakdown of Medication

Medication Target Symptoms	**N**	**%**
Attention	11	37
Hyperactivity	7	23
Aggression	3	10
Self Injury	1	3
Anxiety	11	37
Irritability	2	7
Temper	2	7
Oppositional	0	0
Seizures	1	3
Sleep	3	10
Stereotypic Behavior	1	3
Depression	0	0
Bipolar Mania	0	0
Mood Stabilizer	1	3
Other	0	0

Table 2.4 Descriptive Statistics for Independent, Dependent and Covariate Variables

Variable (Measure)	**N**	***M***	***SD***	**Min**	**Max**	**% Above Clinical Threshold**
ADHD Total Symptom Score (Conners 3 P-S Raw Scores)	30	13.20	8.15	0	28	60%
Autism Severity (ADOS-2 Comparison Score)	30	5.67	2.35	1	10	73%
Social Problems (CBCL Raw Score)	29	3.14	2.10	1	8	30%
IQ (Leiter-R Standard Score)	30	39.60	6.28	36	56	N/A
Adult Independence Composite (CLQ Original Composite)	30	4.27	1.48	2	6	N/A
Adolescent Independence Composite (CLQ Adapted Composite)	30	5.30	2.00	2	9	N/A

Table 2.5 ADHD T Scores Above Clinical Cut

	N	**%**
ADHD Presentations (Total)	**18**	**60%**
ADHD Inattention Presentation	4	13%
ADHD Hyperactivity/Impulsivity Presentation	2	7%
ADHD Combined Presentation	12	40%

Table 2.6 Adult Independence – Current Life Questionnaire (CLQ)

Independence Composite Score		**N**	**%**
	Very Low Independence (0-2)	5	17
	Low Independence (3-4)	11	37
	Moderate Independence (5-6)	13	43
	High Independence (7-8)	1	3
	Very High Independence (9-10)	0	0
Independence Domain			
Residence	Independent	0	0
	Parents	30	100
	Group Home	0	0
Employment	Full Time	0	0
	Part Time	3	10
	Unemployed	27	90
Assistance needed in everyday life	No Assistance	0	0
	Minimal Assistance	14	47
	Moderate/Considerable	16	53
Leisure Activities	>6 Activities	23	76
	3-5 Activities	5	17
	0-2 Activities	2	7
Friendships	>3 Friends	7	24
	1-2 Friends	16	52
	No Friends	7	24

Table 2.7 Adolescent Independence – Current Life Questionnaire (CLQ)

Independence Composite Score		**N**	**%**
	Very Low Independence (0-2)	2	7
	Low Independence (3-4)	8	27
	Moderate Independence (5-6)	10	32
	High Independence (7-8)	8	27
	Very High Independence (9-11)	2	7
Independence Domain			
Assistance needed in everyday life	No Assistance	0	0
	Minimal Assistance	14	47
	Moderate/ Considerable	16	53
Leisure Activities	>6 Activities	23	76
	3-5 Activities	5	17
	0-2 Activities	2	7
Friendships	>3 Friends	7	24
	1-2 Friends	16	52
	No Friends	7	24
Involvement in Activities with People without Disabilities?	Yes	28	93
	No	2	7
Friends Without Disabilities?	Yes	14	47
	No	16	53
Romantic Relationship	Yes	3	10
	No	27	90
Driver's License/Permit	Yes	3	10
	No	27	90
Involvement in Finances	Yes	15	50

CHAPTER III

RESULTS

Preliminary Analyses

As previously stated, assumptions were examined prior to analyses. First, three extreme outliers were detected for IQ through visual examination of boxplots and examination of standard scores, specifically z-scores. First under the examination of boxplots, five outliers for IQ were originally identified in our FXS population. Under more critical analysis, the standard of a z-score greater that +2.5 or less than -2.5 is an indicator of an extreme outliers was used (Tabachnick & Fidell, 2007), and three IQ scores fit this criteria. These three outliers were removed from the IQ data before analyses. There were no other outliers detected in the remaining variables. It was found that ADHD symptoms, IQ and autism severity violated the assumption of normality, so appropriate transformations were performed in order to reduce skewness and improve homoscedasticity. The ADHD data was positively skewed and resulted in a Box-Cox transformation ($\lambda = 0.63$) that was conducted before the primary analyses. IQ data were also positively skewed and transformed using the Box-Cox transformation ($\lambda = -0.16$). Finally, autism severity data were observed to be leptokurtic, so they were also transformed using a Box-Cox transformation ($\lambda = 1.30$). All other variables did not violate assumptions, thus did not require transformations. Also, collinearity and multivariate outliers were examined in each regression model. Concerning multivariate

outliers, each model was examined for outliers using Mahalanobis distance's criteria of p = .001; no outliers were detected. Collinearity was assessed following the examination of correlations using the standard provided by Tabachnick and Fidell (2007), which suggests that multicollinearity exists if a correlation of >.90 is found. By this standard, no multicollinearity was detected amongst the variables.

Pearson correlations were conducted to determine if correlational relationships were present between ADHD symptoms, covariates identified in the literature (IQ and autism severity), and the dependent variables of social problems, adult independence, and adolescent independence. Refer to Table 3.8 for the correlation matrix. As seen in Table 3.8, only autism severity and IQ were significantly correlated with the adolescent independence dependent variable. ADHD was not significantly correlated with any of the dependent variables. Also, neither ADHD nor the covariates were significantly correlated with the adult independence or social problems. Finally, possible age effects were examined and no significant relationships were found between age and any of the variables in the study. This suggests that the trends observed in the study are stable across the ages in this sample.

Primary Analyses

The research questions in this study proposed to examine the relationships between ADHD symptoms and social problems, adult independence, and adolescent independence accounting for IQ and autism severity. Three separate regressions models were run to address each research question.

Social Problems. In the first regression model, the relationship between ADHD and social problems was examined with IQ and autism severity as covariates. Results

indicated that the overall model was non-significant, thus no significant effects of ADHD, or the covariates, on social problems were found; see Table 3.9.

Adult Independence. A second regression model examined the relationship of ADHD and adult independence with IQ and autism severity included as covariates. Regression results indicated that the overall model was non-significant, thus no significant effects of ADHD, or the covariates, on adult independence were found; see Table 3.10.

Adolescent Independence. Finally, a third regression model examined the relationship of ADHD and adolescent independence with IQ and autism severity included as covariates. Regression results indicated a significant effect for the overall model, F (3, 25) = 4.276, p = .016, R^2 = .368. The model suggests that ADHD was not related to adolescent independence. However, autism severity (β = -.396, p = .032) was significantly related to adolescent independence with higher autism severity scores related to lower adolescent independence scores. Also of note, the relationship between IQ (β = .349) and adolescent independence approached significance (p = .058), reflecting a trend for higher IQ scores to be related to higher adolescent independence scores. This model was then analyzed using adjustments specified by Bonferroni's correction for multiple comparisons. The overall model remained significant, however autism severity was no longer a significant predictor. The observed power of this finding was .82 given the sample size, common alpha and effect size (GPower 3.1 Software). See Table 3.11 for the regression model parameters and estimates.

Table 3.8 Correlation Matrix

Variables	1	2	3	4	5	6	7
1. ADHD Scores							
2. IQ Scores	-.18						
3. Autism Severity Score	.14	-.19					
4. Social Problems	.26	.12	-.15				
5. Adult Independence	-.06	.15	-.29	-.05			
6. Adolescent Independence	-.16	.46*	-.39*	-.05	.84**		
7. Age	-.24	.15	-.31	.32	.08	.13	

$p = .05$* $p = .01$**

Table 3.9 Effects of regression model parameters for social problems

	Effect	Estimate	SE	β	*t*	*p*
Social Problems	*Intercept*	1.777	1.110	--	1.602	.124
	ADHD	.224	.120	.384	1.875	.075
	IQ	.044	.527	.017	.084	.934
	Autism Severity	-.047	.094	-.102	-.496	.625

$p = .05$* $p = .01$**

Table 3.10 Effects of regression model parameters for adult independence

	Effect	Estimate	SE	β	*t*	*p*
Adult Independence	*Intercept*	5.335	.861	--	6.198	.000
	ADHD	-.028	.090	-.064	-.316	.755
	IQ	.099	.409	.049	.242	.811
	Autism Severity	-.126	.073	-.347	-1.713	.101

$p = .05$* $p = .01$**

Table 3.11 Effects of regression model parameters for adolescent independence

	Effect	Estimate	SE	β	*t*	*p*
Adolescent Independence	*Intercept*	6.787	.997	--	6.807	.000
	ADHD	-.071	.104	-.117	-.680	.504
	IQ	.949	.474	.349	2.002	.058
	Autism Severity	-.194	.085	-.396	-2.285	.032*

p = .05* *p* = .01**

CHAPTER IV

DISCUSSION

The purpose of the current study was to investigate the prevalence of ADHD symptoms within a sample of adolescent and young adult males with FXS and the impact that ADHD symptoms have on socialization and independence. Adolescents and young adults with FXS typically experience high amounts of social problems and very low levels of proficiency in independent living (Bailey et al., 2009; Frolli et al., 2014; Hartley et al., 2011), which makes it extremely important to better understand what contributes to these deficits and how to potentially intervene and improve outcomes. Despite this importance, very little attention has been paid to the developmental period of adolescence in the FXS population, especially how comorbid conditions, such as ADHD, impact these individuals as they transition from childhood to adulthood. To date, only one study has addressed the impact of ADHD on social problems in adolescent and young adults with FXS (Chromik et al., 2015) and a separate study examined the impact of autism on independence in adolescents with FXS (Hyusti et al., 2014). In addition, no previous work has utilized specific narrow band measures designed to document ADHD symptoms. Rather, existing work has relied on broad-band measures and general parent report. The current study addressed the gaps in the literature by investigating the relationship of ADHD to social problems and independence in adolescent and young adult males with FXS. To our knowledge, this is the first study explicitly examining the

unique impact of ADHD symptoms, autism severity, and cognitive abilities onsocialization and independence in a sample of adolescent and young adult males with FXS. The current study examined the influence of ADHD syptomatology on social problems and independence within the parameters of the dynamic systems theory (Smith & Thelen, 2003; Thelen, 1992, 2008; Thelen & Smith, 1998). This theory examines outcomes while accounting for the developmental interactions of multiple mechanisms (the impact of FXS, cognitive abilities, and additional comorbidities), which share overlapping, common features and influence each other over time. For example, FXS leads to lower cognitive abilities, which in turn affects an individual's ability to regulate processes such as attention or impulsive behavior. The interaction and culmination of FXS, cognitive abilities, and additional comorbidities affect how these individuals function in their environments and impaired functioning may manifest itself in social problems or a lack of proficiency in independence skills. The current study aimed to investigate how ADHD symptoms manifest in adolescent and young adult males with FXS and how ADHD symptoms in turn affect social problems and independence during this developmental period.

ADHD in adolescents and young adults with FXS

Results from this study indicate that 60% of the sample was above the clinical threshold for ADHD symptoms, and the average number of total symptoms endorsed was 13.20 (range: 0 – 28, SD= 8.15). Specifically 40% reported elevated symptoms consistent with ADHD - Combined presentation (N = 12), 13% reported elevated symptoms consistent with ADHD – Inattentive presentation (N = 4), and 7% reported elevated symptoms consistent with ADHD – Hyperactive/Impulsive presentation (N = 2). The

measure used for this study however does not address other details necessary for DSM-V criteria, such as age of onset, persistence of symptoms, and settings. Previous studies using parental report of ADHD symptoms in childhood and diagnostic checklists for presentation settings report 53% of children met diagnostic criteria for ADHD, specifically 31% for ADHD – Inattentive type, 7.4% for ADHD – Hyperactive type, and 14.8% for ADHD- Combined type (Sullivan et al., 2006). In a separate study, 93% of a small sample of males with FXS (N= 14; age: 4-22) were above clinical thresholds, but the separate ADHD presentation or overall symptoms endorsed was not specified (Farzin et al., 2006). Another study reported trends in ADHD symptoms throughout the lifespan where 84% of males with FXS report problems with inattention and 66% report problems with hyperactivity/impulsivity (Bailey et al., 2008). Even given this information, there are no studies reporting prevalence rates explicitly for adolescents or adults who have clinically elevated levels of any of the presentations of ADHD and little information is available about the persistence of ADHD symptoms in FXS in adulthood. In the current study, participants' age was not related to ADHD symptoms, reflecting the stability of symptoms in this age group. ADHD symptoms would also be expected to be stable and persist into adulthood based on the literature available about ADHD symptoms across the lifespan. In comparison, trends in idiopathic ADHD reflect a prevalence rate of approximately 7% in childhood (Thomas et al., 2015) and between 3 to 6% in adulthood (Barkley, 2006; Faraone, Biederman, & Monuteaux, 2002). So, while symptoms may still be present beyond childhood, developmental trajectories of idiopathic ADHD imply a decline in the severity or the impairing manifestation of symptoms overtime, a trend not observed in FXS. In summary, our prevalence of ADHD symptoms above the Conners'

clinical thresholds in adolescents and young adults with FXS is generally consistent with rates reported in other studies specifically investigating ADHD symptoms in children with FXS; however, our prevalence rate is lower than those rates reported for the entire lifespan of individuals with FXS in studies employing broad ratings of problem behaviors.

One possible explanation for the current study's prevalence of symptoms and how it differs from the literature could be due to the result of a more intentional, narrow focused measure used to identify ADHD symptoms, suggesting less "false positives" and more true cases were identified. This study utilized an ADHD-specific measure for symptoms (Conners 3; Conners, 2008), which improves the precision of identifying ADHD symptoms and also raises the threshold for impairment, qualities that broad-band measures do not necessarily possess. Thus, it is possible that the current study more accurately captures the rate of ADHD symptoms in this adolescent and young adult sample of males with FXS. Additionally, this study is also unique in that it explicitly studies the developmental period of adolescence and young adulthood and this restricted age range may account for differences in prevalence rates when compared to previous studies which have focused on children (under the age of 10) or the broader lifespan (4 years+).

Another consideration when interpreting these findings concerning ADHD symptoms is medication usage amongst participants and the subsequent effects. In the complete sample, 53% (N =16) were taking medication for a range of symptoms and 40% (N = 12) were taking medication for inattention and/or hyperactivity (see Table 2.3). A correlation revealed that if a participant was on *any* medication (not just medication

targeted at inattention or hyperactivity), this was significantly related to higher rates of total ADHD symptoms (p = .002). Individuals with a constellation of impairments are likely to be taking one or more medications to address these concerns. Typically beginning between the ages of 6-10 and continuing across the lifespan, it has been reported that 50% of males with FXS took medication to address multiple symptoms, including anxiety, inattention, hyperactivity, and anger or aggression. While prescriptions for hyperactivity and inattention gradually reduce throughout adulthood in this population, the expected effects of any medication would be to reduce the level of impairment experienced by these individuals. In the literature, males with FXS yield impressive rates of responding to medications effectively, including stimulant medication (67-75%), antidepressants (50-70%) and antipsychotics (76%; Bailey et al., 2012; Berry-Kravis et al., 2012; Berry-Kravis & Potanos, 2004; Hagerman et al., 2009; Roberts et al., 2011). Similarly, parents are likely to report less severe symptoms on ratings scales, given the ratings scales ask for recent symptom and behavior presentation for an individual, and the medication may lessen the degree to which parents observe these impairing symptoms.

Social Problems

In the current study, 30% (N= 9) of the adolescents and young adults displayed social problems that fell above the threshold for clinical impairment. Specifically, on a scale of 11 items, the average social problems raw score was 3.15 (SD= 2.10; range: 1-8) and 9 participants had *t* scores in the "at risk" range (range: 67-70; M= 57.36; SD= 5.77). The average symptom count of social problems was 2.57 (SD = 1.55). The most commonly endorsed social problems were speech problems (N= 22), dependence (N=

15), clumsiness (N= 12), and a preference for younger individuals (N= 11). This study then examined the relationship between ADHD symptoms and social problems. Social problems were not related to ADHD symptoms, which is contrary to our hypothesis. It is worth noting, that while the relationship of ADHD and social problems was not significant, the relationship indicated a trend (p = .075). This suggests that increased ADHD symptoms are associated with increased social problems when controlling for ID and ASD. This trend supports previous findings that ADHD symptoms do uniquely impair the degree to which individuals with FXS can successfully navigate social situations and relationships (Chromik et al., 2015; Frolli et al., 2014). While definite conclusions cannot be drawn at this time from the current sample, awareness of this trend highlights the impact ADHD symptoms have on social functioning and potential areas for intervention for improved outcomes.

One consideration is the scale used to measure social problems on the CBCL. This scale includes items such as: jealousy, loneliness, dependence, difficulty getting along with others, preference for younger friends, difficulty being liked, and a history of being teased. This scale seems appropriate for children and adolescents with idiopathic ADHD, who report higher rates of peer rejection, lower levels of relationship satisfaction and association with deviant peer groups, (Bagwell et al., 2001; Barkley, 2006; Friedman et al., 2003; Hoza, 2007; Mariano & Harton, 2005; Sibley et al., 2012; Wehmeier et al., 2010). In comparison, individuals with ID and/or FXS and elevated ADHD symptoms have more instances of social isolation, problems making friends, and overall problems with social skills (Mayes, Calhoun, Mayes, & Molitoris, 2012). Hence, while individuals with ID and FXS experience social problems, these problems result in isolation and

withdrawn behavior that are not overtly disruptive or problematic in the same manner that peer rejection, difficulty getting along with others or being liked, or teasing/bullying are, and these problems are common in idiopathic ADHD. In turn, this restricted, isolate socialization trends may have resulted in lower scores on the CBCL social problems scale.

Similar to our study, Chromik and colleagues also examined ADHD and social problems (social problems *t* scores range: 50 – 81; M= 61.15; SD= 8.00). While both studies focus on similar relationships in adolescent and young adults, some differences exist between the studies. First, Chromik's sample endorsed higher levels of ADHD symptoms (ADHD-T *t* score: M= 77.0, range: 57 – 109; ADHD-C raw score: M= 6.61; SD= 7.18; range: 0 - 30) in comparison to the present sample (inattention M = 69.0; hyperactivity/impulsivity M = 63.5; *t* score ranges: 42 to 90), which in turn may have resulted in the robust relationship of ADHD to higher rates of social problems in Chromik's study and an inability to find a significant relationship in ours. Additionally, due to medication use in the current study, this factor may have resulted in lower ratings of ADHD which could explain our lack of evidence for a relationship between ADHD symptoms and social problems. Second, Chromik's study also included IQ scores as a covariate, however their sample's IQ (IQ M = 66.26; SD= 19.41; range: 40 to 116) was approximately 27 points higher than the current study, so the current study is a very low cognitive functioning profile in comparison (IQ M = 39.60; SD = 6.28; range: 36-56). Lower functioning males may not encounter or demonstrate the social problems specified on the CBCL as frequently as higher functioning peers, which may result in parents not endorsing elevated levels of social problems. Third, Chromik's study did not account for

autism or any other possible confounding, comorbid condition that could affect the interpretation of the relationship between ADHD symptoms and social problems. Investigations have shown that individuals with FXS on average endorse at least 4 comorbidities (Bailey, Raspa & Olmstead, 2010) with nearly 70% of males with FXS meet criteria for ASD (Klusek, Martin, & Losh, 2014; McDuffie et al., 2014; Thurman et al., 2014). This finding is further supported by a widely recognized overlap of ADHD and ASD symptoms in the FXS and non-FXS literatures (Larson et al, 2011; Rommelse et al., 2011; Simonoff et al., 2008). So, it is difficult to draw definitive conclusions regarding the unique contributions of ADHD in relation to social problems from Chromik's study if the possible co-contributing symptoms, such as symptoms of ASD, are not accounted for and ruled out as possible contributors to social problems.

Independence

Based on previous literature and specified in our research question, a combination of FXS, cognitive impairment, and additional comorbidities (e.g., ADHD, ASD) was expected to influence an individual's ability to attain independence. The distinctions among markers of independence in adolescence and adulthood resulted in the employment of two separate measures of independence with the intent to accurately capture developmentally appropriate outcomes. The complete sample was included in the analyses of both scales to assess which scale most appropriately captures the abilities in this developmental period of transition.

Adult Independence. Adult independence was specified on the CLQ as independence in residence, employment, friendships, leisure activities, and the amount of assistance needed on a daily basis. The current sample had 17% (N= 5) fall in the Very

Low category of adult independence, 37% (N= 11) in Low, 43% (N= 13) in Moderate, and 3% (N= 1) had High independence. 100% percent of the sample lived at home, 90% were unemployed, 53% needed moderate to considerable amounts of assistance daily, 76% reported having 1 or more friends, and 93% reported being involved in 3+ activities. In comparison, Hartley's sample of males with FXS (age: 22 years+), 19% had very low levels of independence, 37% had low levels, 34% had moderate levels, while 8.5% had a high level of independence and .5% (n= 1) had a very high level of independence (Hartley et al., 2011). The two studies had commensurate levels of very low and low levels of independence and both report similar findings regarding assistance, friendships and activities; however Hartley's adult sample reported more variability in the individuals displaying moderate to very high levels of independence, with more individuals falling in these higher levels of independence. Similarly, Hartley's sample also reported more employment (60%) and less instances of residing with parents (70%).

This study investigated if ADHD symptoms were related to independence in adulthood and subsequently, found no evidence of a relationship between ADHD symptoms and adult independence in adolescent and young adult males with FXS when controlling for IQ and ASD. Similarly, IQ and ASD were also not related to adult independence. As previously mentioned, past research has not investigated the influence of ADHD on the level of independence achieved by adolescents and young adults with FXS. While the literature does report that comorbid conditions do impact skill mastery and independence in a broad sense (Bailey et al., 2009; Hartley et al., 2011), the literature regarding the contributions of specific comorbid conditions is scant. So, one interpretation of these findings is that ADHD is not impacting achievement of adult

independence in this sample of adolescent and young adult males with FXS. Another possible explanation may be that due to medication, a subsequent improvement in symptoms of ADHD was observed, a trend previously noted in the literature (Bailey et al., 2012; Berry-Kravis and Potanos, 2004; Hagerman et al., 2009; Roberts et al., 2011) and thus resulted in a null finding between ADHD symptoms and adult independence. An alternative interpretation, however, may actually suggest that this measure (CLQ adult independence) does not best capture developmentally appropriate standards for independence in an adolescent or young adult FXS population. A measure that accounts for restrictions in adolescence (e.g., residence considerations, restrictions on employment, etc.) as well as important adolescent "milestones" (e.g., driving a vehicle, involvement in personal finances, etc.) perhaps may more accurately measure independence in this particular age range.

Adolescent Independence. A new scale was created from items on the CLQ and included the items: assistance needed daily, leisure activities, number of friendships, activities with individuals who do not have a disability, involvement in finances, romantic relationships, and holding a driver's permit/license. From the adult independence measure, the items of friendships, assistance needed daily, and leisure activities were included in the new adolescent independence composite while the items of residence and employment were not included due to the residential and employment restrictions commonly applied to all adolescents. The other items (e.g., romantic relationships, driving, finances, etc.) included were chosen from the larger CLQ due to previous studies employing similar items to measure independence in adolescents across populations (Conti-Ramsden & Durkin, 2008; Smith et al., 2013; Van Petegem et al.,

2012; Wallace et al., 2000). Based on this new adolescent independence scale, the current sample had 7% (N= 2) fall in the Very Low category of adolescent independence, 27% (N= 8) in Low, 32% (N= 10) in Moderate, 27% (N= 8) had High independence, and 7% (N= 2) had Very High Independence. In this sample 53% needed moderate to considerable amounts of assistance daily, 76% reported having 1 or more friends, 47% reported having a friend without a disability, 93% reported being involved in 3+ activities, 93% were involved in activities without people with disabilities, 10% held drivers licenses, 10% reported having a romantic relationship, and 50% were involved in their personal finances. In previous research, adolescents only display independence in personal care skills (i.e., hygiene, eating) and scattered communication skills (Bailey et al., 2009). In an explicit investigation of adolescent and young adult males with FXS, 100% of the sample scored in the non-independent range on a scale measuring independence in orientation and memory, money management, home and transportation management, health and safety, and social adjustment (Hustyi et al., 2014). The current sample reported 34% were at high or very high levels of independence, suggesting over a third of these adolescents and young adults with FXS display some levels of independent functioning which is in contrast to Hartley and colleagues findings (2011).

When a relationship between ADHD symptoms and adolescent independence was examined, the present findings suggest that ADHD symptoms were not related to adolescent independence. It is worth noting again that no studies have investigated the impact of ADHD symptoms on independence in adolescence and as such, the current, novel findings suggest ADHD symptoms are potentially less impairing on adolescent independence in comparison to other factors. Alternatively, autism symptom severity and

IQ were found to have greater impact on achieving higher levels of independence than ADHD symptoms. Specifically, as autism severity scores increased, the level of adolescent independence decreased. This sample had an average autism severity score of 5.67 (moderate) and 73% were above the clinical cutoff for autism. Interestingly, the current findings echo results found in Hustyi's study (2014), in which they reported 65.7% of the sample of adolescent and young adult males with FXS were above the clinical threshold for autism and autism symptoms were also found to significantly impact independence. Both studies also employed measures of independence that probed for proficiency in similar domains that adolescents across populations (FXS and non-FXS) need to master. Also, the relationship between IQ and adolescent independence was trending towards significance ($p = .058$). Specifically, when IQ increased, levels of adolescent independence increased, suggesting that in this sample, as cognitive skills improved, one would subsequently expect higher levels of achievement in the domains of independence. So, given this a new scale, there are no other studies to make a direct comparison of findings. However, across current and previous studies, autism symptoms appear to be the most impairing considerations for obtaining proficiency in domains of adolescent independence in males with FXS, above and beyond the impacts of ADHD symptoms or cognitive abilities. Given the stability of the symptoms and levels of independence across ages in this sample, one would also expect to find a similar relationship in adult ages.

With this concordance in findings, the need for treatments and interventions targeted to manage or alleviate autism symptoms is highlighted. Features of autism that may impact independence include social and communication deficits, rigidity in routines,

and a range of repetitive behaviors that may impede adaptability and independent functioning on a daily basis. A variety of interventions have been shown to be effective in the management of impairing symptoms, including interventions extending into adolescence and adulthood. It is a common belief that early intervention on these symptoms results in better outcomes later in life. If interventions can be utilized early in childhood for individuals with FXS, perhaps some of the deficits observed in independence and skill mastery can be addressed before the onset of adolescents and early adulthood, a time meant for the acquisition of new skills before they transition fully into adulthood. This will hopefully improve the outcomes of these individuals for the remainder of the lifespan. Finally, future research is needed to draw more definitive conclusions about developmentally appropriate measurement of independence in adolescents with FXS and also the impact that ADHD, autism, or cognitive abilities may have in adolescent and young adult males with FXS.

Limitations

There are several limitations to this study. First, when the sample of this study is compared to sizes of other projects concerned with broad parental surveys of levels of independence in adult outcomes that do not employ direct assessment (N = 200-1200+; Bailey et al., 2009, Hartley et al., 2011), the sample is small (N= 30). However, this study is comparable size to studies comparing comorbid conditions with FXS affecting adult outcomes that use direct assessment of traits in samples (N= 40-70; Chromik et al., 2015; Hustyi et al., 2014). Not including females limits our findings to males with the full syndrome as opposed to females with varying degrees of impairment which could encompass a broader, more comprehensive representation of individuals with fragile X.

A lack of comparison group is another limitation which restricts our interpretations to adolescent to young adult males with the full fragile X mutation.

Participant characteristics should also be considered. First, this sample was cognitively low functioning with over two-thirds of the sample having an IQ score of 36. Second, the majority of this sample was Caucasian (n= 24) and from families of higher socioeconomic status (SES). Third, our sample had a high degree of autism symptoms with 73% falling within the ASD diagnostic category. Thus, findings might not be generalizable to the larger population of adolescent and young adult males with FXS who have higher IQs, lower ASD symptomology or who represent more ethnic and economic diversity.

Finally, the study relied on parent reporting for ADHD symptoms, social problems, and independence in adulthood and adolescence rather than direct observations through experimental design. Consistent with most studies that utilize parent-reporting measures, results could be confounded by the sample mothers' memories or interpretations of items. Future studies should employ direct participant observation measures (see Hustyi et al., 2014) including biomarkers to eliminate possible error of parent reporting and directly observe behavior.

Summary and Implications

The current findings are important in several domains. First, this work utilized narrow-band measures to document the prevalence of ADHD symptoms in adolescents and young adults with FXS, which has not yet been reported. Second, this study documented the relationship of ADHD features to social problems and independence in adolescent and young adult males with FXS controlling for autism severity and IQ. Third,

we developed a novel measure of independence in adolescence. We found that 60% of the sample was above the clinical threshold in regards to ADHD symptoms. Despite this high prevalence of ADHD symptoms, we report no relationship of ADHD symptoms to social problems and adolescent or adult independence with autism severity related to adolescent independence. Additionally, this study identified that a new measure of adolescent independence may better capture developmentally appropriate features of independence in adolescence, and as such the adult independence measure may not be most appropriate. Given the limited literature available on how ADHD symptoms affect developmental outcomes in adolescence, further research is needed in order to follow up on the present findings and examine potential impairment caused by ADHD symptoms in other outcomes.

These findings have several implications. Notably, our results indicate that ADHD symptoms persist throughout adolescence and young adulthood to a high degree implicating the need for continued surveillance and treatment of these features. Our results also imply that features of autism are salient in determining adolescent independence so efforts to target the decreased severity of autism features including identified behavioral therapies (i.e., Applied Behavior Analysis; Lovaas, 1987) and interventions promoting self-monitoring, communication, adaptive skills and social support are warranted (Hong et al, 2012; Hendricks& Wehman, 2009).

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