

ATTENTION AND BEHAVIORAL INHIBITION IN YOUNG MALES WITH FRAGILE
X SYNDROME AND/OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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ABSTRACT

JULIE ANNE HAMMER: Attention and Behavioral Inhibition in Young Males with Fragile X Syndrome and/or Attention-Deficit Hyperactivity Disorder
(Under the direction of Deborah Hatton and Rune J. Simeonsson)

Previous research of the behavioral phenotype in fragile X syndrome (FXS) has found that boys with FXS often have problems with inattention, hyperactivity, and impulsivity; furthermore, recent research has found many boys with FXS have symptoms of attention-deficit/hyperactivity disorder (AD/HD). Similarly, neuropsychological studies in boys with FXS have found deficits in sustained attention and inhibitory control. However, due to minimal research in this area, lack of appropriate comparison groups, and inconsistent measures, these results have yet to clarify the nature and severity of these deficits in boys with FXS. Similarities found in these disorders (i.e., FXS, AD/HD) allow an examination of these two groups to delineate AD/HD symptoms in males with FXS. This study examined sustained attention and inhibition in 57 boys with full mutation FXS, 48 boys without disabilities matched on mental-age (MA) to the boys with FXS, and 30 boys diagnosed with AD/HD using adapted visual and auditory continuous performance tests (CPTs), a standardized measure of sustained attention from the Leiter-R, and an experimental Day/Night task of inhibition.

The performance of the boys with FXS who demonstrated sufficient understanding of the CPTs in order to complete the tasks was compared to the boys without disabilities, matched on mental age, and boys verified to have a diagnosis of AD/HD. Boys with FXS

consistently demonstrated greater declines in inhibitory control and sustained attention over the length on the auditory and visual CPTs than the other groups. Regarding response time to hits on the CPTs, boys with FXS responded significantly slower to targets on the visual CPT, while groups did not differ on the auditory CPT. Similarly to the CPTs, the boys with FXS demonstrated greater difficulty inhibiting their automatic response on the experimental Day/Night task than the boys with AD/HD and the MA-matched peers. On the standardized measure of sustained attention, there were no significant differences between the boys with FXS and the boys with AD/HD. Furthermore, no child or family variables predicted performance on the measures of sustained attention and inhibition in boys with FXS.

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ABBREVIATIONS

ABC	Aberrant Behavior Checklist
AD/HD	Attention-Deficit/Hyperactivity Disorder
ADOS	Autism Diagnostic Interview Schedule
ANT	Amsterdam Neuropsychological Tasks
ASI	Adolescent Symptom Inventory
CANTAB®	Cambridge Automated Neuropsychological Test and Battery
CARS	Childhood Autism Rating Scale
CBCL	Child Behavior Checklist
CNT	Contingency Naming Test
CPT	Continuous Performance Test
CSI	Child Symptom Inventory
DS	Down Syndrome
EF	Executive Function
ECI	Early Childhood Inventory
FXS	Fragile X Syndrome
HFA	High Functioning Autism
ID	Intellectual Disability
IQ	Intelligence Quotient
MA	Mental age
MR	Mental Retardation
NICHD	National Institute of Child Health and Human Development

PDD	Pervasive Developmental Disorder
TEA-Ch	Test of Everyday Attention
TOH	Tower of Hanoi
TS	Tourette's Syndrome
WATT	Wilding Attention Test for Children
WCST	Wisconsin Card Sorting Task

CHAPTER I

Introduction

Along with autism, symptoms of attention-deficit/hyperactivity disorder (AD/HD) in boys with fragile X syndrome (FXS) are the most prevalent behavioral difficulty in FXS, with prevalence estimates ranging from 36%-74% (Backes, Genc, Schreck, Doerfler, Lehmkuhl, & von Gontard, 2000; Baumgardner, Reiss, Freund, & Abrams, 1995; Bregman, Leckman, & Ort 1988; Freund, Reiss, & Abrams, 1993; Hagerman, 1987; Hatton et al., 2002; Sullivan et al., 2006). In addition, symptoms of AD/HD appear to be more prevalent in FXS compared to other genetic disorders (Backes et al., 2000; Munir, Cornish, & Wilding, 2000a). Studies on the neuropsychological profile in FXS have documented deficits similar to those observed in individuals with AD/HD, including difficulties with inhibitory control and sustained attention, along with other executive function deficits (Cornish, Munir, & Cross, 2001; Munir et al., 2000a;; Sullivan et al., 2007; Wilding, Cornish, & Munir, 2002). Difficulties with inhibitory control appear to be a primary deficit among those with FXS which has also been recently suggested in individuals AD/HD (Barkley, 1997) and has been supported in both adults and children with AD/HD (Berlin, Bohlin, Nyberg, Janols, 2004; Nigg, 2001; Scheres et al., 2004; Stevens, Quittner, Zuckerman, Moore, 2002). Thus, it seems that problems with attention and poor inhibitory control represent one of the greatest behavior challenges in males with FXS.

Thus, a better understanding of attention problems and inhibition in boys with FXS will allow early detection and treatment of potential symptoms of AD/HD in children with

FXS. Early detection and treatment of AD/HD symptoms in children with FXS may allow parents, teachers, and other professionals to focus more on their learning and less on their behavior (Sullivan et al., 2006). Furthermore, interventions applicable to those with AD/HD should at least be generally applicable to those with FXS, considering developmental level (Hagerman & Hagerman, 2002).

Due to minimal research on deficits in attention and inhibition among children with FXS and because of the similarities in the neuropsychological profile in those with AD/HD and FXS, a comparison of these groups is needed to better delineate the nature of these deficits in those with FXS. To date, there have been no comparison studies of individuals with FXS to individuals with verified clinical diagnoses of AD/HD; thus, the purpose of this study was to compare boys with FXS to MA-matched boys clinically diagnosed with AD/HD to elucidate sustained attention and inhibitory control in the boys with FXS. Findings will potentially have implications for future interventions in individuals with FXS.

CHAPTER II

Literature Review

Neuropsychological Constructs

Attention

Attention is a broad and complex construct. Many neuropsychologists often describe the term of *attention* to include several different types: 1) initiation or focusing of attention, 2) sustaining attention, 3) selective attention, and 4) shifting of attention (Denckla, 1996; Mirsky, 1989; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Sohlberg & Mateer, 1989; Zubin, 1975). Most commonly, however, attention is often conceptualized into only three different aspects: 1) sustained, 2) selective, and 3) divided attention. Sustained attention refers to the ability to remain on task over a period of time. Individuals with a deficit in sustained attention often begin a task performing similarly to peers without such deficits; however, performance typically becomes worse the longer they remain on task. Selective attention refers to the ability to focus attention on relevant stimuli while ignoring irrelevant stimuli. Divided attention, however, refers to the ability to perform two tasks together, altering from one task to another. Sustained attention, as a neuropsychological construct, has been found to be impaired in individuals with FXS and will be the primary focus for this study (Munir et al., 2000a; Sullivan, et al., 2007).

Behavioral Inhibition

Barkley (1997) defined behavioral inhibition to be: a) inhibition of the initial prepotent response to an event; b) stopping of an ongoing response, which permits a delay in

the decision to respond; and c) protection of this delay from disruption from competing events or responses (interference control). A *prepotent* response, according to Barkley (1997), refers to a response in which immediate reinforcement, either positive or negative, is available or has been previously associated with that response. This response has also been conceptualized as an automatic response to stimuli. Behavioral inhibition in this study refers to the inhibition of a prepotent response and is referred to as response inhibition.

Relation of Attention and Behavioral Inhibition to Executive Function

The term executive function (EF) is an umbrella term that refers to a set of cognitive functions that enable individuals to demonstrate goal-directed behavior, usually in novel contexts with competing response alternatives (Denckla, 1996; Pennington & Ozonoff, 1996). More specifically, EFs encompass different cognitive domains such as inhibition, working memory, planning, and cognitive flexibility or set shifting (Ozonoff, 1997; Pennington & Ozonoff, 1996). Pennington (1997) developed an empirical model of EF and identified three aspects to EF: working memory, set shifting or cognitive flexibility, and inhibition. Although attention is not considered to be an exclusive domain of EF, it is an important cognitive process and is critical for the execution of other EFs, particularly working memory. The ability to attend allows an individual to hold, manipulate, and recall the information just presented to him/her.

Disorders

Fragile X Syndrome

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability (ID) with an estimated prevalence of 1: 4,000 in males and 1:8,000 in females (Crawford et al., 2001). FXS results from a mutation of the fragile X mental retardation gene

(FMR1) on the long arm of the X chromosome related to the fragile site Xq27.3. Individuals with the full mutation have trinucleotide repeats (CGG) of 200 or more that is associated with methylation and reduction of the FMR1 protein that is believed to influence normal brain development.

Although fragile X syndrome affects both males and females, the cognitive, behavioral, and physical phenotype varies with males often being more affected than females due to the X-linked inheritance of the mutation. Males with full mutation FXS typically present with mild to moderate ID, communication delays, and distinctive physical characteristics (i.e., a long face, prominent ears, hyperextensible joints) and behavioral features (i.e., eye gaze aversion, hand flapping, perseverative speech).

Generally, researchers have found that males with FXS have moderate to severe ID (Dykens, Hodapp, & Leckman, 1987; Skinner et al., 2005). Additionally, a significant number of males with FXS exhibit autistic-like behaviors, and many meet diagnostic criteria for autism (Bailey, Hatton & Skinner, 1998; Cohen, 1995; Hatton et al., 2006; Kau et al., 2004; Rogers, Wehner, & Hagerman, 2001). In addition, individuals with FXS exhibit behaviors consistent with AD/HD and/or meet diagnostic criteria for AD/HD (Backes et al., 2000; Baumgardner, Reiss, Freund, & Abrams 1995; Borghraef et al., 1987; Bregman et al., 1988; Hagerman, 1987; Hatton et al., 2002; Sullivan et al., 2006).

Behavioral Phenotype in FXS

In addition to high prevalence rates of AD/HD in males with FXS, research on the behavioral phenotype in children with FXS has also revealed core deficits in attention, hyperactivity, and impulsivity. Results from Baumgardner et al. (1995) suggested that teachers and parents identified a profile of behaviors specific to males with FXS that included

significantly higher hyperactivity, stereotypic movements, and inappropriate speech on the *Aberrant Behavior Checklist (ABC)*; Freund & Reiss, 1991). Items tapping excessive activity, restlessness, impulsivity, and distractibility distinguished males with FXS from the group with developmental delay. Turk (1992) argued that the deficit in attention in individuals with FXS may not be fully explained by the level of intellectual functioning, later confirmed by Baumgardner et al. More recently, young boys with FXS were found to have significantly more problem behaviors than a group with Down syndrome and a group with nonspecific cognitive disabilities (Turk, 1998). On one significant item on the *CBCL* (Achenbach & Edelbrock, 1983) “can’t sit still, restless or hyperactive,” parents rated boys with FXS as being significantly more restless and hyperactive and as having significantly more problems with attention span than both control groups. Thus, Turk provided support for a deficit in attention specific to the fragile X behavioral phenotype.

Kau, Reider, Payne, Meyer, and Freund (2000) found that young males with FXS, albeit not significant, exhibited deficits in motor skills and attention, along with increased hyperactivity, decreased social withdrawal, and greater degrees of positive mood, compared to boys with generalized developmental delays that had been referred to a behavioral disorders clinic. Einfeld, Tonge, and Turner (1999) examined emotional and behavioral problems in individuals with FXS longitudinally using the *Developmental Behavior Checklist (DBC)*; Einfeld & Tonge, 1995) and found that disruptive behavior decreased significantly over time while antisocial behavior increased. However, despite this significant increase in antisocial behavior over time, the authors mentioned that these behaviors did not represent a major problem for individuals with FXS. In a recent review article, Cornish, Sudhalter, and Turk (2004) argued that the FXS phenotype is characterized by deficits in inhibitory control,

leading to perseverative responding in behavioral features, such as impulsivity and hyperactivity, similar to those with AD/HD, and in perseverative and tangential language.

Attention-Deficit/Hyperactivity Disorder (AD/HD)

Attention-Deficit/Hyperactivity Disorder (AD/HD) is considered to be one of the most pervasive childhood disorders. It is characterized by a persistent pattern of inattention and/or hyperactivity/impulsivity that is considered to be more severe and more frequently displayed than that typically observed in individuals at the same level of development (American Psychiatric Association, 1994). To meet diagnostic criteria for AD/HD, these symptoms must be observed early in life, be pervasive across many situations and settings, and be chronic. Symptoms of inattention in toddlers or preschool children are less observed than symptoms of hyperactivity or impulsivity typically because young children experience few demands for sustained attention in their everyday lives so this deficit can easily go unnoticed early in life. However, in school-age children, symptoms of inattention affect classroom work and academic performance and become more readily observed by teachers and parents. Currently, there are three subtypes of AD/HD: 1) ADHD-Combined Type; 2) AD/HD-Predominately Inattentive type; and 3) AD/HD-Predominately Hyperactive-Impulsive type (American Psychiatric Association, 1994). The American Academy of Pediatrics requires that in order to be diagnosed with AD/HD, the child should meet DSM-IV criteria for AD/HD and that clinicians should must obtain evidence directly from parent(s)/caregiver(s) and school teacher(s) about the occurrence of symptoms across various settings, age of onset, duration of symptoms and the child's degree of impairment. They state that behavior rating scales may be used but warn that the efficacy of such scales have not been proven definitively. The AAP also states that the evaluation must include an assessment

of co-existing conditions. According to professional standards by the American Academy of Child and Adolescent Psychiatry (2007), there are several recommendations for assessing AD/HD including but not limited to clinical interviews with the parent and/or patient assessing current symptomology, family history, and functioning at school or preschool setting, neuropsychological and psychological testing (rating scales, cognitive and achievement), computerized testing of attention and/or inhibitory control, evaluating the presence of comorbid disorders, and do potential laboratory or neurological testing. AD/HD is often comorbid with other disorders. The most prevalent is oppositional defiant disorder and conduct disorder, suggesting more oppositional and rule-breaking behavior in individuals with AD/HD. The estimated prevalence of AD/HD in school-age children is 3-7% (American Psychiatric Association, [APA], 1994). This disorder preferentially affects boys with an approximate 3:1 male-to-female ratio (American Psychiatric Association, 1994). This disorder is believed to persist into adolescence in approximately 50-80% of cases and into adulthood in approximately 30-50% of cases (Barkley, 1996). Within the cognitive domain, children with AD/HD have been shown to have significant deficits in sustained attention, inhibitory control, hyperactivity, and in selective attention (Barkley, 1990, 1991).

AD/HD Symptomology

Fragile X Syndrome

In early studies, researchers have reported high prevalence rates of AD/HD in children with FXS. Hagerman (1987) found that 73% of a sample of 37 pre-pubertal boys with FXS met *Diagnostic Statistical Manual of Mental Disorders-Third Edition (DSM-III;* American Psychiatric Association, 1980) criteria for attention deficit disorder and were also rated in the hyperactive range by their parents on a norm-referenced rating scale (Conners,

1973). Bregman et al. (1988) reported attention problems in 100% of 14 males with FXS; however, only 71% fulfilled *DSM-III* criteria for AD/HD. Furthermore, Borghraef et al. (1987) found that pre-pubertal boys with FXS were twice as likely to be diagnosed with Attention Deficit Disorder as similarly aged boys with non-specific mental retardation. Baumgardner et al. (1995) reported an exceptionally high prevalence of AD/HD (73%) in males with FXS using a *DSM-III* diagnostic interview.

More recently, Backes et al. (2000) reported that 74% of their sample of 49 boys with FXS met diagnostic criteria for AD/HD. This high prevalence of AD/HD among boys with FXS was significantly higher than that of the control group with tuberous sclerosis. Furthermore, boys with FXS had a high rate of psychiatric comorbidity, with 26.5% meeting criteria for two psychiatric diagnoses. Hatton et al. (2002) found that 56% of a sample of 59 boys with FXS scored in the borderline or clinically significant range on attention problems, as rated by their parents. Interestingly, higher maternal education was associated with more attention problems, while medication use and autistic behavior were not.

In the only study on the prevalence of AD/HD symptoms in children with FXS using a parent and teacher report measure, Sullivan et al. (2006) recently found that 54-59% of boys with FXS met diagnostic criteria for either AD/HD-inattentive type only, AD/HD-hyperactive type only, or AD/HD-combined type only. This study also found that boys who were rated as meeting DSM-IV criteria were more likely to be on medication and have younger mental ages.

Intellectual Disabilities and Other Developmental Disabilities

Because many individuals with FXS have mild to moderate ID and autistic symptoms, it is important to examine the prevalence of AD/HD symptomology in other

related disabilities, such as mental retardation, autism, and pervasive developmental disorder. Das and Melnyk (1989) found the prevalence of AD/HD to be 33% in junior and senior high school students with mild MR on a teacher rating scale. Diagnoses of pervasive developmental disorder (PDD) or any autism-spectrum disorders (ASDs) are exclusionary criteria for a diagnosis of AD/HD, according to current diagnostic classifications; however, AD/HD-like symptoms have frequently been found among individuals with PDD and high-functioning autism (HFA; Frasier et al., 2001; Goldstein & Schwebach, 2004; Hastings, Beck, Daley, & Hill, 2005; Hattori, Ogino, Abiru, Nakano, Oka, & Ohtsuka, 2006). However, because many researchers have specifically excluded children with ID from studies of AD/HD and vice versa to avoid confounding results, little is known about the impact of AD/HD in children with IDs (Burack & Enns, 1997).

Neuropsychological Profile

Response Inhibition and Sustained Attention in FXS

Neuropsychological researchers have reported difficulties with attention and behavioral inhibition in young males with FXS (Cornish et al., 2001; Munir et al., 2000a; Wilding et al., 2002). Using three comparison groups, Munir, Cornish, and Wilding compared attention and inhibition in young males with FXS to males with Down Syndrome (DS), and to typically developing males who were rated by their teachers as having either “good” or “poor” attention based on the *ACTeRS*, a measure of attention and hyperactivity (Ullmann, Sleator, & Sprague, 1984). Males with FXS performed significantly worse on computerized, experimental measures of sustained, selective, and divided attention as well as on a measure of inhibition.

Specifically, on the measure of selective attention, the *Wilding Attention Test for Children (WATT; Wilding, 1997)*, males with FXS detected significantly fewer correct targets and made more false alarms (i.e., when the child responds to a non-target stimulus) than the Down syndrome group, suggesting greater difficulty in discriminating between target and distractor and/or in shifting their attention and inhibiting impulsive responding to incorrect stimuli. Furthermore, both syndrome groups found fewer correct targets and made more false alarms, albeit not significant, than the two control groups. Additionally, on the measure of divided attention (*WATT; Wilding, 1997*), males with FXS demonstrated greater difficulty organizing search at the same time as shifting attention from one type of target to another. On the task of sustained attention (*WATT; Wilding, 1997*), males with FXS detected fewer correct targets, albeit not significant, but made significantly more false alarms in comparison to all three groups.

Interestingly, however, on one of the executive function tasks, the Same-Opposite task, a task from the adapted *Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999)*, males with DS demonstrated significantly more difficulty organizing their responses, compared to all three groups. Only 68% of the males with FXS, compared to 88% of the males with DS, were able to complete the opposite condition on this task. Furthermore, on another task of executive function, the Walk task (*TEA-Ch; Manly et al, 1999*), males with FXS demonstrated significantly worse inhibition than all three groups. These findings suggest a pattern of attention deficits and impairments in inhibition specific to FXS. Although Munir et al. described the most detailed neuropsychological study in males with FXS to date and used comparison groups of boys with “good” and “poor” attention, it has a number of limitations. The “poor” attention group,

most representative of an “AD/HD” group, was categorized solely on the basis of one teacher report measure of unknown psychometric and technical adequacy. Children were not professionally diagnosed or confirmed to have AD/HD by a physician. Furthermore, the psychometric adequacy of the experimental task used to measure the various aspects of attention was unknown. These limitations provided the support for this current study to advance our knowledge of the neuropsychological profile of males with FXS.

In a follow-up analyses of the Munir et al. study (2000a), Wilding et al. (2002) reported that on the single target visual search, the only type of error for the group with FXS was a run of repeated responses on targets. Interestingly, for the control groups, shape confusions were the most frequent type of false alarm, comprising about half of the errors in these groups. However, individuals with FXS appeared to discriminate between targets and non-targets efficiently, never selecting on non-targets. Wilding et al. argued that a possible explanation for this high rate of repetitions was a weakness in inhibiting repetition of successful responses and switching attention to respond to a new stimulus. Wilding et al. again argued for a “specific-syndrome deficit” in inhibition in boys with FXS.

Consistent with previous studies in young males with FXS, Cornish et al. (2001) argued that the most significant impairment in 15 adult males with FXS appeared to be on a task that required the ability to switch attention from a previously reinforced stimulus pattern to a novel stimulus. Furthermore, in a study of toddlers with FXS and Williams syndrome, Scerif, Cornish, Wilding, and Karmiloff-Smith (2004) found that groups with FXS and Williams syndrome differed in the types of errors made on an adapted computerized task. Toddlers with FXS made more repetitive errors by touching a previously found target, while toddlers with Williams syndrome, confused distractors with targets more often. This finding

was consistent with Wilding et al.'s (2002) previous findings in older children with FXS, suggesting an early deficit in inhibition in individuals with FXS.

Munir, Cornish, and Wilding (2000b) examined memory functioning in 25 males with FXS on tasks presumed to tap specific components of the Baddeley model (1986) of working memory-- the phonological loop, the visuospatial sketchpad, and the central executive. Males with FXS performed significantly worse on measures of meaningless verbal memory, including nonword repetition and the backward digit span, both placing a high demand on attentional capacity. However, there were no significant differences between males with FXS and males with Down Syndrome on measures requiring fewer demands on attention.

In a very recent study of attention and inhibition in children with FXS using adapted continuous performance tests (CPTs), Sullivan et al. (2007) found that boys with FXS demonstrated initial difficulty paying attention at the beginning of visual and auditory tasks; however, their ability to sustain attention over time was similar to that of their MA-matched peers. Furthermore, boys with FXS had greater difficulty inhibiting impulsive responding over time on both visual and auditory CPTs compared to their MA-matched peers. This study was also one of the very few studies to examine child and family predictors of sustained attention and response inhibition and found that higher mental age consistently predicted better sustained attention and inhibition in boys with FXS.

In another recent study of executive function in children with FXS, Hooper, Hatton, Schaaf, Sullivan, Hammer, Sideris, et al. (2007) found that boys with FXS showed significant deficits in cognitive flexibility/set-shifting, inhibition, and working memory

compared to boys matched on mental age. However, there were no differences in processing speed.

Response Inhibition and Sustained Attention in AD/HD

With the introduction of Barkley's model (1997) of executive function deficits in individuals with AD/HD, a tremendous shift occurred in the way researchers and clinicians conceptualized specific deficits in AD/HD. This model suggested that problems with sustained attention are secondary to primary deficits in inhibitory control among individuals with AD/HD. Evidence substantiating poor inhibition in those with AD/HD comes from several research studies that have used motor-inhibition tasks, such as the Go-NoGo paradigm (Iaboni, Douglas, & Baker, 1995; Trommer, Hoepfner, Lorber, & Armstrong, 1988), the stop-signal paradigm (Schachar & Logan, 1990), and delayed response tasks (Gordon, 1979; Sonuga-Barke, Taylor, Sembi, & Smith, 1992). Furthermore, numerous research studies have demonstrated that children with AD/HD produce greater errors of commission (i.e., when a child responds to a non-target stimulus) on continuous performance tasks (Barkley, 1991; Barkley, DuPaul, & McMurray, 1990). Poor inhibition has also been evident in individuals with AD/HD on tasks that require stopping of an ongoing response when signaled to do so or when feedback suggests that the response is maladaptive (Schachar & Logan, 1990). Recent research studies on the specific executive function profile in children with AD/HD have also documented deficits in inhibitory control (Berlin, Bohlin, Nyberg, & Janols, 2004; Nigg, 2001; Scheres et al., 2004; Stevens, Quittner, Zuckerman, & Moore, 2002).

Unlike consistent results suggesting poor inhibitory control in children with AD/HD, researchers have found inconsistent results regarding deficits of sustained attention among

individuals with AD/HD. Some researchers have argued that sustained attention appears to be a specific deficit associated with AD/HD (Barry, Klinger, Bush, & Hawkins, 2001; Heaton et al., 2001; Hooks, Millich, & Lorch, 1994; Stins et al., 2005; Swaab-Barneveld et al., 2000; Wilding, 2005; Wu, Anderson, Castiello, 2002), while other researchers have argued that AD/HD is more uniquely characterized by hyperactivity and that sustained attention deficits are common in most of the major child psychiatric diagnostic groups (Halperin, Matier, Bedi, Sharma, & Newcorn, 1992; Swaab-Barneveld et al., 2000).

Furthermore, researchers have found selective attention to be relatively intact in those with AD/HD (Barry, Klinger, Bush, & Hawkins, 2001; Heaton et al., 2001; Stins et al., 2005; Wu, Anderson, Castiello, 2002). Barry et al. (2001) examined attention in 10-year old children with AD/HD and found a specific impairment in sustained attention relative to children without AD/HD, using the *Conners' Continuous Performance Test (CPT; Conners, 1994)*, indicated by the lower d' prime scores and higher Beta scores while selective attention appeared to be intact. These results were consistent with findings from previous research studies on selective attention in individuals with AD/HD (Aman, Roberts, & Pennington, 1998; Pearson, Yaffee, Loveland, & Norton, 1995). Wu et al. (2002) also reported that the children with AD/HD had a specific deficit in sustained attention. Additionally, Wu et al. found that comorbid learning disability (LD) and AD/HD was associated with deficits in selective attention (measured by the Sky Search test) and attentional capacity (measured by the Digit Span Forward subtest).

Recently, Stins et al. (2005) found that 34 boys with AD/HD responded slower, were less accurate, and were more prone to make an accidental response than the control group on the Sustained Attention Dots task, a subtest from the *Amsterdam Neuropsychological Tasks*

(ANT; de Sonneville, 1999). Interestingly, however, the rate of increase in errors was the same for both groups. Similar to the sustained attention task, on the selective attention task, boys with AD/HD responded slower, were less accurate, and were more impulsive than the control group. Moreover, the percentage of false alarms on the selective attention task was significantly higher in the children with AD/HD.

Response Inhibition and Executive Function Deficits in Other Developmental Disabilities

Unlike the paucity of research in FXS, there has been a considerable amount of research examining executive function deficits in individuals with autism, including behavioral inhibition. Furthermore, researchers have advanced research on this topic by comparing EF deficits in children with autism to children with other neurodevelopmental disorders, particularly AD/HD, in order to specify a unique profile of EF deficits in those with autism. Although inhibitory control appears to be relatively intact in those with autism (Ozonoff, 1997), contrary to those with FXS and AD/HD, researchers have found that individuals with autism have a number of executive function deficits, particularly in cognitive flexibility, planning, and working memory (Bishop, 1993; Goldberg et al., 2005; Hughes, Russell, & Robbins, 1994; Joseph, 1999; Ozonoff & Strayer, 1997; Ozonoff & Jensen, 1999). Inconsistent findings in executive function deficits in autism lead to research attempting to specify the neuropsychological profile in children with autism. Deficits in EFs in those with autism are particularly relevant to individuals with FXS because of the high prevalence rate of autism in those with FXS, ranging from 25% to 47% (Bailey, Hatton & Skinner, 1998; Cohen, 1995; Hatton et al., 2006; Kau et al., 2004; Rogers, Wehner, & Hagerman, 2001).

Hughes et al. (1994) found significant executive dysfunction in the domains of attentional set-shifting and planning in a young group with autism. Later, Ozonoff and Strayer (1997) found that a group of children with autism with no mental retardation was relatively unimpaired compared to age and IQ matched normal controls on two tests of inhibition. Both performed similarly on all variables of the Stop-Signal task; there were no group differences in the reaction time or accuracy on either normal or signal trials. Similarly, there were no group differences in the performance of the *Negative Priming task* (Tipper, 1985), which measures the ability to ignore irrelevant information during cognitive processing.

An interesting and more recent study by Ozonoff and Jensen (1999) examined executive function deficits including planning, cognitive flexibility, and inhibition in children with autism, compared to children with Tourette syndrome (TS), AD/HD, and normal controls. As predicted, the group with autism demonstrated difficulties on the *Wisconsin Card Sorting Task* (WCST; Grant & Berg, 1948) and the *Tower of Hanoi* (TOH; Borys, Spitz, & Dorans, 1982), believed to be indicative of deficits in planning and flexibility, but performed in the average range on the measure of inhibition, the Stroop test. These deficits were significantly relative not only to the normal control group but also the groups with other neurodevelopmental disorders, both AD/HD and TS. Conversely, the group with AD/HD demonstrated difficulty on the Stroop task, a measure of inhibition but not on the *WCST* or the *TOH*, suggesting distinct neuropsychological profiles in each of the different neurodevelopmental disorders. Contrary to the researchers' hypothesis, children with TS demonstrated no deficits relative to the normal control group. Ozonoff and Strayer (2001) examined working memory in individuals with high-functioning autism relative to

individuals with Tourettes syndrome and to a typically developing control group and failed to find an autism-specific impairment across three tasks and five dependent measures of working memory. Furthermore, both IQ and age predicted performance in all groups.

Recently, Goldberg et al. (2005) compared executive function components of inhibition, planning, cognitive flexibility, and working memory in children with high-functioning autism (HFA), children with AD/HD, and typically developing normal controls on the *Cambridge Automated Neuropsychological Test and Battery (CANTAB®; Cambridge Cognition Cognition, 1996)* tasks. Results from this study indicated that there were no group differences on response inhibition, planning, or set-shifting tasks. However, on the spatial working memory task, children with HFA made significantly more between-search errors compared to controls on the difficult problems (8-box) and on the mid-difficulty problems (6-box). The children with AD/HD, however, only made significantly more errors compared to the control group on the most difficult problems (8-box), suggesting that spatial working memory appears to be more severely impaired in those with HFA than in AD/HD, even though both groups demonstrated an impairment.

Research has suggested deficits in attention in individuals with IDs and AD/HD on an adapted *Continuous Performance Test (CPT; Pearson, Yaffee, Loveland, & Lewis, 1996)*. Pearson et al. (1996) found that children with IDs and AD/HD made more errors of omissions (i.e., children failed to respond to a target stimulus) and commission (i.e., when children responded to non-target stimulus) than did their peers with ID only. Interestingly, however, although children with ID and AD/HD made more errors suggestive of an attention deficit, there was no evidence of a “true deficit” in sustained attention because their performance did not decline as time on task lengthened. However, the elevated number of

errors of commission suggested a greater degree of impulsive responding in the ID/ADHD group. Pearson et al. did find a deficit in a visual selective attention; sorting time of children with ID and AD/HD was slower in the presence of highly salient distractors than for the group with ID only. This finding suggests that the differences between children with and without AD/HD (who also have an ID) are more evident when more effortful processing is required for task performance.

Summary

Although deficits in sustained attention and inhibition, as neuropsychological constructs, have been commonly found in males with FXS, only two groups of researchers has specifically examined these aspects in males with FXS. Due to minimal research in this area, lack of appropriate comparison groups, and inconsistent measures, these results have yet to clarify the nature and severity of these deficits in boys with FXS. Similarities found in these disorders (i.e., FXS, AD/HD) allow an examination of these two groups to delineate sustained attention and response inhibition in males with FXS.

In contrast to FXS, EFs in autism research have been widely studied; many researchers have compared individuals with autism to those with other neurodevelopmental disorders to further specify deficits unique to individuals with autism. This type of clinical comparison has yet to be done in FXS and is needed to advance research in this area. A sample of boys with AD/HD is the most appropriate comparison group given similar deficits in sustained attention and behavioral inhibition.

This study examined sustained attention and response inhibition, as neuropsychological constructs in three groups: 1) boys with FXS, 2) boys diagnosed with AD/HD, and 3) typically developing peers, matched on mental age to the boys with FXS by

investigating differences on both computerized and standardized measures of sustained attention and an experimental measure of response inhibition.

Four research questions and associated hypotheses were addressed in this study:

1) Controlling for mental age, are there significant differences in sustained attention among boys with FXS, their MA-matched peers, and boys diagnosed with AD/HD?

No significant differences will be found on the measures of sustained attention among the groups.

2) Controlling for mental age, are there significant differences in behavioral inhibition in boys with FXS, their MA-matched peers, and boys diagnosed with AD/HD?

Boys with FXS will have greater difficulty with inhibitory control compared to the boys with AD/HD and their MA-matched typically developing peers.

3) Controlling for mental age, are there significant differences in mean response times of hits on the visual and auditory CPT among boys with FXS, their MA matched peers, and boys with AD/HD?

It is expected that the boys with AD/HD will have slower mean reaction times for hits on both the visual and auditory CPT compared to the boys with FXS.

4) What child and/or family variables (i.e., maternal education, medication use, chronological age, autism status (total CARS score), and T-score on DSM-ADH Problems subscale on the Child Behavior Checklist) predict performance on all measures of attention and inhibition in males with FXS?

Based on previous research in males with FXS, it is expected that autistic status (total CARS score), T-scores on the Attention Problems subscale on the *CBCL*, and maternal

education will predict performance on measures of attention while autistic status (total *CARS* score) will predict performance on measures of inhibition.

CHAPTER III

Methods

Participants

The participants for this study included (a) 57 boys with full mutation FXS, ranging in age from 7 to 13 years, who had already participated in the *Attention, Memory, and Executive Function* longitudinal study of children with FXS; (b) 53 typically developing males matched on mental age and ethnicity to the boys with FXS, who had already participated in the *Attention, Memory and Executive Function* longitudinal study; and (c) 30 boys with clinical diagnoses of AD/HD, ranging in age from 5-8 years, who were recruited primarily through ongoing studies at the Duke ADHD program and through a monthly advertisement in the *Carolina Parent*, a local publication. Data from the boys with FXS and their MA-matched peers were taken from their first assessment in the longitudinal study. Table 1 includes child and family demographics for all three groups.

A smaller subset ($n = 18$) of the original sample of 57 boys with FXS was used to examine sustained attention on the Attention Sustained subtest from the Leiter-R because this subtest was added into the research protocol the third year of the longitudinal study, as data collection was considerably slowing down. Thus, very few boys with FXS were administered this subtest. Only data for the children who were administered this task and were deemed to understand the task (i.e., raw score greater than 0) were used for the analysis. The mean mental age of this sample was 70 months ($SD = 8.2$ months) and the mean chronological age

was 143 months (SD = 20.5 months). A majority were of European American descent (83.3%) and 16.7% were African-American.

Boys with FXS

A majority of this sample of boys with full mutation FXS were of European American descent (86%), 11% were African-American, approximately 2% were Hispanic, and 2% were Asian. Per parent report, a majority of the sample of boys with FXS were taking psychotropic medication at the time of the assessment (71%). In the sample of boys with FXS, the mean mental age was 63 months (SD = 8.6 months) and the mean chronological age was approximately 120 months (SD = 20.6 months). For calculation of the mean mental age, a total of 56 boys were used as the overall sample because the Leiter-R was not administered to one child with FXS during their first assessment. The mean total score on the *Childhood Autism Rating Scale* (CARS; Schopler, Reichler, & Renner, 1988) was 28.9 (SD = 6 points) which is considered to be in the non-autistic range. However, approximately 28% (n = 16) were rated to have a total CARS score in the autistic range (≥ 30). In order to calculate the maternal education and medication information, a total of 56 boys with FXS were used as the overall sample because both pieces of information were not available for one child. Maternal education varied in the sample with FXS; approximately 23% were college graduates or had higher degrees and approximately 38% had some college education, and approximately 39% of mothers were high school graduates. All children were diagnosed with full mutation FXS using DNA analyses. In terms of ratings of attention problems on the Child Behavior Checklist (CBCL; Achenbach, 1991; Achenbach & Rescorla, 2001), nine boys with FXS (17.54%) were rated to be in the Borderline range on the Attention Problems subscale while four boys (7%) were rated to be in the Clinically Significant range. On the

DSM-oriented scales on the CBCL, the DSM-ADH Problems subscale, 10 boys with FXS (17.54%) were rated to be in the Borderline range and three boys (5.3 %) were rated to be in the clinically significant range on the Attention Problems (mean T-score = 60.58) and/or DSM-ADH Problems (mean T-score= 58.63) subscales on the CBCL. The children with FXS were from five southern or Mid-Atlantic States. Signed consent for participation was obtained from the children's parents. Each child's family received a small stipend (\$25) for participating, and parents received a brief summary of their child's assessment.

Mental-Age Matched Typically Developing Peers

The typically developing boys were matched on mental age, ethnicity, and gender to the boys with FXS. On average, the difference in mental ages of the pairs of boys was less than 2 months. The mean mental age in this typically developing sample of boys was 62 months (SD = 10.7 months) and the mean chronological age was 60 months (SD = 11.1 months). Exclusionary criteria for enrolling the typically developing children in the study included not having any significant delays or disabilities as well as not taking any medication at the time of the assessment. Thus, CARS were not completed for the MA-matched peers, and no children were taking medication at the time of the assessment. The education level of the mothers of the MA-matched boys was high, 62.9% were college graduates or had a higher degree, 25.8% had some college education, and 11.3% were high school graduates.

Boys with AD/HD

A majority of the sample of boys with AD/HD were of European decent (70%); 20% were African-American, approximately 6.7% were Hispanic and 3.3% were Native Hawaiian or other Pacific Islander and Hispanic/Latino. Per parent report, a majority of the boys with AD/HD were taking psychotropic medication (63.3%), primarily targeting their

AD/HD symptoms. The mean mental age for the boys with AD/HD was 82 months (SD = 14.8 months) and the mean chronological age was 82 months (SD = 9.6 months). Although the boys with AD/HD have a higher mean mental age and chronological age to the boys with FXS and their MA-matched peers, mental age was controlled for in all of the inferential statistical models. The CARS was completed on all boys with AD/HD. The mean CARS score for the boys with AD/HD fell in the non-autistic range (15.6 points) and had little variability across the sample (SD = 0.8 points). There were no boys with AD/HD that were rated to be in the autistic range (≥ 30). The education level of the mothers of the boys with AD/HD was high; 51.9% were college graduates or had a higher degree, 44.4 % had some college education and 3.7% were high school graduates. These percentages are based on a total sample of 27 because this information was not available on three children.

This sample of boys with AD/HD was recruited through two primary sources, including the Duke AD/HD program's ongoing studies and an advertisement in the *Carolina Parent*. A majority of the sample was recruited from the *Carolina Parent* advertisement (63.3 %), approximately 26.7% were recruited through the ongoing studies at the Duke AD/HD program, approximately 6.7 % were referrals from families and who had already participated in the study and one child was referred from a previous colleague. In this sample recruited, 30 % were diagnosed with ADHD-Combined type, 13.33 % were diagnosed with AD/HD-Predominately Inattentive type, 16.67 % were diagnosed with AD/HD-Predominately Hyperactive/Impulsive type, approximately 43 % of the sample did not have a specified type of AD/HD listed in their medical records, and medical documentation of AD/HD for three children were never received, even after several attempts to collect these medical records. For the three children that no medical documentation was received on their

AD/HD diagnosis, one child had a rating on the Attention Problems subscale in the borderline range on the Child Behavior Checklist (CBCL; and fell in the clinically significant range on the ADHD-predominately hyperactive/impulsive subscale on the Symptom Inventory (Gadow & Sparfkin, 2002), another child had a clinically significant rating on the DSM-ADH Problems subscale on the CBCL and the third child was rated to be in the average range on both the Attention Problems and ADH Problems subscale and on the ADHD subscales on the Symptom Inventory. Generally, for the overall sample of boys with ADHD there were 17 (56.7 %) boys rated to be in the borderline range and 17 boys in the clinically significant range on either the Attention Problems subscale and/or the ADH-Problems (DSM oriented) subscale on the CBCL. It is important to note that the diagnosis of AD/HD in this sample came from documentation of AD/HD from the child's primarily physician and/or licensed psychologist, and was not based on research criteria.

Parent and teacher Conner's forms were collected on the boys with AD/HD only to substantiate their diagnosis by a professional. The mean on the parent rating scales for the Conners' ADHD Index (n = 30), a commonly used index for identifying children/adolescents "at risk" for AD/HD was 67.47 (SD = 9.73). Unfortunately, fewer data were able to be collected on the teacher rating scales (n = 20). The mean on the teacher rating scales for the Conners' ADHD Index was 59.7 (SD = 9.73). Several attempts (maximum of three contacts were made for each teacher) were made to follow up the teachers that failed to return the forms but attempts were unsuccessful. Parent ratings on the Symptom Inventory rating scale were relatively high for boys with AD/HD in which data were completed and returned (n=24); 33.33% of the boys with AD/HD met clinical criteria for AD/HD-Inattentive type (mean T-score = 63.71), 50% (mean T-score = 68.38), met criteria for AD/HD-

Hyperactive/Impulsive type, and 25% (mean T-score= 67.92) met criteria for AD/HD-Combined type. On the CBCL, the mean T-score for the boys with AD/HD on the Attention Problems subscale was 65.37 and 66.63 for the DSM-ADH Problems subscale. Ten of the boys were rated to be in the Borderline range on the Attention Problems subscale and seven were rated to be in the Clinically Significant range. For the DSM-ADH Problems subscale, seven boys with AD/HD were rated to be in the Borderline range and ten boys were rated to be in the Clinically Significant range. In addition to AD/HD, per mother report, two children were also diagnosed with sensory integration dysfunction, one child with sensory integration disorder, and one child was also diagnosed with oppositional defiant disorder (ODD). Signed consent for participation was obtained from the children's parents and teachers. Each child's family received a small stipend (\$25) for participating and parents received a brief summary of their child's assessment.

Instrumentation

Data were collected using computerized and standardized measures of sustained attention and an experimental task of response inhibition. Additionally, child behavior rating scales were given to the parent(s)/caregiver(s) to briefly describe problem behavior and diagnostic symptoms in all of the groups. Additionally, the parent(s)/caregiver(s) of boys with AD/HD were also given a parent and teacher rating scale of AD/HD symptoms, in order to substantiate their already verified diagnosis of AD/HD by a professional.

Measures of Sustained Attention

To assess sustained attention, three separate measures were administered: (a) the adapted computerized visual *Continuous Performance Test (VCPT)*, (b) the modified

auditory *CPT* (*ACPT*; Keith, 1997), and (c) the Attention Sustained subtest from the *Leiter International Performance Scale-Revised* (*Leiter-R*; Roid & Miller, 1997).

Two measures of sustained attention were adapted for use in the sample with FXS in the *Attention, Memory, and Executive Function* study: the adapted visual *CPT*, based on the *Halperin Visual Continuous Performance Test* (Halperin, Sharma, Greenblatt, & Swartz, 1991), and a modified auditory *CPT*, based on the *Keith Auditory Continuous Performance Test* (Keith, 1994). Both *CPT* tasks were created and administered on a laptop computer using Presentation® (Neurobehavioral Systems, Inc., 2006) software for the *Attention, Memory, and Executive Function* study. This software is essentially a detailed program for producing visual and auditory stimuli displays. It can present complicated and high rate stimuli without delay, ensuring the precise and accurate presentation of stimuli because the entire stimulus procedure is loaded prior to its display. Presentation® generated data provide temporal accuracy of less than one millisecond with complete timing of stimulus onset and response onset. All data were stored in a text logging file that was easily imported into Microsoft Excel and SAS for analysis.

The adapted visual *CPT* displayed 59 black and white pictures on a laptop computer, consisting of six animal stimuli, based on similar complexity, including a dog (target stimulus, $n = 15$), pig, lion, elephant, giraffe, and rabbit. The total duration of the visual *CPT* was 177 seconds with an inter-stimulus interval (ISI) of 2 seconds and a stimulus interval of 1 second. Participants were randomly given one of six possible forms. The auditory *CPT* consisted of 21 stimulus words, including *dog* (target stimulus, $n = 20$), *teach*, *face*, *need*, *room*, *drop*, *feet*, *low*, *fire*, *gift*, *show*, *race*, *beg*, *five*, *may*, *toy*, *shoe*, *large*, *cap*, *else*, and *look*. The total duration for the auditory *CPT* was 192 seconds with an ISI of 1.8 seconds and

a stimulus interval of 0.2 seconds. The adapted visual and auditory CPT tasks were significantly shorter than ones developed for use for children without disabilities than can range between 7- 14 minutes (Conners, 2000; Conners, 2001). However, a pilot test of the original CPTs with the sample of children with FXS revealed that they could not complete them. Pearson et al. (1996) adapted the CPTs for use in children with intellectual disabilities (ID) and also set a precedent for use of adapted CPTs when children with ID are unable to complete the standardized measures.

Both the visual and auditory CPT tasks were administered on a computer with an external mouse attached. All children were administered the visual CPT first, based on the recognition of the visual versus auditory strengths in FXS (Braden, 2002; Barry, 2003). Children were instructed to press the computer mouse button marked by a sticker when he saw or heard the target stimuli, a “dog.” In addition, children were instructed to refrain from clicking the mouse when they saw or heard anything else. Practice sessions were included for both the visual and auditory tasks. The visual practice session presented three target stimuli and lasted 30 seconds. The auditory practice session presented five target stimuli and lasted 48 seconds. All children practiced each task at least once and could practice up to two more times, if needed. All videotapes of these tasks for the boys with FXS and their MA-matched peers were reviewed to determine if the each child understood the tasks during the practice session. Children were deemed to understand the task if they independently made at least one hit preceded and proceeded by a correct rejection. This criterion was arbitrarily determined but it seems to be a reasonable and adequate method for determining whether the children understood the CPT. Videotapes of the boys with AD/HD were not reviewed afterwards, as had been done in the other groups; instead, to avoid this laborious task, it was merely noted

during the CPT administration (visual and auditory) whether these boys met this predetermined criteria and understood the task based on the criteria mentioned previously.

The visual and auditory CPT yields scores for number of errors of commission (false alarms; e.g., responding to a non-target stimulus), the inverse of false alarms, the number of correct rejections (e.g. when the child does not respond to a non-target stimulus), number of errors of omission (misses; e.g. failing to respond to a target stimulus), and number of hits, indicating a correct response to target stimulus. To measure sustained attention across the duration of the CPT tasks, the boys' responses to target stimuli (e.g., dog) were coded. When the boys clicked the compute mouse when target stimuli were displayed (a correct response or "hit"), the responses were coded "1," and children who did not click the mouse when target stimuli were displayed (an incorrect response or "error of omission; miss") were coded "0."

To measure inhibition across the duration of the task, the boy's responses to non-target stimuli were coded. When children did not click the computer mouse when non-target stimuli were displayed (this correct response or "correct rejection") were coded "1," but when children did click the computer mouse when non-target stimuli were displayed (an incorrect response or "error of commission; false alarm") these were coded "0." Although typically errors of commission (i.e., false alarms) and errors of omission (i.e., misses) are reported in past research and in clinical practice, the number of hits is directly and inversely proportion to the number of misses, and the number of correct rejections is directly and inversely proportional to the number of false alarms. Consequently, in order to present capabilities rather than deficits, percentages of hits and correct rejections were used as reference points in the graphs, which has been previously done in research in boys with FXS

(Sullivan et al., 2007). The cumulative percentages of hits and correct rejections were calculated and used in subsequent inferential statistical analyses to measure sustained attention and response inhibition.

Additionally, to measure sustained attention, the Attention Sustained subtest from the *Leiter-R* (Roid & Miller, 1997) Attention and Memory battery was administered to the boys with FXS and to the boys with AD/HD. This timed standardized subtest consists of visually scanning and crossing out objects that look exactly like the target picture at the top of each page as quickly as possible. Because this subtest was added to the research protocol in the third year of the longitudinal study, only 21 boys with FXS were administered this subtest. Three boys received a raw score of 0 so their data were excluded from analyses because they did not demonstrate understanding of the task. Only one MA-matched child was administered this subtest, but his data was not used in analysis. Twenty-nine of thirty boys with AD/HD were administered this subtest. In addition, one child's data was excluded due to an administration error that potentially invalidated the subtest. Due to significant chronological age differences, raw scores were used in group comparisons and mental age was used as a controlled variable. The internal consistency reliability coefficient of the Attention Sustained subtest is .83 for 2 to 10 year olds and .92 for 11 to 20 year olds.

Measures of Response Inhibition

In addition to the CPTs, the *Day/Night* (Gerstadt, Hong, & Diamond, 1994) experimental task was administered to measure behavioral inhibition. In the *Day/Night Task* (Gerstadt et al., 1994), an experimental task designed to measure behavioral inhibition, boys were shown two cards: one white with a yellow sun, the other black with a white moon. They were instructed to say "night" when presented with the sun card, and "day" when presented

with the moon card. This task assesses inhibitory control by requiring the participant to state the word “day” when presented with the card with the moon, and “night” when presented with the card with the sun. Once the boys demonstrated an understanding of the rules, 16 trials were administered, 8 with each card in a mixed order that is the same for each child. Scores used in the analysis included the total correct score (out of total possible of 16 trials).

Measures of Behavior/Emotional Problems

Due to the age range of the children with FXS and the longitudinal data collection protocol, parent(s)/caregiver(s) completed either the *Child Behavior Checklist* for ages 6-18 years (*CBCL*; Achenbach & Rescorla, 2001) or the previous version, the *CBCL* for ages 4-18 years (Achenbach, 1991) to assess behavior/emotional problems. Additionally, depending on the chronological age of the child, an age appropriate version of the *Symptom Inventory* (Gadow & Sparfkin, 2002) was also completed for all groups. Due to the fact that the boys with AD/HD were chronologically younger, the parent/caregiver either completed the current version of the *CBCL* for ages 6-18 years (Achenbach & Rescorla, 2001) or the *CBCL* for ages 1½-5 (Achenbach & Rescorla, 2000) to assess problem behavior and also completed an age appropriate *Symptom Inventory* to assess symptoms based on the *DSM-IV*. These data were used primarily describe the samples of boys with FXS and the boys with AD/HD, as rated by their parent(s)/caregiver(s).

Achenbach developed the *CBCL* (Achenbach, 1991; Achenbach & Rescorla, 2001) for parents as a measure of problem behavior in children. On the most recent version of the *CBCL 6-18* (Achenbach & Rescorla, 2001), a 112 item-standardized questionnaire, the parent(s)/caregiver(s) indicates whether each item is “not true” (0), “somewhat or sometimes true” (1), or “very true or often true” (2) for their child “now or within the past 6 months.”

Syndrome scales from the *CBCL* were derived from a statistical factor analysis of the items; and with the revision of the scales in 2001, items can also be sorted based on their similarity to *DSM-IV* (American Psychiatric Association, 1994) diagnoses, resulting in additional *DSM*-oriented subscales. In addition to the *DSM*-oriented scales, there are eight subscales, or syndrome scales, that were derived from items and factor analyzed on the *CBCL 6-18* years version. These subscales include Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. These factors contribute to three broad scales: Internalizing, Externalizing, and Total Problems. T-scores for the Total Problems, Internalizing, and Externalizing scales are considered clinically significant when they are above 63 and are considered to be borderline clinically significant when they are 60 to 63. T-scores for the eight syndrome subscales are considered clinically significant when they are 70 and above and are considered to be borderline clinically significant when they are 67 to 70. The internal consistency alpha coefficient was high for Total Problems (.94) and ranged from .82 on the Anxious/Depressed syndrome scale to .92 on the Somatic Complaints and the Attention Problems subscale. The test re-test reliability was moderately high for Total Problems (.81) and ranged from .64 on the Somatic Complaints scale to .82 on the Aggressive Behavior scale. Because two sets of norms for the *CBCL* (current or previous version) could introduce unnecessary variability, all data collected with the earlier version in the sample with FXS were re-scored using the current norms for all analyses, consistent with recommendations in the manual of the current version. Any boys in the control group with AD/HD, ages 6 years and older, were administered the new *CBCL 6-18* version which took approximately 20 minutes to complete.

Because the boys with AD/HD are chronologically younger to the boys with FXS; some of the children's parents completed the *CBCL 1½-5* (Achenbach & Rescorla, 2000). The *CBCL 1½ to 5* is a 99-item standardized questionnaire in which parents or caregivers rate statements describing child behaviors on a three-point scale as either 0 "not true", 1 for "sometimes true" or 2 "very true or often true," based on the preceding 2 months. The *CBCL 1½ to 5* produces scores on the following factors: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior. These factors contribute to three broad scales: Internalizing, Externalizing, and Total Problems. Internal consistency for the *CBCL* Total Problems score was reported at .76 with a range from .53 on the Withdrawn subscale to .64 on the Anxious/Depressed subscale. Test-retest reliability for the Total Problem score was .90 with a range on subscales from .68 on the Anxious/Depressed subscale to .92 on the Sleep Problems subscale. This questionnaire was completed by parent(s) /caregiver(s) of children with AD/HD and took approximately 20 minutes to complete.

As part of the longitudinal study, depending on child's chronological age, the parent(s)/caregiver(s) of the MA-matched peers either completed the previous version of the *CBCL, ages 4-18 years* (Achenbach, 1991) or the most recent version, the *CBCL ages 6-18* (Achenbach & Rescorla, 2001) or the younger version, the *CBCL ages 1 ½--5 years* (Achenbach & Rescorla, 2000).

Symptoms Based on the DSM-IV

The *Childhood Symptom Inventory-4: Parent Checklist (CSI-PC; Gadow & Sprafkin, 2002)* and *Adolescent Symptom Inventory-4: Parent Checklist (ASI-PC; Gadow & Sprafkin, 2002)* were completed for the sample of boys with FXS. Parent(s)/caregiver(s)

either completed the child or adolescent version of the measures depending upon the child's chronological age. Because the boys with AD/HD were chronologically younger, parent(s)/caregiver(s) of children under the age of 6 years completed the *Early Childhood Symptom Inventory (ESI-PC)* (Gadow & Sprafkin, 1997). For children ages 6-12 years old, the *CSI-PC* (Gadow & Sprafkin, 2002) was completed. For all *Symptom Inventories*, items are rated on 4-point Likert-type scale for frequency of the child's overall behavior, "never" (0), "sometimes" (1), "often" (2), and "very often" (3). The items are based on the diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (American Psychiatric Association, 1994). The following scales comprise the *CSI-PC*: AD/HD-Inattentive type, AD/HD-Hyperactive type, AD/HD-combined type, Oppositional Defiant Disorder, Conduct Disorder, Generalized Anxiety, Social Phobia, Separation Anxiety Disorder, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Motor Tic Disorder, Vocal Tic Disorder, Tourette's Disorder, Major Depressive Disorder, Dysthymic Disorder, Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified, Schizophrenia, Enuresis, and Encopresis. The *ASI-PC* has all of the same subscales as the *CSI-PC* but contains a few other relevant subscales for this age group, including Panic Attack, Bipolar Disorder, Drug Use, and Eating Disorders but does not include Pervasive Developmental Disorder. The *ECI-PC* has additional subscales of Selective Mutism, Reactive Attachment Disorder, and Sleep Disturbances that neither the *CSI-PC* nor the *ASI-PC* contains. Scoring algorithms are used to determine whether children meet *DSM-IV* criteria for various diagnoses. Additionally, norms are available to convert raw data into T-scores as well.

As part of the longitudinal study, depending on children's chronological age, parent(s)/caregiver(s) of the MA-matched peers either completed the *Early Child Symptom Inventory* (Gadow & Sprafkin, 1997) or the *Childhood Symptom Inventory* (Gadow & Sprafkin, 2002).

Measures of General Intellectual Functioning

The *Leiter International Performance Scale-Revised (Leiter-R; Roid & Miller, 1997)* is a nonverbal measure of intelligence that was used to assess the cognitive functioning in both groups. For the purpose of this study, the four subtests from the Visualization and Reasoning Battery that comprise the Brief IQ Screener were administered to the participants. These subtests include Figure Ground, Form Completion, Sequential Order, and Repeated Patterns, and do not overlap with the *Leiter-R* subtest selected as the measure of sustained attention. The *Leiter-R* yields scaled scores for each of the subtests and an overall IQ estimate that was used to match the group with FXS to their typically developing peers. Originally, boys with FXS were expected to be matched on mental age and ethnicity to the boys with AD/HD; however, due to limited time and financial constraints, this was not feasible. Thus, mental age was a covariate in statistical analyses. The *Leiter-R Brief IQ Screener* is appropriate for individuals aged 2 to 20 years and has been shown to produce scores consistent with longer IQ batteries such as Wechsler Intelligence Scale for Children-III (Wechsler, 1991) with a correlation coefficient of .85. The internal consistency reliability coefficient of the Brief IQ Screener is .88 for 2 to 5 year olds, .90 for 6 to 10 year olds, and .89 for 11 to 20 year olds. The Brief IQ screener also has good test-retest reliability of .96.

Autistic Behavior

To assess autistic characteristics in the sample of boys with full mutation FXS and the boys with AD/HD, the *Childhood Autism Rating Scale (CARS)* (Schopler, Reichler, & Renner, 1988) was completed by the trained child examiner immediately after the assessment has taken place. The *CARS* is a 15-item measure, with each item measured on a Likert scale, in which a professional rates the child in each of the 15 areas using a score from 1 (within normal limits for age or skill level) to 4 (severely abnormal for age or skill level). The *CARS* includes the following areas: Relating to People; Imitation; Emotional Response; Body Use; Object Use; Adaptation to Change; Visual Response; Listening Response; Taste; Smell, and Touch Responses; Fear and Nervousness; Verbal Communication; Nonverbal Communication; Activity Level; Intellectual Response; and General Impression of Autism. The *CARS* was completed after the professional had observed the child in enough contexts to be able to rate all 15 items. The item scores are added to create a total score, which can be used as a continuum of autistic behavior. In addition, total scores on the *CARS* can be interpreted as non-autistic (15-29.5), mildly or moderately autistic (30-36.5), and severely autistic (37 or higher). The *CARS* has good internal consistency (.94), inter-rater reliability (.71), and test-retest reliability (.88).

AD/HD Symptoms

Because AD/HD is often diagnosed using different diagnostic standards, in order to substantiate an AD/HD diagnosis by a professional in the sample with AD/HD, two norm-referenced screening measures were used to assess these symptoms across two different settings, both at home and at school. The *Conner's Parent Rating Scale-Long Version* (Conners, 1997) was given to the parent(s)/caregiver(s) to complete. Additionally, a teacher rating form, the *Conner's Teacher Rating Scale-Long Version* (Conners, 1997) was either

mailed to the child's most recent teacher or given to the teacher by the child and/or their parent(s)/caregiver(s) to complete after the child's parent(s)/caregiver(s) had given consent. These forms are frequently used to measure AD/HD symptoms and behavior in school and clinical settings. Each scale takes approximately 15 minutes to complete. These measures were only given to the parent(s)/caregiver(s) with boys with verified clinical diagnoses of ADHD; this measure was not used diagnostically, only to substantiate AD/HD diagnoses, which were verified through obtaining each child's medical records and/or a psychological report.

Background Information

The General Information Form that had been used with boys with FXS and their MA-matched peers was also to be used for the group with AD/HD to provide background information on the child's age, ethnic background, parents' educational level, income, and dates of diagnosis. See the Appendix for a copy of the General Information Form.

Medication Status

The Medication History Form that had been completed for the boys with FXS and their MA-matched peers was also used with boys with AD/HD to provide detailed information about history of medication use, per parent report. It also provided detailed information about the type of doctor who prescribed the medication, type of medication, where the medication is administered, dosage, frequency of medication use, and target symptoms of each medication. See the Appendix for a copy of the Medication History Form.

Procedures

As previously mentioned, data collection for the males with FXS and their MA-matched peers had been completed as part of their participation in the longitudinal study of *Attention, Memory, and Executive Function* in children with FXS. Select data from each child's first assessment were used for the purposes of this research study. Following IRB approval and adhering to HIPAA guidelines, recruitment for the group with AD/HD was completed two ways: 1) in a monthly local advertisement in the *Carolina Parent*, a popular publication for families, and through 2) the Duke University ADHD program where staff members distributed flyers, describing this study to families currently participating in ongoing ADHD research studies at Duke University. Towards the end of data collection, recruitment was also done by having the researcher personally meet some of the families at the ADHD clinic, before their study visit, to discuss this study in detail. Consent to contact these families along with their contact information was obtained during this initial recruitment meeting. Occasionally, study visits were scheduled at this meeting.

Participation was voluntary; the advertisement and flyers provided information about the study along with a contact name and phone number for more information. Follow-up phone calls were made to families who had expressed interest and were willing to have their child participate in this study. During the initial phone call, interested families were given more detailed information about the purpose of this study, the description and rationale for the measures to be used, and the anticipated time commitment. Also, exclusionary criteria (e.g., co-morbid diagnoses) were ruled out with the parent/caregiver to determine if their child has been diagnosed with any other disability that would exclude him from being enrolled in the study. If the child met any of these criteria, then, the study coordinator immediately informed the parent/caregiver that unfortunately the child would not be able to

participate in this study. During this initial phone call, parents were told that a copy of relevant medical records and/or a psychological report, verifying their child's AD/HD diagnosis, would need to be obtained during the study visit. The university institutional review board (IRB) approved HIPPA consent form was signed by all families to allow access to this medical information and in some cases allow access to this information by the child's pediatrician. Twenty-seven of thirty children were verified to have a diagnosis of AD/HD by either a pediatrician and/or a licensed psychologist. Documentation for three children could not be obtained despite several attempts. One of these children's pediatrician's office had the medical documentation but failed to mail the documents after several attempts to obtain this information and follow-up phone calls to the pediatrician's office by the researcher. However, these children had T-scores in the clinical range on the Conners ADHD Index for at least one Conner's Rating scales (parent or teacher). Once verbal consent had been obtained and initial criteria have been screened over the phone, an assessment was scheduled. Based on family preference, all assessments were done in the child's home.

At the beginning of the assessment, the researcher reviewed forms with the parent(s)/caregiver(s) including the consent, general information, medication history form, and the child behavior rating scales. Details about each form were described and any questions were answered. Once the consent form had been signed by the parent/caregiver, then, the researcher spent a short time describing to the child what he would be doing, establishing rapport with the parent(s)/caregiver(s) and the child. After the assessment had been completed with the child, the research assistant collected the remaining forms from the parent(s)/caregiver(s) and scanned the forms to ensure that all items had been completed.

Attempts were made to avoid outside interference (i.e., siblings, transition times) during test administration. Equipment, such as the laptop computer, test protocols, video cameras, and a VCR player from the Carolina Fragile X Project were used to minimize cost. The visual and the auditory CPTs and the Day/Night task were videotaped to ensure accuracy of scoring.

Due to limited time constraints and financial resources and the nature of the project, it was not feasible to match the groups on mental age as was originally intended. However, mental age was used as a covariate in statistical analyses. In terms of cognitive functioning, boys with AD/HD and typically developing peers were required to obtain average IQ scores on the Leiter-R (standard scores of 80-120). However, a few boys with AD/HD received scores minimally higher and one minimally lower than the preset range. These children were included in analyses because the difference was very minimal and mental age, which uses an IQ score to be generated, was controlled for in subsequent analyses.

As previously mentioned, all efforts were made to screen for comorbid disorders among the boys with AD/HD. This screening process was done through documenting parental report of additional diagnoses on the General Information Form as well as obtaining copies of past psychological reports, confirming such diagnoses. These reports, however, were obtained after a HIPAA consent form had been signed by the parent(s)/caregiver(s) and approved through the IRB. However, because the boys with AD/HD (ages 5-8 years) were chronologically younger than the boys with FXS (ages 7-13 years), the issue of comorbidity was minimal since the boys with AD/HD were often very young.

The assessment took approximately two hours to complete, with frequent breaks integrated into the session. Families were given \$25.00 for their participation and children

received a small toy, which they could choose for participating. The brochures, consent forms, and measures to be administered were approved by the university's institutional review board prior to the study commencement.

Data Management

The data were scored by the study coordinator/research assistant. Once the data had been double checked for accuracy, they were sent to statistics to be double entered and verified by the data programmer to ensure accuracy. Then, the data were sent back to the researcher (data manager) for verification. The researcher for this study oversaw and ensured that all data were entered and verified as 100% correct.

CHAPTER IV

Results

Data Analyses

Prior to analyses, in order to determine if there was sufficient sample size, a power analysis was conducted, using Cohen's f (1988). For ease of interpretation, one typical model was chosen as the basis for the power analysis. The power analysis was calculated using G-Power Version 3.0.8 (Faul, 2006). A univariate analysis of covariance, controlling for mental age, was run, setting power at .8 and assuming an alpha of .05. Results suggested a minimum of 48 children were needed for sufficient power to detect differences among the groups, which was far exceeded in this study's total sample size ($n = 140$).

To measure sustained attention, children's correct responses to target stimuli (i.e., dog) on the CPT were coded as hits when children correctly clicked on the mouse when a target stimulus was presented. When the children failed to click on the mouse when a target stimulus was presented (an incorrect response), their responses were coded as misses. To measure inhibition, children's responses to nontarget stimuli were coded. When children did not click the computer mouse when a nontarget stimulus was displayed (correct response), their responses were coded as correct rejections. However, when children incorrectly clicked the mouse when a nontarget stimulus was displayed (an incorrect response), their responses were coded as false alarms. Traditionally, the number of misses and false alarms (e.g., errors of omission and commission) are reported in the literature (Ballard, 2001; Riccio, Reynolds,

Lowe, & Moore, 2001); however, the number of hits is directly and inversely proportional to the number of misses, and the number of correct rejections is directly and inversely proportional to the number of false alarms. Thus, for ease of interpretation, comparability and consistency with recent literature on the CPT in children with FXS (Sullivan et al. 2007), correct responses (hits and correct rejections) were used in analyses and as reference points in the graphs.

Generally, regarding sustained attention for the boys with FXS, it was a noteworthy result that only 60% and 49% of the boys with FXS demonstrated sufficient understanding on the visual and auditory CPT tasks, respectively, in order to complete the tasks. Thus, for the subsequent analyses, only a subset of the boys with FXS was included in the inferential models.

All variables in each model were first screened for collinearity to determine if they met assumptions for each statistical test prior to analysis. The Benjamini Hochberg- method for adjusting P-value was calculated to control for type I error when running multiple tests; and, therefore, an alpha of .05 was used to determine significance (Benjamini & Hochberg, 1995). Descriptive statistics are presented in Table 2 on all dependent variables.

Research Question 1: Controlling for mental age, are there significant differences on three different measures of sustained attention among boys with FXS, their MA-matched peers and boys diagnosed with AD/HD? To address the first research question comparing group differences on the CPT measure of sustained attention, cumulative percentages of hits at 2 or 3- second intervals (i.e. each stimulus) based on the possible cumulative number of hits on the visual and auditory CPTs, respectively, were calculated. Percentages of hits were calculated for all groups throughout the length of the tasks (visual and auditory CPT) to

assess the ability to maintain attention over the duration of the tasks and identify differences among the groups. Hierarchical linear modeling (HLM) was employed to analyze the CPT data using SAS “proc mixed” [SAS Institute, 2003] . HLM is particularly suited to the CPT data because of dependence of observation due to multiple measures for each individual. This dependence was controlled by the estimation of random effects (Burchinal & Applebaum, 1991; Raudenbush & Bryk, 2002).

Sustained Attention

Table 3 compares descriptive characteristics for the boys with FXS who were able to complete the CPT tasks and for those who were not. Although autistic characteristics were not able to be included as a predictor variable in the inferential models, Table 4 suggests that children who were not able to complete the CPTs had higher ratings on the CARS, with approximately 62.5% meeting autism cut off. There were no differences, however, on medication status and parent ratings of attention problems on the CBCL and Symptom Inventories for children who were able to complete the CPTs and those who were not.

Visual CPT

For the boys with FXS ($n = 34$) who demonstrated understanding of the visual CPT task, their MA-matched peers ($n = 48$), and for the boys diagnosed with AD/HD ($n = 30$), Table 4 indicates a significant main effect for time [$F(1,109) = 6.03$; $p = 0.0269$], after controlling for mental age. This indicates that for every 10 stimuli there was a .03 percent decrease in cumulative percentage of hits on the visual CPT. There was also a significant main effect for group [$F(2,109) = 9.27$; $p = 0.0012$], after controlling for mental age, indicating that boys with FXS had significantly lower means of percentages of hits, compared to both groups.

Auditory CPT

For the boys with FXS ($n = 28$) who demonstrated understanding of the auditory CPT task, their MA-matched peers ($n = 48$), and the boys diagnosed with AD/HD ($n = 30$), Table 4 indicates that there is a significant two-way interaction with time and group [$F(2,103) = 5.93$; $p = 0.0074$]. Given the presence of this interaction, lower order effects will not be described. This two-way interaction for the auditory CPT is clarified in Figure 1. Multiple t -tests were run to further clarify this interaction at three different time points: the beginning (1st second), middle (96 seconds), and end (192 seconds) of the auditory task (total duration = 192 seconds). Significant differences were found between boys with FXS and boys with AD/HD at the beginning of the task [$t(103) = 3.67$; $p = 0.0004$] and at the middle of the task [$t(150) = 2.27$; $p = 0.0243$] but not at the end of the task (192 seconds). Additionally, significant differences were also found at the beginning of the task [$t(103) = -3.30$; $p = 0.0013$] between boys with FXS and their MA-matched peers. Figure 1 indicates that the boys with FXS had significantly fewer cumulative percentage of hits at the beginning of the task but as the task progressed, their percentage of hits increased, resulting in a slightly higher percentage of hits at the end of the task compared to typically developing boys. Comparatively, the boys with AD/HD and the MA-matched peers performed similarly at the beginning of the task but performance decreased across the length of the auditory task, resulting in fewer percentages of hits at the end of the task.

Attention Sustained (Leiter-R)

To further answer the first research question, using the second, additional measure of sustained attention (Attention Sustained subtest from the Leiter-R), raw scores were analyzed using univariate analysis of covariance (ANCOVA) to determine if group differences existed,

after controlling for mental age. Because of significant chronological age differences among the groups, only raw scores could be analyzed on this subtest. There were no significant differences found on the raw scores among the groups, controlling for mental age [$F(2, 43) = 0.28; 0.060$]. Because the Attention Sustained subtest was added to the research protocol in the third year of the Attention, Memory, Executive Function study, only 21 boys with FXS were administered this subtest. Additionally, three boys received raw scores of 0 and thus, did not demonstrate understanding of the task, so for the analyses only 18 boys with FXS were used. Twenty-eight boys with AD/HD were administered this subtest and their data were used for analyses. One of the MA-matched peers was administered this subtest, but his data was not used in analyses.

Additionally, in terms of ratings of attention problems on the Child Behavior Checklist (CBCL; Achenbach, 1991; Achenbach & Rescorla, 2001), nine boys (17.54%) with FXS were rated to be in the Borderline range on the Attention Problems subscale while four boys (7%) were rated to be in the Clinically Significant range. On the DSM-oriented scales on the CBCL, the DSM-ADH Problems subscale, 10 boys with FXS (17.54%) were rated to be in the Borderline range and three boys (5.3 %) were rated to be in the clinically significant range on the Attention Problems (mean T-score = 60.58) and/or DSM-ADH Problems (mean T-score = 58.63) subscales on the CBCL.

Research Question 2: Controlling for mental age, are there significant differences on three different measures of behavioral inhibition in boys with FXS, their MA-matched peers, and boys diagnosed with AD/HD? To address the second research question on behavioral inhibition, CPT data were analyzed first. First, cumulative percentages of correct rejections at 2 or 3- second intervals (i.e., each stimulus) based on the possible cumulative number of

correct rejections on the visual and auditory CPTs, respectively, were calculated. Percentages of correct rejections were calculated for all groups including boys with FXS, their MA-matched peers, and boys with AD/HD throughout the length of the task to assess stability in their ability to inhibit over the duration of the tasks and identify differences among the groups. Again, HLM was used to analyze the CPT data using SAS “proc mixed” [SAS Institute, 2003]), as in the first research question.

Behavioral Inhibition

Visual CPT

Table 4 indicates the presence of a significant two-way interaction with group and time [$F(2,109) = 12.71$; $p = 0.0012$]. This interaction is clarified in Figure 2. Multiple t-tests were run to further clarify this interaction at the beginning of the task (1st second), middle (89 seconds), and at the end (177 seconds) of the visual task (total duration = 177 seconds). Significant differences were found for boys with AD/HD ($n = 30$) and the boys with FXS ($n = 34$) at the middle of the task [$t(149) = 2.18$; $p = 0.0309$] and at the end of the task [$t(207) = 2.60$; $p = 0.0099$]. Additionally, boys with FXS were significantly different than their MA-matched peers at the middle of the task [$t(149) = -1.82$; $p = 0.0702$] and at the end of the task [$t(207) = -3.19$; $p = 0.0016$]. Figure 2 indicates that the cumulative percentage of correct rejections for the boys with FXS is similar to their MA-matched peers and the boys with AD/HD at the beginning of the visual CPT task. However, as the task progressed, the boys with FXS made significantly fewer correct rejections than their MA-matched peers and the boys with AD/HD. Interestingly, the typically developing peers actually increased their percentage of correct rejections across the task while the boys with AD/HD remained consistent over time.

Auditory CPT

Table 4 indicates a significant two-way interaction with time and group [$F(2,103) = 7.32$; $p = 0.0026$]. This interaction is clarified in Figure 3. Due to the presence of an interaction, lower order effects will not be discussed. Multiple t-tests were run to further clarify this interaction, as previously described. Significant differences were found between boys with FXS and boys with AD/HD [$t(194) = 2.10$; $p = 0.0371$] and their MA-matched peers [$t(194) = -2.69$; $p = 0.0077$] at the end of the task. Figure 3 indicates that all groups performed similarly at the beginning of the task. At the end of the task, however, the boys with FXS made significantly fewer correct rejections than the boys with AD/HD and their MA-matched peers.

Day/Night Task

To further answer the second research question on behavioral inhibition, a second, additional measure of inhibition, the Day/Night experimental task was analyzed using ANCOVA (total number correct out of 16 trials as the dependent variable). A significant main effect for group was found [$F(3,118) = 11.90$; $p < .0001$]. Boys with FXS obtained significantly fewer total correct responses than boys with AD/HD (Cohen's $d = 1.0$) and their MA-matched peers (Cohen's $d = .9$).

Research Question 3: Controlling for mental age, are there significant differences in mean response times of hits on the visual and auditory CPT among boys with FXS, their MA matched peers, and boys with AD/HD? To address the third research question, mean response times of hits on both the visual and auditory CPTs were analyzed using ANCOVA. Table 4 indicates that there is a significant main effect for group on the visual CPT [$F(3,108) = 3.75$; $p = 0.0267$], indicating that the boys with FXS had a significant lower mean on the

visual CPT. Thus, boys with FXS responded significantly slower to targets than their MA-matched peers (Cohen's $d = .4$). There were no significant group effects on the auditory CPT.

Research Question 4: What child and/or family variables (i.e., maternal education, chronological age, autism status (total CARS score), medication status and T-score on DSM-ADH Problems subscale on the Child Behavior Checklist predict performance on measures of attention and inhibition in males with FXS? To examine the effects of predictors on performance for all measures of attention and inhibition in boys with FXS, six univariate analyses of variance were conducted. The independent variables in this model included maternal education, chronological age, autism status as measured by the total CARS score, medication status (dichotomous variable-either on or off medications) and the T-score on the DSM-ADH Problems subscale on the CBCL. The Benjamini Hochberg- method for adjusting P-value was calculated to control for type I error when running multiple tests; therefore, an alpha of .05 was used to determine significance (Benjamini & Hochberg, 1995). There were no significant predictors for the measures of sustained attention: percentages of hits on auditory CPT [$F(6, 20) = 0.93$; adj. $p = .7392$]; percentages of hits on visual CPT [$F(6, 26) = 0.69$; adj. $p = .6566$]; and Attention Sustained subtest (Leiter-R) [$F(6, 13) = 2.99$; adj. $p = .1383$]. Similarly, there were no significant predictors for the measures of inhibition: percentages of correct rejections on auditory CPT [$F(6, 26) = 1.78$; adj. $p = .4635$]; percentages of correct rejection on visual CPT [$F(6, 26) = 0.54$; adj. $p = .7750$]; and Day/Night total [$F(6, 35) = 0.79$; adj. $p = .8730$].

CHAPTER V

Discussion

Integration of Findings

Despite the similarities in the neuropsychological profile and symptomology of AD/HD to FXS, there have been no comparison studies of these two groups to clarify deficits of sustained attention and inhibition in boys with FXS. Thus, the purpose of this study was to compare boys with FXS to MA-matched boys clinically diagnosed with AD/HD on measures of sustained attention and inhibition to elucidate these deficits in the boys with FXS.

Findings may have important implications for future interventions and perhaps lead to earlier detection and treatment of AD/HD symptoms in boys with FXS.

Sustained Attention

Although it was hypothesized that there would be no significant differences on the measures of sustained attention among the boys with FXS and the boys with AD/HD, this hypothesis was not completely supported. On the visual CPT, there were significant main effects for group and time, suggesting that the performance of boys with FXS declined over time and ended with significantly fewer percentages of hits, compared to boys with AD/HD and the MA-matched typically developing peers. This finding is inconsistent with previous research by Munir et al. (2000a), where no significant differences were found for the number of targets detected between the boys with FXS and the comparison groups, including the “poor attention” group, most comparable to the boys with AD/HD. However, although this

study did not find significant differences, Munir et al. (2000a) did find a similar trend where boys with FXS detected fewer targets compared to the control groups. The lack of significant findings from the Munir et al. (2000a) study could be attributed to the study's limited sample size.

On the auditory CPT, although there was a significant interaction with group and time for percentage of hits, this interaction revealed that although the boys with FXS had more difficulties with attention at the beginning of the task than the boys with AD/HD and their MA-matched peers, as the task progressed, boys with FXS increased their percentage of hits, resulting in a slightly higher percentage at the end of the task, than both comparison groups. Thus, this finding suggests that although the boys with FXS had more difficulty paying attention at the beginning of the task, they were able to sustain their attention across the length of the task, consistent with Sullivan et al. (2007) findings in boys with FXS.

One possible explanation of significant group differences in attention at the beginning of the auditory task, indicated in the interaction, is that boys with FXS may have had more difficulty adjusting to the change in stimuli and modality, compared to the other two groups. This finding is particularly interesting because we would have expected a decline in their ability to maintain their attention on the second task (auditory), similar to the typically developing peers and boys with AD/HD. This lack of decline in maintaining their attention, however, may suggest that the boys with FXS “failed to lose interest” in the task. This failure to lose interest has been previously reported in children with ID (Schafer and Peeke, 1982). This increase in percentages of hits (attention) was very minimal, but emphasizes the importance of examining performance over time. If only the cumulative percentage of hits at

the end of the task had been analyzed, most likely, significant differences would not have detected and the trend of their attention over time would be unknown.

Examining the data using a cumulative percentage across the length of the task permitted examination of attention and inhibition across time. Although d-prime is frequently used (e.g., Hooks et al., 1994) to measure sustained attention on the CPT, this researcher choose not to use d-prime because it does not permit a comparison between responses to targets (measure of sustained attention) and nontargets (measure of response inhibition) as separate measures would. Because d-prime accounts for the possible inflation in hits due to false alarms, data were screened prior to analyses to determine if high rates of false alarms might account for the increased number of hits, similar to Sullivan et al. (2007). Other CPT researchers (Halperin et al., 1992; Pearson et al., 1996) have examined CPT performance using univariate analyses variance in blocks of time to identify performance differences at the beginning, middle, and end of the task. However, this method of analyzing changes in blocks of time instead of as continuous data may obscure possible findings because a change may occur within a block of time (Sullivan et al., 2007).

The hypothesis regarding sustained attention was supported on the Attention Sustained subtest from the Leiter-R. There were no significant group differences between boys with FXS and boys with AD/HD. These inconsistent results between the CPTs and this subtest may be because this subtest appears to be more a measure of visual scanning than sustained attention. The maximum time limit on the Attention Sustained subtest is 60 seconds, which seems hardly sufficient to measure sustained attention. Additionally, on the CPTs, most of the significant differences between the groups did not emerge until the middle or end of the tasks, which was beyond the maximum 60 second limit on this Attention

Sustained subtest. Although CPT tasks purportedly measure sustained attention, other factors, besides attention may have been impacting their ability to perform and complete these tasks, such as social anxiety and/or hyperarousal as other researchers have found in individuals with FXS and autistic behavior (Roberts, Boccia, Bailey, & Hatton, 2001). It is hard to speculate whether difficulties with attention found in this study truly represent “attention” problems in boys with FXS or if their attention problems are manifested as anxiety problems. This study was not designed to differentiate between these two so only speculations can be made at this point. However, given that this study separates specific measures of sustained attention and includes more than one measure of attention, including the cumulative percentage of hits on the CPT and raw scores on the Attention Sustained subtest from the Leiter-R, the results from this study arguably measure sustained attention and not anxiety.

Generally, regarding sustained attention for the boys with FXS, it was a noteworthy result that only 60% and 49% of the boys with FXS demonstrated sufficient understanding on the visual and auditory CPT tasks, respectively, in order to complete the tasks. This finding is consistent with Munir et al. (2000a), where only 68% of the boys with FXS were able to complete the Same-Opposite task, a measure of executive functioning, compared to 88% of the boys with Down Syndrome. Thus, despite inconsistent results regarding sustained attention in boys with FXS across multiple measures (i.e., adapted CPTs and Attention Sustained subtest on the Leiter-R), approximately half of the boys with FXS could not demonstrate sufficient understanding of the CPTs in order to complete them which was not the case for any boys with AD/HD. Generally, it appeared that boys with FXS who were not

able to complete the CPTs had higher ratings on the CARS, with approximately 62.5% meeting autism cut off.

Response Inhibition

Although inhibition has been widely studied in individuals with AD/HD (e.g., Berwid, Kera, Marks, Santra, Bender, & Halperin, 2005; Gordon, 1979; Iaboni, Douglas, & Baker, 1995; Nigg, 2001; Schachar & Logan, 1990; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Trommer, Hoepfner, Lorber, & Armstrong, 1988), there is little research in the area of response inhibition in children with FXS (Hooper et al., in press; Munir et al., 2000a; Sullivan et al., 2007; Wilding et al., 2002). However, based on previous research in this area, it was predicted that the boys with FXS would exhibit greater difficulty with inhibitory control, compared to boys with AD/HD and their MA-matched typically developing peers. This hypothesis was supported on both measures of response inhibition. Boys with FXS began the task similarly as the other groups on the visual CPT task; however, by the middle of the task, the boys with FXS showed a greater decline in inhibitory control, resulting in significantly fewer cumulative percentages of correct rejections than boys with AD/HD and their MA-matched peers at the end of the task. Similarly, on the auditory task, boys with FXS demonstrated a greater decline in inhibitory control when compared to the other two groups, while the performance of the boys with AD/HD and the MA-matched typically developing peers remained relatively consistent. This finding is particularly interesting because this decline in inhibitory control happened quickly into the task (approximately 1 minute 30 seconds). It would be interesting for future researchers to use longer CPT versions (7-14 minutes) to clarify this trend in the boys with FXS. Consistent with the results on the CPT tasks, the boys with FXS demonstrated greater difficulty with inhibiting their automatic

response on the Day/Night task. This difficulty with inhibitory control is consistent with research in young males and toddlers with FXS (Hooper et al., in press; Munir et al., 2000; Scerif, 2004; Sullivan et al., 2007; Wilding, 2002).

This finding that boys with FXS consistently exhibit a significant greater difficulty with inhibitory control compared to boys with AD/HD is noteworthy, particularly because recent research of inhibitory control in those with AD/HD (Nigg, 2001) and Barkley's (1997) model support a primary deficit in inhibition and secondary deficits in sustained attention. Furthermore, in addition to their intellectual disabilities, many boys with FXS also have this significant behavioral difficulty with inhibiting impulsive responding that most likely impedes on their lives, both academically and socially. As discussed in a later section, this finding has implications for interventions in boys with FXS, particularly at school, when demands are high.

Response Time on the CPTs

It was hypothesized that the boys with AD/HD would demonstrate significantly slower (greater) mean response time to hits (targets), compared to both boys with FXS and their MA-matched typically developing peers. However, it was expected that the boys with FXS and the boys with AD/HD would have more comparable mean reaction times, than typically developing peers. This hypothesis was not supported; boys with FXS had significantly slower (greater) mean response times to hits (targets) on the visual CPT than the MA-matched typically developing peers, inconsistent with previous research in young males with FXS (Munir et al., 2000a; Sullivan et al., 2007). However, the boys with FXS had more comparable response times to boys with AD/HD, as predicted but the boys with FXS responded slower to hits. Although previous research did not find significant differences in

the mean response time to targets (hits), these researchers did find a similar trend, where the boys with FXS displayed greater mean times to respond to a target in comparison to the “good attention group.” No significant group differences were found on response time of hits on the auditory CPT, consistent with Scerif et al.’s (2004) findings in toddlers with FXS using a measure that was fairly simplistic (i.e., fewer distracters). These inconsistent results across the visual and auditory CPTs may perhaps be explained by “practice effects.”

Although the tasks were slightly different in the types of stimuli presented and the modality, the overall goal of the task was the same (i.e., click when you see a picture of a dog or when you hear the word dog). Because the visual task was administered first, it is possible that it took the boys with FXS more time to process the incoming input/stimuli and adjust to the task compared to their MA-matches. Another potential explanation for this finding is that because the visual task consisted of distracters that were similar (i.e., pictures of animals) to the target (i.e., dog), this task required more effortful processing in the boys with FXS because it was harder to distinguish between distracters and the target. In comparison, the auditory CPT task consisted of several unrelated words that were not animals (i.e., shoe), which made the discrimination between targets and distracters potentially easier. This theory is consistent with research that has shown that individuals with ID do not perform as well as individuals without ID on tasks that require more effortful processing, even when matched on cognitive abilities (Tomporowski et al., 1990). On the auditory task, all three comparison groups had substantially greater (slower) mean response time to hits than the visual task, albeit not significant from each other. These slower response times might have been due to the fact that the auditory task was the second administered; therefore, fatigue may have been a factor, possibly reducing processing speed.

Given that boys with FXS have difficulties with attention, it seems logical that the boys with FXS had slower mean response time to hits; however, because boys with FXS also have significant difficulties with inhibition, it seems that their responses to hits should be much quicker but, in fact, they are much slower in comparison to other groups. Although this result seems contradictory, recent research has found significant and reliable differences in response time variability distributions between AD/HD and normal controls on discrimination tests (Leth-Steensen, Elbaz, & Douglas, 2000). Leth-Steensen et al. (2000) mentioned that the positive skewing of response time distributions may reflect the presence of “periodic attention lapses” in children with AD/HD. Furthermore, Epstein et al. (2006) found that patients that had been medicated had much less positive skew than non-medicated patients suggestive of fewer and less severe lapses in attention throughout the task.

Although this study analyzed the child’s first response to a hit (target), future research should investigate perseverations on hits and false alarms, similar to Wilding et al. (2002) and as suggested in previous research (Sullivan et al., 2007), to clarify inhibition in boys with FXS.

Impact of Child and/or Family Predictors on Performance of Measures of Sustained Attention and Response Inhibition

It was expected that autistic status (total *CARS* score), T-scores on the Attention Problems subscale on the *CBCL*, and maternal education would predict performance on measures of attention while autistic status (total *CARS* score) would predict performance on measures of inhibition. This hypothesis was not supported. There were no significant predictors of performance on the measures of sustained attention and inhibition. This study was one of the very few studies to examine the impact of various child and family

characteristics such as parent ratings of behavior and medication use on measures of sustained attention and inhibition and is inconsistent with previous research in FXS (Hatton et al., 2002; Sullivan et al., 2007). Hatton et al. (2002) found that mothers with higher education rated their children as having more attention, thought, and total problem behavior on a rating scale. Sullivan et al. (2007) found significant interactions of time and psychotropic medication use and time and MA for visual and auditory attention and visual inhibition skills in boys with FXS. For auditory inhibition skills, Sullivan et al. (2007) also found significant interactions with time and whether boys met diagnostic criteria for ADHD-hyperactive type on teacher ratings and between time and MA.

A previous study has also found MA to be positively correlated with better sustained attention while chronological age was unrelated (Cornish, et al., 2001). These inconsistent results may have due to the fact that MA was not included in the model for this study; instead, chronological age was included and no significant differences were found. It remains unknown why this study failed to find significant findings for other previously found predictors (e.g., maternal education). This lack of significant findings is the reason that more research in this area is needed to identify and examine potential predictors of attention and inhibition in children with FXS.

Implications for Intervention

Early detection and treatment of AD/HD symptoms in boys with FXS is important because it allows professionals to intervene at an earlier age, allowing teachers to focus more on their learning than their behavior (Sullivan et al., 2006). Because of behavior similarities in children with AD/HD and FXS, interventions applicable to those with AD/HD should be

generally applicable to those with FXS, of course, making modifications for the child's developmental level.

One of the most common interventions for those with AD/HD is pharmacological interventions (i.e., stimulant medications); stimulant medications may help children with FXS manage their AD/HD symptoms in the classroom, when the demands on attention become most prominent. Besides a pharmacological intervention, behavior management strategies may also be beneficial when teaching children with FXS. Some behavior strategies that may be helpful for children with FXS (as they are for those with AD/HD) include providing small group instruction, structure and predictability with visual schedules and cues, if possible, to reduce anxiety, one-on-one instruction, preferential seating (e.g., seated towards the front of the class), and behavioral modification techniques, such as token economies to target specific problem behaviors (Hagerman & Hagerman, 2002).

Clearly, as in the general population with ADHD, a comprehensive treatment plan is most appropriate for boys with FXS. One treatment such as a stimulant medication should not be implemented in place of behavioral management strategies or vice versa; instead, both should be implemented together to effectively treat the symptoms.

Limitations and Future Directions

Validity of Adapted CPTs

Several issues must be considered when interpreting the findings from this study. The first and most obvious limitation to this study is the questionable discriminant validity of the adapted CPTs used in this study. On the visual and auditory CPTs, the boys with AD/HD performed similarly to the typically developing peers and had near perfect cumulative percentages of hits and correct rejections. Thus, these adapted CPT tasks appear to be too

simplistic in its type of stimuli (presence or absence of dog stimuli) and were perhaps too short in length (approximately 3-4 minutes) for the boys with AD/HD. Because these CPTs were relatively short and simple, they limited my ability to generalize these findings to longer periods of time and to more complex computerized attention tasks. This said, however, it was necessary to adapt these CPTs so that they were appropriate for children with intellectual disabilities. It was noteworthy that only 60% and 49% of the boys with FXS demonstrated sufficient understanding on the visual and auditory CPT tasks, respectively, in order to complete it. This finding is consistent with Munir et al. (2000a), where only 68% of the boys with FXS were able to complete the Same-Opposite task, a measure of executive functioning, compared to 88% of the boys with Down Syndrome. However, if the CPT tasks would have included more complex stimuli, such as letter stimuli found in traditional CPTs or had longer durations, fewer boys with FXS may have demonstrated sufficient understanding in order to complete the tasks. Additionally, it must be pointed out that the lack of significant differences found between the boys with FXS and AD/HD on some of the measures of sustained attention (auditory CPT and Attention Sustained subtest from the Leiter-R) may be attributable to the fact that the measures used in this study have a maximum duration between 3-4 minutes, which does not seem like a sufficiently long period of time to measure sustained attention. However, it should be mentioned that longer CPTs may have actually been more challenging for the boys with FXS and for children with other developmental disabilities in general. Other valid and reliable preschool measures of sustained attention used in clinical settings to detect and diagnose AD/HD early in childhood in conjunction with several other methods, such as the Kiddie Conner's CPT and other measures (Conners, 2001; Mahone, Pillion, Hoffman, Hiemenz, & Denckla, 2005) could be

tried in FXS future studies; however, the longer duration (i.e., seven minutes) may prove to be more challenging for the boys with FXS and may result in more boys with FXS not being able to complete the task. It might also be interesting for future studies to change the inter-stimulus interval (ISI) or change the ratio of targets to non-targets on the CPTs to explore any differences, as other studies have (Berwid et al., 2005). In addition, similar to the widely used Conner's CPT, future studies should consider using CPTs that require children to *withhold* their responses by requiring them to click on all stimuli except the target. This seems to be a more taxing measure of sustained attention because the child would be required to maintain their attention the entire duration, opposed to targets that occur more infrequently.

Additionally, these adapted CPTs had parameter differences for the visual and auditory tasks which may have been a limitation to this study. The ISI and stimulus interval for the auditory and visual tasks varied; the auditory task had a faster ISI (1.8 seconds) and stimulus interval, possibly contributing to the differences present between the two tasks.

Validity of Attention Sustained Subtest

Similarly, the Attention Sustained subtest also did not seem like a sufficient measure of sustained attention. Although this subtest is a standardized, norm referenced test of sustained attention, unlike the adapted CPTs used in this study, the interpretation of these results are limited to due a several reasons. First, the maximum duration of the test is 60 seconds; this required time limit to attend to the task seems hardly sufficient to measure "sustained attention." The task requirements on this subtest appear to be a measure of visual scanning and processing speed. Lastly, this paper and pencil task requires adequate graphomotor skills, which may have been more difficult for some children than others and

potentially confounded results. Based on these significant limitations in the measures used in this study, it is clear, however, that more standardized measures of sustained attention need to be developed and normed for children with developmental disabilities.

Impact of Autistic Behavior

Another limitation to this study is that the impact of autistic behavior on sustained attention and inhibition couldn't be examined in models comparing the boys with FXS to the boys with AD/HD. Because mental age and total CARS score (autistic behavior) were collinear in this sample, both could not be included as predictors in the models. Perhaps more reliable measures of autistic behavior such as the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore & Risi, 2000) should be used in future studies. This measure may have permitted examination of the impact of autistic behavior and MA on attention and inhibition among the boys with FXS and AD/HD.

Impact of Medication Use

A third, yet important limitation to this study is that medication effects could not be well addressed in this study for number of reasons. First, children already enrolled in the longitudinal study of *Attention, Memory, and Executive Function* were not told to discontinue their medication 24-48 hours prior to the study assessment; thus, many of the children with FXS were taking their medications on the day of the assessments. Due to potential confounds when interpreting results, the boys with AD/HD recruited for this study were not told to discontinue their medications on the day of the assessment. Ideally, however, all children in this study would have discontinued their medication at least 24 hours prior to the assessment and future studies should require children to be off any psychotropic medication when being assessed on neuropsychological measures. Secondly, when initially controlling for mental

age and medication status (either on or off medications), it was found that medication status was collinear with group status and could not be included as a predictor in the main comparison models, but its impact could only be examined in the boys with FXS (research question 4). This collinearity was due to the fact that one of the exclusionary criteria included that the typically developing boys could not be taking any medication. A majority of the boys with FXS and AD/HD were taking psychotropic medications; the boys with FXS who were taking medications were usually taking more than one medication and in several cases the target symptom was not attention, making it even more difficult to interpret the effects. In addition, many of the boys with AD/HD were assessed late afternoon or early evening due to school schedules; thus, even if the child had taken medication that day, by the time of the assessment, the medication most likely had worn off, making interpretation of medication effects even more difficult.

Limited Sample Size

This study was also limited by the relative small sample size in the boys with ADHD ($n = 30$). A larger sample size in this group would have made differences more robust. It is possible that the small sample sizes in the groups may have resulted in finding lack of significant differences on the Attention Sustained subtest (Leiter-R). Unfortunately, because the Attention Sustained subtest was added to the research protocol in the third year of the *Attention, Memory, Executive Function* study, due to time constraints with data collection, only 21 boys with FXS were administered this subtest. Only eighteen of the twenty-one children with FXS demonstrated sufficient understanding of the task. Furthermore, only one typically developing child was administered this subtest. Thus, their performance couldn't be compared with the other two groups.

Impact of Varying Subtypes of AD/HD

Additionally, another potential limitation is that due to time and financial constraints on data collection, boys with all three subtypes of ADHD were enrolled in the study. This heterogeneity of subtypes in neuropsychological profile may have confounded results. Future research should enroll only one subtype of AD/HD (e.g., ADHD-hyperactive/impulsive type) in order to control for any variability in the child's neuropsychological profile.

Teacher Ratings of AD/HD Symptoms in Boys with AD/HD

As mentioned previously, Conners' rating scales were given to the parent(s)/caregivers(s) and teachers of the boys with AD/HD as an additional measure to substantiate their AD/HD symptoms both at home and school. However, inconsistent ratings between parents and teachers, with fewer problem behaviors endorsed by the teachers led to lower means on the Conners' ADHD Index (parents = 67.47; teachers = 59.7), not allowing some AD/HD diagnoses to be fully substantiated by parent and teacher report of symptoms. This under endorsement of AD/HD symptoms by the teachers has also been found in recent research in children with FXS along with other clinical groups (Faraone et al., 2005; Pearson et al., 2003; Sullivan et al., 2006). The inconsistency between parent and teacher ratings could be due to several reasons. The first most obvious reason is that children often display different behaviors at home than at school because these two settings, with two different caregivers, may present different challenges for the child. Secondly, it is possible that the child's behavior is indeed the same; however, parents and teachers have different expectations and perspectives of the child's behavior. A third possible explanation for the inconsistent ratings is the timing of the child's assessment within the academic calendar. For children who were seen late into summer, their teacher from the previous year filled out the

form because he/she best knew the child in a classroom setting; however, their recollection of the child's behavior was diminished at that point. Furthermore, for children who were seen in the beginning of the school year (within the first few months), the teacher's most likely did not know the child well enough to accurately rate their behavior. It is likely that a combination of all these possibilities explains the inconsistency of parent and teacher report of AD/HD symptoms in the boys with AD/HD. Despite these limitations, twenty-seven out of the thirty boys with AD/HD were rated by their parents to be at least in the Mildly Atypical range, suggesting a potentially significant problem in a majority of the boys with AD/HD. Furthermore, twenty-seven out of thirty boys had medical documentation of their AD/HD diagnosis by a professional.

Clearly, more studies and better instruments are needed to measure sustained attention and inhibition in boys with FXS. Future studies are needed to pilot such measures and more extensive research is needed to further elucidate the attention deficit in boys with FXS.

Summary and Future Research

This study provides important neuropsychological findings (i.e., deficits in sustained attention and inhibitory control) in boys with FXS. Findings from this study suggest consistent deficits in inhibition and inconsistent deficits in sustained attention in boys with FXS. Future research is needed to clarify the deficit in attention, particularly sustained attention in boys with FXS. Furthermore, it will be interesting for future studies to examine broader executive function deficits (e.g., working memory, set-shifting) in boys with FXS which was beyond the scope of this study. Additionally, it will be important for future research studies to examine all aspects of attention, including selective, divided, and

sustained attention to determine if there is a “task specific” deficit rather than a global deficit in attention as suggested by Munir et al. (2000a). Future research in this area should also examine the effects of tangible reinforcers in boys with FXS for their potential to improve attention and impulsivity as suggested in previous research (Sullivan et al., 2007).

Table 1

Child and Maternal Demographics

	FXS (<i>n</i> = 57)	ADHD (<i>n</i> = 30)	MA-Matched Peers (<i>n</i> = 53)
Mean age in months (SD)	120 (20.6)	82 (9.6)	60 (11.1)
Ethnicity			
White	86%	70%	83%
African-American	11%	20%	15%
Hispanic	2%	7 %	2%
Asian	2%	0%	--
Native Hawaiian or Other	--	3 %	--
Cognitive Ability ^a			
Mean brief IQ score (SD)	57.8 (10.4)	103.4 (14.8)	106.8 (9.2)
Mean mental age in months (SD)	63 (8.6)	82 (14.8)	62 (10.7)
Maternal Education ^b			
College Graduate or Higher	23%	51.9%	62.9%
Some College	38%	44.4%	25.8%
High School Graduate	39%	3.7%	11.3%
Medication ^c			
No Medication	33.9%	36.7%	100%
Stimulant Only	28.6%	63.3%	--
Stimulant plus one other medication	8.9%	--	--
Single medication other than stimulant	21.4%	--	--
Other medication combinations	14.3%	--	--
CARS			
Mean Score (SD)	28.9 (6.0)	15.6 (0.8)	--
Score of 30 or higher	32.1%	0%	--

^a A Leiter-R was not administered to one child with FXS and seven MA-matched peers.

^b Maternal education was not obtained for three boys with AD/HD.

^c No data on medication history was obtained for one child with FXS.

Table 2

Descriptive Statistics of Dependent Variables

	FXS (<i>n</i> = 57)	ADHD (<i>n</i> = 30)	MA-Matches (<i>n</i> = 53)
Attention			
Visual Hits (CPT)			
M (SD)	12.7 (2.7)	14.7 (0.6)	14.2 (1.3)
<i>n</i>	34	30	48
Auditory Hits (CPT)			
M (SD)	16.6 (4.4)	18.3 (1.7)	17.0 (2.6)
<i>n</i>	28	30	48
Attention Sustained			
M (SD)	45 (30.5)	56.5 (17.0)	--
<i>n</i>	21	28	--
T-scores Attention Problems (CBCL)			
M (SD)	60.6 (5.9)	65.4 (7.4)	51.3 (2.0)
<i>n</i>	57	30	49
T-scores DSM ADHD Problems (CBCL)			
M (SD)	58.6 (6.7)	66.6 (8.2)	51.2 (2.6)
<i>n</i>	57	30	49
Response Inhibition			
Visual Correct Rejections (CPT)			
M (SD)	37.4 (7.7)	41.2 (2.1)	41.1 (2.2)
<i>n</i>	34	30	48
Auditory Correct Rejections			
M (SD)	67.3 (7.6)	70.8 (4.6)	71.1 (4.9)
<i>n</i>	28	30	48
Day/Night			
M (SD)	9.2 (5.0)	13.5 (3.8)	13.0 (3.0)
<i>n</i>	43	30	50
Processing Speed			
Mean Response Time of Hits (Visual)			
M (SD)	8888.6 (3133.3)	7445.5 (1329.7)	7944.7 (1071.0)
<i>n</i>	34	30	48
Mean Response Time of Hits (Auditory)			
M (SD)	11763.2 (1727.9)	11167.4 (1362.5)	11838.8 (1397.3)
<i>n</i>	28	30	48

Note. Dashes indicate that data for this group were not collected.

Table 3

Comparison of Descriptive Characteristics on Boys with FXS Who Were and Were Not Able to Complete the Visual and Auditory CPT Tasks.

	Could Complete CPTs (<i>n</i> =33)	Couldn't Complete CPTs (<i>n</i> = 23)
Psychotropic Medication Use	100%	100%
Mean CARS Score	25.77	33.61
Met CARS cut off for Autism (≥ 30)	2 (6.1%)	15 (62.5%)
CBCL		
Mean T-Score on Attention Problems	59.82	61.39
Met Borderline or Clinically Significant Range	4 Borderline; 1 Clinically Significant	5 Borderline; 2 Clinically Significant
Mean T-Score on DSM-ADH	59.03	58.00
Met Borderline or Clinically Significant Range	6 Borderline; 2 Clinically Significant	4 Borderline; 1 Clinically Significant
Child Symptom Inventory		
Mean T-Score on ADHD-Inattentive	65.96*	64.00*
Mean T-Score on ADHD-Hyperactive-Impulsive	63.56*	57.65*
Mean T-Score on ADHD-Combined	65.63*	61.04*
Met Criteria for ADHD-Inattentive	44.44%*	39.13%*
Met Criteria for ADHD-Hyperactive/Impulsive	22.22%*	21.74%*
Met Criteria for ADHD-Combined	18.52%*	13.04%*

* Data not available for at least one child.

Table 4

Test of Effects on CPT Performance

	Estimate	Standard Error	<i>df</i>	F	Adjusted <i>p</i>
Visual CPT (<i>n</i> = 112)					
Cumulative Percentage of Hits					
Group			2,109	9.27	0.0012*
ADHD vs. TYP	0.0098	0.0361			
FXS vs. TYP	-0.1334	0.0348			
Time	-0.0003	0.0001	1, 109	6.03	0.0269*
Time x Group			2,109	0.74	0.5232
ADHD vs. TYP	0.0002	0.0002			
FXS vs. TYP	0.0002	0.0002			
Cumulative Percentage of Correct Rejections					
Group			2,109	1.46	0.2831
ADHD vs. TYP	0.0450	0.0269			
FXS vs. TYP	0.0089	0.0259			
Time	0.0003	0.0001	1,109	1.72	0.2559
Time x Group			2,109	12.71	0.0012*
ADHD vs. TYP	-0.0003	0.0001			
FXS vs. TYP	-0.0007	0.0001			
Auditory CPT (<i>n</i> = 106)					
Cumulative Percentage of Hits					
Group			2,103	7.87	0.0021*
ADHD vs. TYP	0.0355	0.0462			
FXS vs. TYP	-0.1564	0.0472			
Time	-0.0006	0.0002	1,103	3.56	0.0933
Time x Group			2,103	5.93	0.0074*
ADHD vs. TYP	0.0002	0.0002			
FXS vs. TYP	0.0009	0.0002			
Cumulative Percentage of Correct Rejections					
Group			2,103	0.31	0.7309
ADHD vs. TYP	-0.0116	0.0160			
FXS vs. TYP	0.0003	0.0164			
Time	-0.0000	0.0001	1,103	12.95	0.0020*
Time x Group			2,103	7.32	0.0026*
ADHD vs. TYP	0.0000	0.0001			
FXS vs. TYP	-0.0004	0.0001			

* *p* < .05

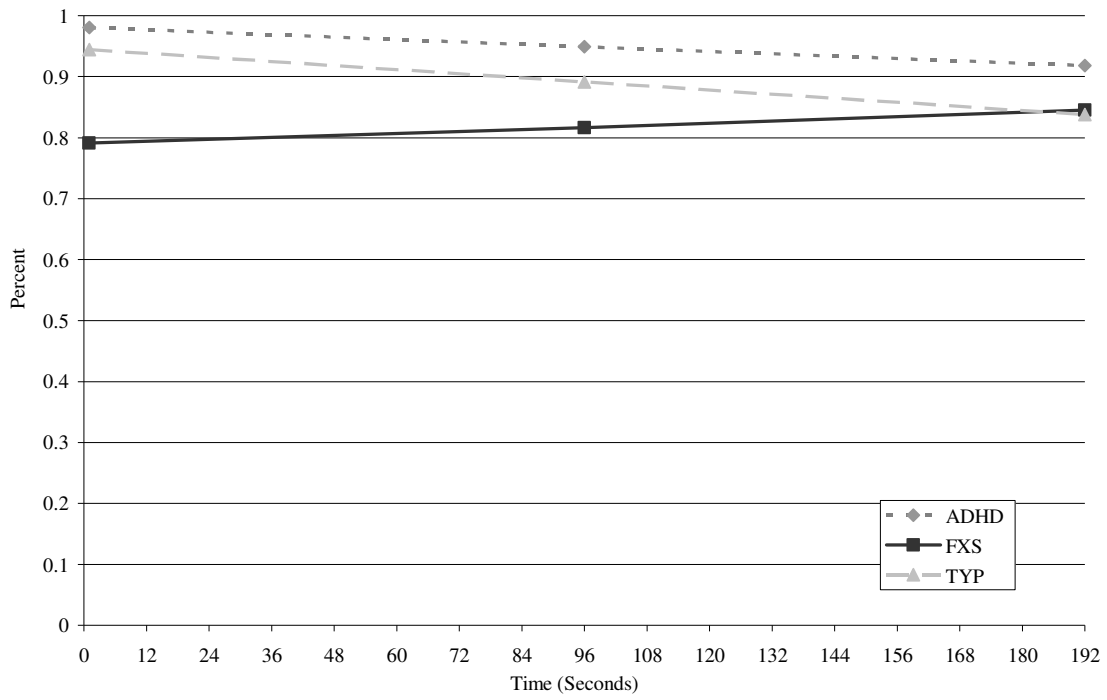


Figure 1. Cumulative percentage of hits by group and time on the auditory CPT.

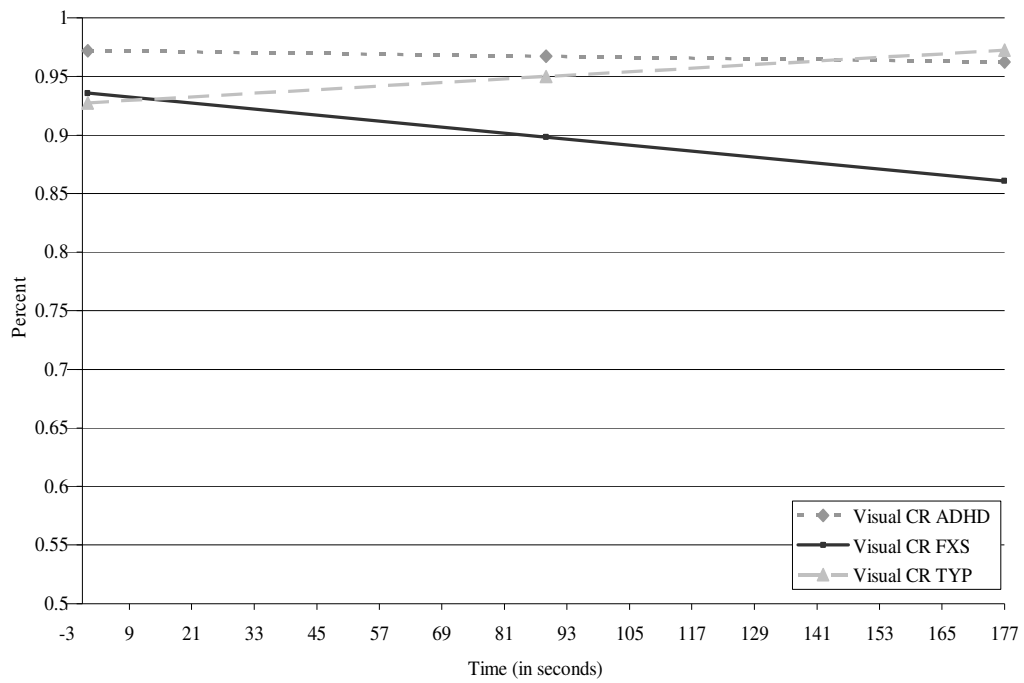


Figure 2. Cumulative percentage of correct rejections by group and time on the visual CPT.

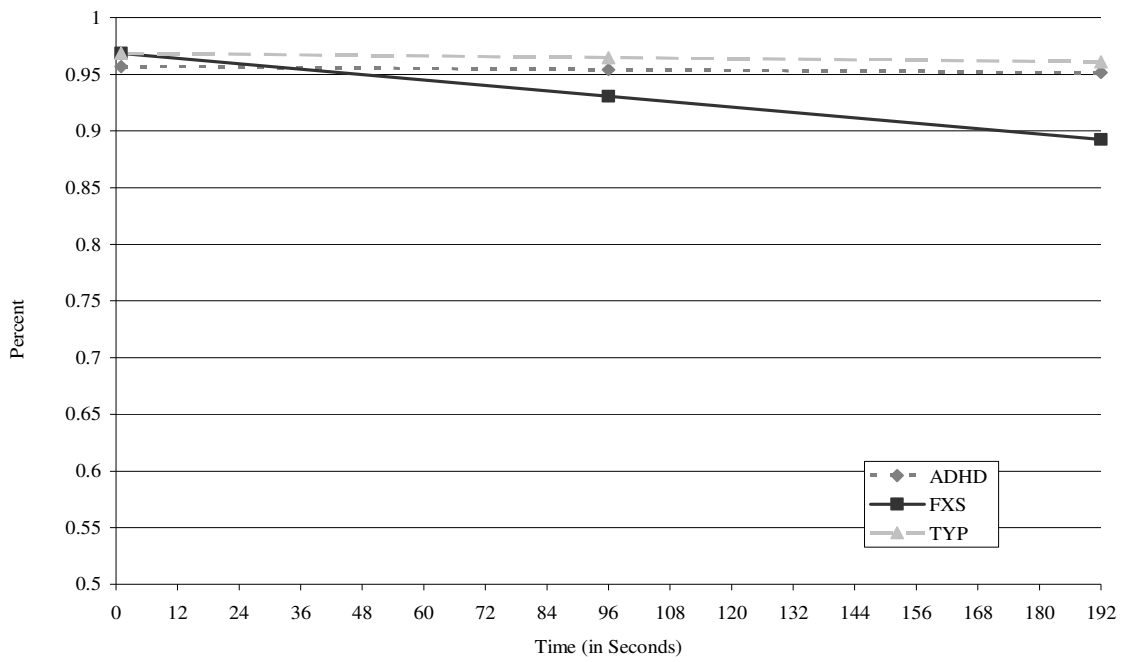


Figure 3. Cumulative percentage of correct rejections by group and time on the auditory CPT.

Appendix
Measures/IRB Approval

Name _____ DOB _____ Date _____
 1st name last initial ID Assess #

General Information Form
(5/9/2006)

Please provide us with some information about your family by answering the following questions. All the information that you provide will be kept **completely confidential** and will help provide us with up-to-date information about the families participating in our studies.

I. Family Information

Household Composition Grid: Please fill out the following chart for all people (include grandparents, step-children etc.) living in your home. For education, race/ethnicity, see choices at bottom.

Name	Gender	Relationship to Child	DOB	Occupation	Education	Ethnicity
(Example) Joseph	M	1	1	Attorney		5
(Example) Judy	F	2	2	Teacher		5
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						

A. Relationship:

1. Self (child)
2. Mother
3. Father
4. Brother
5. Sister
6. Grandmother
7. Grandfather
8. Other (specify)

B. Education:

- 0-11 = Less than High School
- 12 = High School Graduate
- 13 = High School & Training
- 14 = Some College
- 15 = Associates Degree
- 16 = College Degree
- 17 = Some post college
- 18 = Masters Degree (M.B.A.)
- 19 = Professional or Advanced Degree (M.D., J.D., Ph.D.)

C. Race/Ethnicity

1. American Indian/Alaska Native
2. Asian
3. Native Hawaiian Other Pacific Islander
4. Black or African American
5. White
6. Hispanic or Latino
7. Other (please specify)

What is the annual gross *household* income (wages before taxes)? _____

Do you receive any of these forms of public assistance/other resources?

Food Stamps	Yes/No	Women Infant and Children (WIC)	Yes/No
Medicaid	Yes/No	Welfare/Public Assistance/TANF	Yes/No
Assistance with child day care	Yes/No	Crisis Intervention Program	Yes/No
CAP-MR	Yes/No	Free or reduced price school meals	Yes/No
Subsidized Housing	Yes/No	Transportation Assistance	Yes/No
Special Assistance to Elderly and Disabled Adults	Yes/No	SCHIP Program (Health Check and/or Health Choice)	Yes/No
Supplemental Security Income (SSI)	Yes/No	Respite Care	Yes/No
Assistance with Energy (heating/cooling)	Yes/No	Other (Please List):	Yes/No

What is mother's **current** marital status (check one)?

- A. Single, Never Married _____
- B. Married _____ Year? _____
- C. Divorced _____ Year? _____
- D. Separated _____ Year? _____
- E. Engaged _____ Year? _____
- F. Widowed _____ Year? _____

Is there a backup number(s) (e.g., parent or grandparent) where we can leave a message if we have trouble contacting you:

Name and relationship:

Phone: _____ Address: _____

Name and relationship:

Phone: _____ Address: _____

For your child diagnosed with AD/HD, what age (in months) did the following events take place?

_____ months Someone became concerned about my child's development or behavior

_____ months A professional confirmed that my child had significant delays or behavior problems

_____ months _____ **Date A professional confirmed that my child had AD/HD**

Has your child been diagnosed with any other disorder besides AD/HD? If so, please specify the diagnosis and the dates of diagnosis. _____

II. School/Services

Does your child attend school/preschool: **YES** **NO**

If yes, how many hours a week does the child attend? _____

What grade is your child in? _____

What type of setting is it (circle all that apply)?

1. Fully Inclusive (includes some typically developing kids)
2. Self-Contained (only includes children with disabilities)
3. Home-based
4. Inclusive & Self-Contained (some time in both settings)

Does your child receive any child care? **YES** **NO**

If yes, what kind of child care is it (circle all that apply)?

1. Home/Relative child care
2. Child care center
3. After-School program

How many hours a week does your child receive child care services? _____

What services does the child receive? How many hours per week?

Speech/Language Therapy _____ hrs/week

Occupational Therapy _____ hrs/week

Physical Therapy _____ hrs/week

Sensory Integration Therapy _____ hrs/week

Special Education/General EI _____ hrs/week

Other: _____ hrs/week

III. Community Inclusion

Does your child participate in any community groups? **YES** **NO**

If YES, please provide the following information:

Type of Group (see chart below)	# times attended per month	# children involved	Are typical children included?
<i>(Example) 3</i>	<i>3-5 times per month</i>	<i>15 children</i>	YES / NO
1.			YES / NO
2.			YES / NO
3.			YES / NO
4.			YES / NO
5.			YES / NO

Type of Group:

1. Athletics/Parks & Rec. Activities
2. Special Olympics
3. Church Related (e.g., choir, sunday school)
4. Music Lessons
5. Scouts
6. Dance
7. Other (please specify)

APPROVAL DATE: 6/07/2007

EXPIRATION DATE OF APPROVAL: 6/05/2008

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)

Submission Type: Renewal

Expedited Category: 7.Surveys/interviews/focus groups

Study #: 06-0297

Study Title: Attention and Behavioral Inhibition in Young Males with Fragile X Syndrome and/or Attention-Deficit/Hyperactivity Disorder

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this research is no more than minimal.

Federal regulations require that all research be reviewed at least annually. It is the

Principal Investigator's responsibility to submit for renewal and obtain approval

before the expiration date. You may not continue any research activity beyond the

expiration date without IRB approval. Failure to receive approval for continuation

before the expiration date will result in automatic termination of the approval for this study on the expiration date.

When applicable, enclosed are stamped copies of approved consent documents and

other recruitment materials. You must copy the stamped consent forms for use with

subjects unless you have approval to do otherwise.

You are required to obtain IRB approval for any changes to any aspect of this study

before they can be implemented (use the modification form at ohre.unc.edu/forms).

Should any adverse event or unanticipated problem involving risks to subjects or

others occur it must be reported immediately to the IRB using the adverse event form

at the same web site.

Study Description:

Purpose: To examine sustained attention and behavioral inhibition in young males with Attention-Deficit/Hyperactivity Disorder (AD/HD), ages 4-7, and compare their performance to extant data on males with full mutation fragile X syndrome (FXS) and typically developing males matched on mental age to the sample with FXS.

Procedures: Administer assessment battery containing measures of sustained attention and behavioral inhibition; ask subjects' teachers and parents to complete behavioral rating scales.

Participants: 45 boys with AD/HD, ages 4-7. Secondary data: 36 boys with full mutation FXS, ages 8-13; and 36 typically developing males, ages 4-7.

Submission Description:

Modification for: Adding three research assistants.

Renewal for: Continued enrollment. 27 (of 40 approved) enrolled to date. Anticipate enrolling an additional 3-13 subjects during upcoming year.

Details:

Call the IRB at 966-3113 if you have any questions. You can now access IRB status information at <https://my.research.unc.edu/>.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), and 21 CFR 50 & 56 (FDA), where applicable.

The University of North Carolina at Chapel Hill holds a Federal Wide Assurance approved by the Office for Human Research Protections, Department of Health and

Human Services (FWA # 4801).

Lawrence B. Rosenfeld, Ph.D.

Office of Human Research Ethics

Co-Chair, Behavioral Institutional Review Board

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