DEVELOPMENT OF A BIOPSYCHOSOCIAL SCREENING INVENTORY FOR FMR-1 GENE MUTATION "AT RISK" STATUS IN YOUNG CHILDREN

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Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
December 2004

DEVELOPMENT OF A BIOPSYCHOSOCIAL SCREENING INVENTORY FOR FMR-1 GENE MUTATION "AT RISK" STATUS IN YOUNG CHILDREN

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NOMENCLATURE

CGG	Cytosine-guanine-guanine, a nucleotide triplet in a strand of DNA
FMR-1	Abbreviation for FraX gene (Fragile Mental Retardation 1)
FMRP	Protein from the FMR-1 gene that is essential for normal functioning of nerve cells.
FraX	> 50 repeats of the CGG nucleotide triplet
FraX Full mutation	> 200 repeats of the CGG nucleotide triplet
FraX-FM	FraX Full Mutation
FraX-pM	FraX Premutation
FraX Pre mutation	60-200 repeats of the CGG nucleotide triplet
FRAXA	Chromosomal fragile site at Xq27.3 that corresponds to the CGG repeat expansion of the *FMR1* gene
FraX	Fragile X Syndrome
MR	Mental Retardation
m-RNA	Messenger Ribonucleic Acid
M-CHAT	Modified Checklist for Autism in Toddlers
No Dx	No diagnosis
PCR	Polymerase Chain Reaction
POF	Premature Ovarian Failure
PDD-NOS	Pervasive Developmental Disability

ACKNOWLEDGMENTS

Without the guidance and inspiration of my Lord and Savior Jesus Christ, the completion of this dissertation would have been impossible. Additionally, there were many pivotal sources of guidance, support, and encouragement.

I extend heartfelt gratitude to Dr. Laura Hubbs-Tait, for her willingness to assume well into the dissertation process, the immense challenge of mentoring me and serving as the chair of my dissertation advisory committee. Thank you so very much for having faith in me. I am also appreciative to Dr. Carolyn Henry, Dr. Stacy Thompson, Dr. Tay Kennedy, and Dr. C. Robert Davis for their guidance, tenacity, and patience with the sometimes-unconventional process of my dissertation advisement. I thank Dr. Davis, for availing himself to my complaints and tears of frustration with the dissertation process in conjunction with my complex life of parenting exceptional children. He not only taught his students with excellence, to *Counsel Parents of the Exceptional Child*, but he modeled those attributes. Additionally, I will be forever grateful to Dr. Patricia Self for years of mentoring, guidance, and insistence that I fully appreciate the complexity of human development. I greatly appreciate the time that Dr. Chengi Wei spent guiding me through surviving the completion of the dissertation. To Dean Patricia Knaub, I extend gratitude for a phenomenal course, *Seminar in Human Environmental Sciences*, in which

the networking that emanated from fulfilling course requirements provided collaborative dissertation research opportunities that I otherwise would not have pursued.

Genuine appreciation is extended to the parents and children who participated in my research studies. Furthermore, I am indebted to Dr. Stephanie Sherman for serving as my external mentor and for availing the Emory University Sherman Laboratory for the FMR-1 Gene Analyses. Additionally, I appreciate Dr. Nancy Carpenter for genetics consultation and the storage of buccal cell specimens at the H.A. Chapman Institute of Medical Genetics. I am also grateful to Dr. Michele Mazzocco, Dr. Ave Lachiewicz, and Dr. Douglas Scambler, for their expert review of the BIPSSI-FX.

I am indebted to Langston University instructor and information technology specialist, Ron Young and his students for developing and maintaining the website used to recruit participants and collect data, for my dissertation research. The numerous hours that he invested as webmaster will be forever appreciated. To my colleague and friend Karen Baicy, I remain eternally grateful for her generosity in supporting me in completing my tasks at Langston University School of Nursing and Health Professions as I persevered through the final days of completing the dissertation process.

Financial support was crucial to the completion of the dissertation. Therefore, I express a profound appreciation for the National Fragile X Foundation Research Fellowship, the Robberson Research Fellowship, the Oklahoma State University College of Human Environmental Sciences Burton W. and Gladys T. Logue Fellowship Distinguished Student Awards, and the Thurgood Marshall Fellowship.

Acknowledgements would be most incomplete without mention of my indebtedness to my friends and family for the numerous sacrifices they have made, as

well as the encouragement and assistance they have provided. I acknowledge gratitude to my parents, Samuel and Bessie Johnson, who both transcended to eternal life during my dissertation process, for instilling in me the belief that with God-ordained perseverance my accomplishment potentials are almost infinite. I could not have completed the arduous process without the confidence that they fostered within me.

I will be eternally grateful to Dr. E. J. Brown for her untiring friendship, support, and mentoring. Furthermore, her willingness to proofread and give in-put on my dissertation, even into the late hours of the night will remain indelible in my mind. When I felt as if I could not continue, she was consistently there to give the not always gentle "push" to persevere. Furthermore, I acknowledge a heartfelt appreciation to Dr. Pamela Price-Hoskins for her in-depth review of my dissertation, prayers, and words of encouragement. To my long-term friends, the Reverend Dr. Janette Chandler Kotey, Dr. Roxanne Mitchell, and Mrs. Edith Kizzie, I will forever appreciate their prayers and support during the arduous process of my dissertation completion. To my dear friend, the Reverend Portia Osborne, I extend many thanks for her prayers, proofreading, and use of her word processing expertise to facilitate the completion of my dissertation. Her late night help was an immense blessing. Furthermore, I offer my heartfelt gratitude to my friend, Caren Meyers, for her willingness to provide secretarial and editorial assistance with my dissertation and many other papers during my doctoral studies. Her "lightening-fast" fingers enabled me to meet numerous deadlines. Furthermore, I thank Pirkko Lackey, my long-term friend, for her constant words of encouragement and her willingness to help me, sometimes at a moments notice, with my special boys so that I might engage in my research and writing of the dissertation. I greatly appreciate the

prayers of Pastor Stephen Rathod and my Covenant Family Church family, and the prayers of Elder and Mrs. Roy E. Davis and the Pentecostal Temple Church of God in Christ family.

I acknowledge gratitude to my Aunt Alma and my Aunt Claudine for their constant reminders that my mom would have wanted me to persevere and complete the dissertation and for their willingness to give me breaks from parenting responsibilities so that I might concentrate on completion of the dissertation. To my "baby sister" Benita, I acknowledge appreciation for her support, maturation, and self-reliance during my dissertation process. I extend heartfelt appreciation to my darling first born, Elizabeth Cynita, for her clerical assistance with my dissertation and the extra help with her brother and her cousin so that I might work on my dissertation. Finally, to my extra special boys, John "J. L." and Sammy, I extend great appreciation for helping me to remain cognizant of the necessity of my dissertation research.

CHAPTER ONE

Fragile X Syndrome (FraX) is one of the few disorders affecting child behavior for which the exact genetic mutation (FMR-1 gene) is known. FraX is the most commonly inherited form of mental retardation and learning disabilities, however, only approximately 10% of persons who have this mutation have been identified (Hagerman, 1997). Therefore, it is imperative to implement enhanced efforts to increase awareness of the syndrome and to facilitate earlier detection.

The gene responsible for FraX, FMR-1, is located on the long arm of chromosome X, in the q 27.3 region. The normal size of triple nucleotide Cytosine, Guanine, Guanine (CGG) is between 6 to 39 repeats. Depending on the size of the expansion, the mutation is categorized into 2 types; the premutation, with an expansion between 55 and 200 CGG repeats and the full mutation, with an expansion of more than 200 repeats (Jin &Warren, 2003).

One in 250 females and 1 in 500 males carries the FMR-1 gene in a premutation state (Turner, Robinson, Wake, Laing, & Partington, 1997). An individual is considered a premutation carrier when 50-200 repeats of the Cytosine, Guanine, Guanine (CGG) nucleotide base pairs of DNA exist on the X chromosome (Turner et al., 1997). A mother has a 50% chance of transmitting FraX to a male or female child because a female typically has two X chromosomes on the 23rd pair, which is responsible for determining gender. The mother contributes an X chromosome to each child she conceives. On the other hand, a male's 23rd chromosome pair consists of an X and a Y chromosome.

Therefore, a man contributes an X chromosome to combine with the woman's X chromosome to reproduce a female. Thus a father who has FraX - premutation, has 100% chance of transmitting the FraX - premutation to each of his daughters. On the contrary, since a father contributes a Y chromosome to a male child, he has a 0% chance of transmitting FraX to a son.

Females are also affected with the actual syndrome (full-mutation - greater than 200 repeats of the (CGG) trinucleotide base pair), but usually less severely and less frequently (Hagerman et al., 1992). FraX occurs relatively equitably in all racial and ethnic groups (Crawford et al., 1999). It is a condition of major epidemiological importance among mentally handicapped males and "must be considered in the differential diagnoses of a child with developmental delay, mental retardation, or learning disability" (Pimentel, 1999, p. 639).

Not only does the prevalence of FraX necessitate focus on diagnosis and therapeutic interventions, but also the emerging data regarding atypical transmission and phenotypic expression warrants close focus on this syndrome (Shapiro, 1997; Sherman, Jacobs, & Morton, 1985). The genetic expression of FraX is atypical in that some female carriers may have clinical symptoms of the disorder and some males who inherited the gene may not be affected clinically (Braat, Smits, & Thomas, 1999; Franke et al., 1996; Franke et al., 1999; Hagerman et al., 1992; Schwartz et al., 1994; Sherman et al., 1985). This phenomenon is of significance, especially in light of the increased number of individuals who may possibly experience behavioral or physiological maladies because of being a premutation-state carrier of the FMR-1 gene (Dorn, Mazzocco, & Hagerman,

1994; Franke et al., 1996; Franke et al., 1999; Johnston et al., 2001), thus complicating early diagnosis and intervention.

Additionally, identifying infants and toddlers with FraX is challenging, because many of the unique behavioral symptoms are not obvious until the child is18 to 24 months of age (Hagerman, 2002). The principal investigator developed the Biopsychosocial Screening Inventory for Fragile X Syndrome (*BIPSSI - FX*), which is a parent survey to screen very young children in clinical and non-clinical settings. The *BIPSSI - FX* includes a Biological Parent Subscale that facilitates identification of the child. Questions in the *BIPSSI - FX* identify parents at risk for the FMR-1 gene mutation. It is anticipated that the inclusion in the *BIPSSI - FX* of characteristics identified repeatedly in research studies (Franke et al., 1999; Lesniak-Karpiak, Mazzocco, & Ross 2003) of intellectually normal carriers, such as premature ovarian failure, depression, anxiety and obsessive-compulsive behaviors, will facilitate identification of carriers as well as accurate detection of FMR-1 gene mutation (the gene that causes FraX) “at risk” status in young children.

Problem Statement

The early identification of children affected with FraX is important because interventions exist that may decrease symptoms (Grandin, 1992; Sallee et al., 1998; Scharfenaker & Stackhouse, 1995; Zisserman, 1992) and research concerning treatment and corrective interventions is increasing (Berry-Kravis, 2004; Chiurazzi et al., 1998; Neri, Pomponi, Pietrobono, & Chiurazzi, 2001;Rattazzi, LaFauci, & Brown, 2004; Torrioli et al., 1999). Former United States legislator Wes Watkins and other members of Congress, have emphasized the responsibility of researchers and practitioners to "learn,

teach, and promote awareness of the incidence, causes, symptoms, effects, and treatment of Fragile X, and support screening for Fragile X to permit early intervention and treatment" (Watkins, 2000, p. 1).

Identification of individuals who have the mutated FMR-1 gene will facilitate their participation in effective technology, research, and educational and behavioral strategies. Early identification and intervention is especially crucial, since timely identification and intervention facilitate a higher quality of life and the possibility of these individuals to be gainfully employed members of communities. The financial burden of care may be decreased from the estimated $1 million to $4 million range spent over a lifetime to provide care for an individual who has FraX (Finucane, 1996). Currently there are no reliable and valid psychometric measures to screen for FMR-1 gene “at-risk status” in infants and toddlers (Bailey, 2004).

Purpose

The study proposed to test the validity and reliability of an instrument, the *BIPSSI-FX* devised to screen very young children and their parents for “at-risk status” for the FMR-1 gene. The principal investigator designed the tool to screen toddlers, preschoolers and, school age children using parent reports.

Objectives

The goal of the study was to test the reliability and validity of the *BIPSSI - FX* in detecting FMR-1 gene mutation in young children. The objectives of this study were to explore the efficacy of the *BIPSSI - FX* to differentiate between children who have FMR-1 gene mutation and those who do not.

Significance

Timely identification of young children who have social or emotional challenges is strongly emphasized by child development specialists (Bailey, Skinner, & Sparkman, 2003). A method of screening young children is crucial to their well-being (Bailey et al., 2002; Squires et al., 1999). Young children's emotional and social problems are often overlooked until the problems have reached serious magnitudes. Screening young children for FraX may empower parents, as front line screeners, to seek an early diagnosis and consequently implement effective early intervention for the child who is at risk for developmental delays or disabilities.

Assumptions

The assumptions underlying this study emanate from the presuppositions of biopsychosocial frameworks of human development, literature regarding Internet studies, and a perusal of primary caregiver comments available on listserv groups for parents of children with FraX, autism, and Down Syndrome (Trisomy 21). The assumptions of this study are:

1. The unique complexities of Fragile X Syndrome may be differentiated from those of other syndromes and disorders.
2. Family composition and interaction partly determine the manifestations of physical, cognitive, and social behavior and biological development of young children with the FMR-1 gene mutation.
3. Primary caregivers who invest in completing online surveys, without compensation, provide valid and reliable information regarding their child's development.

The principal investigator reviews the pertinent theories and existing screening tools for FraX and discusses the development of the *BIPSSI-FX* in Chapter Two. Chapter Three provides a detailed account of the methods including the statistical tests of the study. A summary of the data analysis plan and the results, including tables and figures are presented in Chapter Four. Finally, discussion of the research findings including interpretations, limitations, and recommendations is presented in Chapter Five.

CHAPTER TWO

REVIEW OF THE LITERATURE

Theoretical Framework

An investigation of the development of young children who are at risk for the FMR-1 gene mutation necessitates the use of a conceptual framework. Discoveries of exact genetic markers of various disorders resulting from the "Human Genome Project" and the current federal government emphasis upon funding biological and genetic based research have impelled researchers from many disciplines to embark upon biosocial-focused studies. Although reluctance to incorporate a biosocial approach to human development and family science remains in some disciplines, leaders in the various disciplines are emphasizing the necessity of incorporating biological variables (Bailey, Hebbeler, Scarborough, Spiker, & Mallik, 2004; Grove, 1995; Udry, 1995). The use of a conceptual framework of sufficient complexity is paramount as multi-disciplinary researchers play key roles in research, practice, and policy, which influence early human development. Hence, the premise upon which the *BIPSSI-FX* is developed is the imperativeness of a careful consideration of the multifaceted dimensions of human development. The theoretical framework for the study is adapted from biosocial (Gottlieb, Walshten, & Lickliter, 1998; Kandel & Squire, 2000) and systems perspectives of human development. The complexity involved in describing the relationship of multiple factors related to FraX needs the clarity and structure that an ecological model

affords, but in a dynamic and contextual manner provided by biopsychosocial frameworks.

Society's focus on health promotion, wholism, and the ability to control phenomena in conjunction with the existence of federal research funding for integrative approaches to complex problems have spawned an increase in studies in which biosocial entities are addressed (Williams & Lessick, 1996). According to Lerner (1998), humans are composed of a biological genotype and a sociological genotype. Lerner (1998) cleverly uses the oxymoron "sociological genotype" to emphasize hereditary influences on humans' behavior in society and "biological genotype" to emphasize the multi-systemic role of genes on the individual, which in turn affects the person's interactions in society. Because of the massive quantity of genes, the likelihood of two people having completely the same genes is virtually impossible. Thus, diversity in studying the role of context and time merits full consideration, as well as the similarities and differences in human development and their influence on society. The framing premise of this study is the unique social interactions of children with FraX. Furthermore, assessment of these interaction patterns may facilitate identification of a child's risk for the FraX genotype, which predisposes an individual for atypical and often challenging interactions in society.

Gottlieb's (2002) Probabilistic Epigenetic Biopsychosocial Conceptual Framework of Development includes four major aspects of human development from a contemporary, dynamic, and contextual perspective (Lerner, 1998). Furthermore, of crucial importance to early human development is that Gottlieb (2002) and other contemporary theorists, such as Lerner (1998), Overton (1998), and Thelen and Smith (1998), define development as change, which occurs over time, and is constant.

Gottlieb (2002) further emphasizes that the multiple levels of development – genetic, neural, behavioral, and environmental – have equal importance; no one level holds greater value than the other does. The levels are multidirectional and inextricably fused, fusion being the process by which the levels of development interact simultaneously (Tobach & Greenberg, 1984). Specifically, the genetic and behavioral levels of Gottlieb's model are the key concepts of this research study. The genetic level of Gottlieb's model includes the basic biological components of human development, which are deoxyribonucleic acid (DNA) – the basic molecule of inheritance. Genetic instructions are encoded in base pairs. Gottlieb next considers the role of ribonucleic acid (RNA) molecules, which function to build proteins. Comparison is made between the FMR-1 gene and the behavioral level of development. The genetic and the behavioral levels are specifically addressed in this research study, although a comprehension of the interaction of each of the levels is important.

In contrast to an organismic worldview of predetermined epigenesis, Gottlieb (2002), terms the process of human development, *probabilistic epigenesis*. In other words, a general anticipated order occurs in the development of the young human, but this order is not concrete, but is probabilistically altered by the interactions of numerous variables. The current dissertation research compares children with different genetic causes of retardation, for example, Down Syndrome (Trisomy 21), with FraX. Although the starting point and pathway for both of these groups of children differ, the typical result is the same: developmental challenges or retardation. This process of differing starting points or pathways and the same endpoint is termed *equifinality* (Gottlieb et al., 1998).

The importance of *equifinality* for FraX is best observed by comparing synaptic pruning in children with FraX, Down Syndrome (Trisomy 21), and no genetic abnormalities. Children without genetic abnormalities undergo a pruning of unused neural pathways, which facilitates neural communication (Greenough et al., 2001; Grossman et al., 2003; Kandel & Squire, 2000; O'Donnell & Warren, 2002) Researchers and theorists believe that children with Down Syndrome (Trisomy 21) undergo overpruning during synaptic development in the early years, whereas children with FraX experience underpruning (Johnston, 2004). Researchers posit that the role of environmental experience and early intervention in the reduction of over - and underpruning is extremely important, although it has not been definitively researched (Churchill et al., 2002; Grossman et al., 2003; Hessl et al., 2001; Kates et al., 2002; O'Donnell & Warren, 2002). The differentiation of these groups of children by under- versus overpruning suggests that the groups should also differ behaviorally and provides a key rationale for the current dissertation research.

Family stress models, systems theories, and ecological theories are commonly used as organizing frameworks for human development and family science studies. However, neither systems theories nor family stress theories explicitly make allowance for *proximal causation* from a biological or genetic perspective. Each of these models has attributes that may be effectively used to interpret aspects of the phenotypic expressions of individuals with FMR-1 gene mutation and of their families. Thus, FraX is defined by the occurrence of changes to the FMR-1 gene. The molecular changes (FMR-1 gene) impact the action of messenger riboneucleic acid (m-RNA), which consequently influences the production of a key protein - the Fragile X Mental Retardation Protein

(FMRP), which is believed to be essential for normal nerve function (Greenough et al., 2001; R. J., Hagerman et al., 2004; Hagerman, 1996b; Jacquemont et al., 2004; Mittal & Pandey, 2002; Warren & Nelson, 1994). The absence of normal nerve functions affects various systems of the body. While the behaviors of the child affected with FraX often holistically impact the primary caregivers, siblings, extended family, conversely each of these entities affects each level of the child's development. Although each of these concepts and the variables, which measure them, are important in research on FraX, the current dissertation research project focuses only on the behaviors of young children that discriminate those with FraX from those with other developmental delays or diagnosed disabilities.

Review of the Literature

Significance

Gaining increased attention is the identification of genetic and other biochemical etiologies of learning disabilities, mental retardation and psychoneurological disorders such as schizophrenia, autism, depression, attention deficit disorder, and anxiety disorders (Williams & Lessick, 1996). The Human Genome Project (HGP), a collaborative international project initiated in 1990 whose goals were to identify and sequence the entire human genome, fueled this fervor with the rapid identification of the genetic basis of disorders that affect behavior such as FraX (Williams & Lessick, 1996). In fact, the identification of the FMR-1 gene, in 1991 was one of the first major findings of the HGP (Williams & Lessick, 1996). Moreover, the attention of funding agencies, society, and researchers focuses upon unveiling genetic causes of developmental, behavioral, and learning disorders. FraX, the most commonly inherited form of mental

retardation (Sutherland, Mulley, & Richards, 1993; Shapiro, 1997), is one of the few disorders affecting child behavior for which the exact genetic sequence is identified. Incidence of males is estimated to range from one in 1500 (Sherman, 1991) to 1 in 4000 (Turner, Webb, Wake & Robinson, 1996). Females are also affected by FraX, but less severely and at a lower incidence. Crawford, Acuña, and Sherman (2001) present a meta-analytic review of epidemiological studies of FMR-1 and the FraX, in which studies from various countries have estimated the prevalence of the full mutation and the premutation. However, most of the populations studied remain Caucasian, with little information about other racial groups. Crawford et al. (2001), estimate the full mutation to range from one in every 3,717 to 1 in every 8,918 Caucasian males in the general population. In the premutation, prevalence estimates range from one in every 246 to 1 in every 468 Caucasian females in the general population. For Caucasian males, the prevalence of the premutation is estimated to be one in every 1,000. Pembrey, Barnicoat, Bobrow, Turner, & Carmichael (2001), assessment of screening strategies of FraX in the United Kingdom found similar prevalence rates as those reported by Crawford and colleagues, for the full mutation and the premutation.

Screening in Young Children

Child development specialists strongly emphasize the importance of timely and accurate identification of young children who demonstrate developmental delays or social or emotional challenges. The importance of screening instruments to accurately identify young children is crucial to their well-being (Bailey et al., 2002; Squires et al., 1999). Few psychometric instruments are currently present to facilitate identification of children younger than 18 – 24 months of age who may be “at risk” for the FraX (Bailey et al.,

2002). Because of this deficit, many of the emotional and social problems of young children are overlooked until the problems have reached serious magnitudes (Bailey et al., 2002; Squires et al., 2001). Additionally, major interventions are more efficacious when implemented early in the child's life. Most children are not formally diagnosed as having social or emotional difficulties until school age or approximately 5.2 years. Moreover, identification for special education does not occur until the child is approximately 8 years of age (Forness, Kavale, McMillian, Asarnow, & Duncan, 1996). Furthermore, Forness, and colleagues (1996) found that formal placement in a program for children with social-emotional challenges typically does not occur until approximately the age of 10 years old, thus possibly missing crucial early intervention, which may impede the child achieving his or potential. In addition to early identification of social and emotional challenges, a multi-system assessment, which includes developmental, cognitive, physical, and familial assessments, is crucial to effectively screen toddlers for FraX.

Overview of Screening Checklists for FraX

Since the exact gene mutation that causes FraX was discovered as a result of the International Human Genome Project, screening studies to facilitate referrals for FMR-1 gene diagnostic tests have proliferated.

The eight checklists reviewed in Table 1 are all meant to facilitate the detection of critical clinical attributes of the genotype that causes FraX, thus providing reliable indicators of individuals who should be referred for diagnostic testing of FMR-1 gene changes. Research design and sampling vary across the studies, in that some only involved professional appraisals or review of clinical records and others also incorporated

parent interviews. Each of those studies emphasizes the cost-effectiveness of using screening checklists to avoid unnecessary costly genetic testing. Note that Bailey et al. (2001b) estimate the costs of DNA testing to range from $200 to $400. In contrast, checklists may be incorporated into routine clinical examinations.

Older screening tools focused heavily on physical characteristics such as macroorchidism (enlarged testicles), elongated face, elongated and/or protruding ears, simian creases (a single crease across the palms) in the palms, hyper extensible finger joints, highly arched palate, broad forehead, flat feet, soft velvety skin, and callused hands (Hagerman, 1991). As is depicted by Table 1, screening tools mostly focus on social, behavioral, and emotional attributes (Bailey et al., 2001). All tools address gaze avoidance or avoidance of eye contact. Additionally, anxious, nervous, or hyperactive behaviors have been included in each of the instruments, and, self-injurious and /or repetitive behaviors are assessed.

Only three checklists (Bailey et al., 2001b; Giangreco, Steele, Aston, Cummins, & Wenger, 1996; and Reiss et al., 1992) assess cognitive functioning of the individual, although most males with FraX have moderate mental retardation and delayed attainment of developmental milestones. Furthermore, only Bailey et al., (2001b) addressed developmental indices. Family history of mental retardation however, is a common thread in checklists for FraX. With the exception of three tools (Maes, Fryns, Ghesquire, & Borghgraef, 2000; Teisl, Reiss, & Mazzocco, 1999; Reiss et al., 1992), all tools reviewed inquire about a family history of mental retardation. However, no characteristics associated either empirically or anecdotally with premutation carriers of

the FMR-1 gene were included on any other tools, except for "maternal female with psychiatric disorder" (Giangreco et al., 1996, p. 612).

Bailey and colleagues (2001b) emphasized the importance of assessing development in infants and toddlers suspected as "at risk" for FraX, and proposed a checklist inclusive of characteristics discriminating typical infant and toddler behaviors from those indicative of autistic behaviors. This proposed checklist includes items from the *Checklist for Autism in Toddlers (CHAT).* Furthermore, the checklist proposed by Bailey and colleagues contributes promising new ideas, in that none of the existing tools includes developmental indices.

Another missing area in existing checklists for FraX is phenotypic characteristics of the child's biological family other than mental retardation. Numerous research studies (Allingham-Hawkins et al., 1999; Franke et al., 1996; Murray et al., 2000) address characteristics associated with premutation carriers at a significantly higher rate than in the general population, such as premature ovarian failure, ovarian cysts, depression, anxiety, or obsessive and compulsive behaviors. In contrast, none of the existing tools specifically addresses emotional and behavioral functions or biological characteristics of the birth parents, siblings, and extended family. This omission may substantially impact the specificity and sensitivity of the screening tool to detect young children who may be at risk for FraX.

Review of Existing Checklist Screening Tools for FraX

Although some of the studies involving aforementioned screening checklists for FraX have yielded sensitivity and specificity data, none has been replicated. Bailey and colleagues' (2001) proposed checklist has not yet been applied to a research study.

Therefore, no data regarding efficacy are available. However, several items included in the developmental subscale were adapted from the widely used Baron-Cohen, Allen, and Gillberg (1992) *Checklist for Autism in Toddlers* (*CHAT).*

Similar to Bailey and colleagues (2001), Lachiewicz, Dawson, and Spiridigliozzi, (2000) found deficits in the existing clinical checklists for assessing FraX "at risk" status in young children and proposed a checklist for FraX. The proposed checklist was based upon the outcomes of a study of comparative symptoms involving a group of 36 boys with FraX and 37 boys with developmental disabilities for whom FraX had been ruled-out. The groups of boys (ages 2.2 years to 10.2 years, with a mean age of 6.1 years) were matched for age. Four of the 42 clinical characteristics of young boys with FraX (hallucal crease, adverse response to touch on the skin, difficulty touching tongue to lips, and elongated face) were present significantly ($p < .0012$) more in the boys who had FraX than in boys with other developmental disabilities. Additionally, predictive trends were seen for the following ten characteristics: elongated face, family history of disabilities (including FraX, autism, mental retardation and learning disabilities), ear length greater than the 75th percentile, hyperextensible joints, hand calluses, brisk deep tendon reflexes, gaze avoidance/poor eye contact, difficulty moving the extended tongue from side to side, testicular volume > mean for age, and previous diagnosis of mental retardation. The clinical characteristics described in more than 80% of the group of boys with FraX were soft skin over the dorsum of the hand and hyperextensible metacarpophalangeal joints(100%), medical history of more than five ear infections (97%), highly arched palate (94%), previous diagnosis of mental retardation (91%), difficulty pronouncing "linoleum" (86%), hallucal crease (83%), elongated face (83%), gaze avoidance/poor eye

contact (83%), and head circumference greater than the 50th percentile (81%). Lachiewicz et al. (2000) proposed a 25-item, four-subscale (behavioral items, past medical history, physical characteristics and oral-motor/language characteristics) clinical checklist to alert professionals to boys who may be positive for the FMR-1 gene mutation, based upon the outcomes of their study and the data from other studies. However, an exhaustive review of the literature has not identified any studies in which the proposed checklist has been used. Therefore, reliability and validity data for the proposed checklist as a whole are not available.

FraX more frequently and more severely affects males than females; therefore, many of the clinical screening checklists have limited their application to males. In keeping with this trend, Maes et al. (2000), tested the 28-item (7 physical characteristics and 21 behavioral traits) phenotypic checklist they developed by comparing a group of 110 boys and men diagnosed with FraX on the basis of both chromosomal and molecular (DNA) analyses with 79 members of the same gender who had mental retardation of unknown causes (FraX and other genetic or chromosomal disorders having been ruled out). The two groups were matched for cognitive age, cognitive level of development, and social adaptation. The scores derived from the checklist of boys seventeen years of age and younger were analyzed both separately from those of the adult participants and were analyzed conjointly. The version of the checklist used in the study conducted by Maes et al. was a revision of an original 69-item checklist, and it included only the 28 items, which were significantly more frequent in boys and men with FraX compared to those negative for FMR-1 gene changes during a preliminary study. This final checklist was designed to meet the following criteria: "1) easy to use and score, 2) contain

relevant items, 3) amenable to scoring in a clinical setting on the basis of direct observation, and 4) items clearly defined to ensure a high level of interrater reliability" (Maes et al., 2000, p. 209). Additionally, demographic data were collected to facilitate accurate interpretation of the results of the checklist. The results from a study in which the tool was used are reported in the following paragraphs.

Maes et al., (2000) designed the checklist to be administered by "any person having medical or psychological-educational qualifications…" (p. 210). Concrete and observable characteristics or examples were provided to facilitate scoring for each of the 28 binomial (yes/no) items. In Maes et al.'s opinion, referral to a physician or genetic counselor is recommended for individuals who score 17 to 25 and a score of 26 or higher makes such a referral essential. The level of the scoring is adjusted in cases in which there are numerous instances of, "not applicable," such as in situations in which a child cannot yet speak. Note that while the checklist is designed to facilitate appropriate referrals, it is not considered as diagnostic.

Linear regression analysis was used in the study conducted by Maes et al. (2000) to examine the items that contributed most to the checklist's discrimination of individuals with FraX from others. The following items revealed the greatest ability to discriminate FraX from other developmental disabilities: large protruding ears, macroorchidism, fearfulness, and hand biting. Hyperextensibility of joints and the following behavioral features demonstrated moderate to low discriminatory ability: hyperactivity, impulsivity, hypersensitivity to changes, gaiety/cheerfulness, avoiding eye contact, and echolalia. The predictability of FraX risk status to checklist score showed that a weighted score (derived using coefficients based on parameters of predictability of FraX with weighted scores

ranging from <17 to >29) of <17 yielded 0% risk of having FraX, a score of 17 to 25 yielded a 23.5% risk, a score of 26-29 yielded an 82 % risk of having FraX, and a score > 29 was indicative of FraX (100% chance).

Cronbach's alpha, used to test the internal consistency of the checklist, was .84 for the total list, .74 for the physical items, and .82 for the behavioral features. The validity of the checklist, measured by *one-way Analysis of Variance (ANOVA)*, revealed a significant difference between the FraX positive group and the FraX negative group on both the physical and the behavioral items, $F(1, 128) = 89.77$, $p<.0001$ and $F(1, 187) = 45.96$, $p< .0001$ respectively. Likewise, the FraX positive group scored significantly higher on the total checklist, $F(1, 128) = 79.03$, $p<.0001$. An analysis of the effect of age on validity revealed that the checklist had the greatest level of validity for the 6-12 year age group and the lowest level of validity with regards to behavioral features for adults over 50 years of age.

The sensitivity of the Maes et al. (2000) checklist, measured by the number of individuals with a diagnosis of FraX, who were correctly identified, was 93%. However, 7% of those who actually had FraX were missed (false-negatives). The percentage of correctly identified control group members (the specificity), was 92.3%, but the checklist incorrectly detected 7.3% of the group as being at risk for FraX (false-positives). Lowering the criterion for referrals for diagnostic testing to score of 17 and above would eliminate all of the false negatives, thus increasing the sensitivity of the tool to 100%, but the specificity of the checklist would decrease to 42.5%, thereby falsely identifying more than half of the control group as "at risk" for FraX. Therefore, the researchers categorize

a score of 17-25 as "referral recommended" and label a score of 26 or higher as "referral for diagnostic testing required" (p. 211).

The Sensitized Affected State Consensus Group Screening Tool (Teisl et al., 1999) is the only study of the eight reviewed (see Table 1), in which females were included in the sample. The inclusion of females is congruent with the goal of the present dissertation research project: to develop a screening tool in which higher functioning children with the mutated FMR-1 gene may be reliably identified. The authors clearly explained the necessity of a tool in which the more subjective behavioral phenotypic expressions might be captured, so that a screening tool may identify the higher intellectually functioning children with FraX, as well as those who demonstrate greater cognitive impairment.

Parents of 55 preschool and school-aged children positive for the FMR-1 gene full-mutation completed a brief 11-item screening questionnaire. Each of the 55 children in the FMR1 positive group was matched for gender, age, and IQ with a child in a pool of 1600 children with learning disabilities or delays of unspecified etiology. The parents of the comparison group also completed the 11-item questionnaire. The questionnaire was truncated to include only the following items, for which highly significant ($p<.01$) or significant ($p<.05$) group differences occurred and on which the FMR-1 positive group scored at least 15% higher than the control group: "taken medication," "avoids eye contact," "nervousness/anxiety," "repetitive movement," "repetitive word/phrase" and "injured-self.

A total score, calculated on a 6-point scale having 1 point for each positive endorsement, was assigned to each of the 110 participants. Seventy percent of the

preschoolers with FraX received scores > 3, whereas only 26% of the control group received a score this high. All of the preschool children who received a score of ≥ 5 had FraX, which means that the specificity and sensitivity of the tool was perfect at this score for the preschoolers. In contrast, this impressive level of specificity or sensitivity was not present in the school-age group. Additionally, when the data were analyzed by gender, the specificity of the tool decreased, thus necessitating false-positives to facilitate effective screening for females.

Three similar studies, conducted by Hagerman, Amiri, & Cronister (1991), Giangreco, and colleagues (1996), and deVries, et al. (1997) tested the efficacy of a checklist to correctly detect a need for DNA analysis for the FMR-1 gene. Each had a goal of eliminating unnecessary testing without risking failure to test individuals who are indeed positive for FraX. Each study used the results genetic testing for FraX as the criterion reference for the brief phenotypic checklists.

Hagerman et al.(1991) reported the findings of a prospective screening of 107 males with mental retardation or severe learning disabilities, ages 1 years to 58 years, in which the 13-item Fragile X Checklist (Hagerman, 1987), was used. The purpose of the study was to utilize a checklist in which a family history of mental retardation, physical traits, and behavioral characteristics typical of FraX were assessed to facilitate identification of prepubertal boys who are at risk for having FraX. The Fragile X Checklist is a modification of a screening checklist developed by Rimland (1984).

The completion of the checklist involved a physical examination of the participant and interview with the parent or guardian. If an item was scored as “not present,” “borderline or present in the past,” “definitely present” these descriptors were quantified

as 0, 1, or 2, respectively. Measurement standards were implemented to facilitate reliability. For example, hyperextensibility of the metacarpal phalangeal joints was measured as extension greater than or equal to 90° when digits 2 through 5 were dorsiflexed while the palm was flat on a table. Furthermore large testicles were quantified as greater than two standard deviations in volume for age or greater than 30 ml in volume for adults. Additionally, hand biting was defined to include the biting of the wrist and hand but not nail biting. Tactile defensiveness was measured as an aversion to touch or other tactile stimuli that are not typically bothersome to others. No descriptors were provided for hyperactivity, short attention span, and perseverative speech. However, a family history of mental retardation was defined as any relative in up to three generations, on either side of the family, and was scored as "2." This item was further clarified by quantifying a relative described as slow or probably retarded, but for whom there was no corroborative cognitive testing, as "borderline" (score 1). Hagerman et al. (1991) compared the mean total scores for the patients who were positive for FraX with those who were FraX negative. The two groups were significantly different (t- test, $p < .001$). Additionally, Chi-square analysis revealed perseverative speech, large or prominent ears, and large testicles, as seen significantly ($p<.005$) more frequently in patients positive for FraX. Tactile defensiveness, poor-eye contact, and a family history of mental retardation, were significant at the $p < .05$ level. Step-wise logistic regression analysis was used to determine which items were most useful in predicting membership to the FraX positive subgroup. This analysis, conducted for the 78 patients for whom there were no missing data, revealed that large testicles and tactile defensiveness were the best independent predictors of membership in the FraX group.

Later, Giangreco et al. (1996) retrospectively analyzed clinical characteristics from the records over a 2 year period of time, of 273 males and 62 females, with a median age of 5.7 years, who had been referred for genetic testing and for whom both karyotype (chromosomal analysis) and the Southern Blot DNA analysis for the FMR-1 gene mutation had been performed. The purpose of the study was to aid primary physicians in containing costs by simplifying criteria for FraX testing in children.

The following six characteristics in the 9-item checklist developed by Giangreco and colleagues (1996) differentiated children who had FraX from children who tested negative for the FMR-1 gene mutation.: 1) "mental retardation," 2) "family history of mental retardation and/or psychiatric disorder," 3) "elongated face," 4) "large or prominent ears," 5) "ADHD" and 6) "autistic-like behavior" (p.612). Therefore, these six items were used to develop a criterion for referral for diagnostic testing for FraX. The items were scored similarly to the scoring of the Hagerman Fragile X Checklist, in that ordinal level measures, 0, 1, or 2 were employed. The mean scores on Giangreco and colleagues' 6-item checklist differed significantly ($p<.0001$) between the FraX positive group ($M = 8$) and the control group ($M = 4$). Thus, Giangreco et al. (1996) concluded that use of the checklist as a prescreening measure, using a score of 4 or less to eliminate those referred for DNA testing, would have reduced the number of individuals tested by 60%, thus increasing the cost-effectiveness of testing. Furthermore, the researchers reported that clinical application of the checklist, revealed 100% accuracy in 6 patients diagnosed to have FraX.

Similarly, de Vries et al. (1999) developed a 7 - item checklist in which the following 4 items were adapted from an earlier checklist for FraX (Laing, 1991, p. 257):

1) “family history of mental retardation” 2) “long jaw and high wide forehead” 3) “ears-large and protruding from the side of the head” and 4) “personality-initial shyness and lack of eye contact followed by friendliness and verbosity with echolalic speech.” Ordinal level measures (0, 1, or 2) were used for scoring in a similar manner to that of Hagerman et al., (1991) and Giangreco et al., (1996). However, de Vries and colleagues used the FMR-1 gene mutation DNA analysis as the criterion reference, whereas this more accurate diagnostic measure was not available for Hagerman et al.’s (1991) study.

de Vries et al. (1999) emphasized the use of pre-selection of clinical features to increase the efficacy of screening programs. Additionally, one researcher, to eliminate challenges of inter-rater reliability conducted all physical examinations of the 896 males and 216 females with mental retardation of unknown origin. The data collected from males 16 years and younger (n=330) and the females of the same age group (n=216) were analyzed separately and conjointly with those of the older subjects of the same gender. However, there was no cross-gender comparison, which is understandable in light the presence of the gender specific characteristic of macroorchidism (enlarged testicles) and no females with FraX were identified. The data were analyzed by percentages of subjects, by group, exhibiting the characteristics of the checklist. In males with FraX, “family history of mental retardation was present for most of the sample (78%), but existed in only 19% of the males without FraX. Similarly, “initial shyness and lack of eye contact followed by friendliness and verbosity with echolalic speech” existed in 63% of the FraX males, but was only manifested in 4% of the non-FraX group. Each of the remaining items of the checklist were manifested more frequently in the males with FraX than those without the FraX: Macroorchidism (59%; 4%), “elongated face” (51%; 7%), “large or

prominent ears" (27%; 11%), "hyperextensible joints" (41%; 23%), "soft/smooth skin" (22%; 4%). Furthermore, de Varies and colleagues concluded the use of the checklist would have allowed exclusion from further testing in 86% of the sample (95% CI 0.83-0.88) without missing any of the newly diagnosed cases.

TABLE 1

BIPSSI-FX 49 Items 5 Subscales	**Bailey et al., 2001 28 Items 5 Subscales**	**Lachiewicz et al., (2000) 25 Items 4 Subscales**	**Maes et al., (2000) 28 Items 2 Subscales**	**Teisl et al., (1999) 11 Items Sensitized Affected State Consensus Group Screening Tool (Reiss, et al., (1992)**	**de Vries (1997) et al., 8 Items Adapted & modified from Laing (1991)**	**Giangreco et al., (1996) 6 Items**	**Reiss et al., (1992) Affected State Screening Questionnaire: Consensus Group 17 Items**	**Hagerman et al., (1991) Fragile X Checklist 13 Items**
Developmental Milestones	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**	**Developmental Milestones**
1. How old was your child when he/she could sit without support?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2. How old was your child when he/she began walking well?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3. At what age did your child first say a first word?	"lack of sound imitation"(p.31)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4. At what age did your child first wave "bye-bye?"	"limited or lack of motor imitation" (p.31)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5. At what age did your child first respond to her or his name?	"communication delay"(p.31)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6. At what age was your child toilet trained?(urine and BM, with not more than 3 accidents while awake in one year)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Overview and Analysis of the BIPSSI-FX with Existing Screening Checklists for FraX

BIPSSI-FX	Bailey et al., (2001)	Lachiewicz et al., (2000)	Maes et al., (2000)	Teisl et al., (1999)	de Vries et al., (1997)	Giangreco et al. , (1996)	Reiss et al., (1992)	Hagerman et al., (1991)
Physical Subscale	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**	**Physical Subscale**
1. Does your child have low muscle tone/ muscle weakness?	"hypotonia" (p.31)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2. Does your child have any seizures?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3. Has your child ever had frequent colds or nasal infections?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4. Has your child ever had cleft lip, cleft palate or an arched palate (top of the inside of the mouth)?	"high arched palate"(p.31)	" highly arched palate" (p.236)	N/A	N/A	N/A	N/A	N/A	N/A
5. Has your child ever had frequent ear infections (more than three per year)?	"frequent otitis media"(p.31)	"more than five ear infections" (p.236)	N/A	N/A	N/A	N/A	N/A	N/A
6. Does your child have problems with his or her eyes?	"strabismus" (p.31)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7. Does your child have a long face and/or long ears?	a. "long or wide forehead" (p. 31) b." long and /or wide and/or protruding ears" (p.31)	a." elongated face" (p.236) b. "ears larger than the 75th percentile" (p.236)	a. "narrow and elongated face"(p.211) b. " large, protruding ears" (p.211)	N/A	a. "long jaw and high, wide forehead" (p.661) b. ears "large (by measurement) and protruding from side of head" (p.661)	a. "elongated face" (p.612) b. " large or prominent ears"(p.612)	N/A	"large or prominent ears"(p.284)

BIPSSI-FX	**Bailey et al., 2001**	**Lachiewicz et al., (2000)**	**Maes et al.,**	**Teisl et al., (1999)**	**de Vries et al., (1997)**	**Giangreco et al. , (1996)**	**Reiss et al., (1992)**	**Hagerman et al., (1991)**
Social and Behavioral	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**
1. Has your child ever avoided looking others in the eye?	a. "Avoidance of eye contact with parent" (p.31) b. "Avoidance of eye contact with examiner" (p.31)	"gaze avoidance" (p.236)	"avoiding eye contact" (p.211)	"ever had difficulty with avoiding looking others in the eye?"(p.283)	"initial shyness and lack of eye contact followed by friendliness and verbosity with echolalic speech"(p.661)	"Autistic-like behavior"- "poor eye contact" (p.612)	"ever had difficulty with avoiding looking others in the eye?" (p.63)	"poor eye contact" (p.284)
2. Has your child had problems at home or school?	N/A	N/A	N/A	N/A	N/A	N/A	"ever had problems at home or school?" (p.63)	N/A
3. Has your child had emotional problems?	N/A	N/A	N/A	"ever had any emotional or behavioral problems?"(p.283)	N/A	N/A	"ever had any emotional or behavioral problems?" (p.63)	N/A
4. Has your child had behavioral problems?	N/A	N/A	N/A	"ever have any emotional or behavioral problems?"(p.283)	N/A	N/A	"ever have any emotional or behavioral problems?" (p.63)	N/A
5. Has your child ever had treatment for emotional or behavioral problems?	N/A	N/A	N/A	"ever received treatment for emotional or behavioral problems?"(p.283)	N/A	N/A	"ever received treatment for emotional or behavioral problems?" (p.63)	N/A
6. Has your child ever taken medication for emotional or behavioral problems?	N/A	N/A	N/A	"ever taken medication for emotional or behavioral problems?"(p.283)	N/A	N/A	"ever taken medication for emotional or behavioral problems?" (p.63)	N/A

BIPSSI-FX	Bailey et al., (2001)	Lachiewicz et al (2000)	Maes et al., (2000)	Teisl et al., (1999)	de Vries et al., (1997)	Giangreco et al , (1996)	Reiss et al., (1992)	Hagerman et al., (1991)
Social and Behavioral	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**
7. Has your child ever had difficulty keeping his or her attention focused?	"lack of joint attention" (p.31)	"short attention span" (p.236)	N/A	"ever had difficulty keeping attention focused?" (p.283)	N/A	"ADHD" (p. 612)	"ever had difficulty keeping attention focused?"(p.63)	"short attention span"(p.284)
8. Does your child talk with people he or she does not know, or has your child done this in the past?	N/A	N/A	N/A	N/A	N/A	N/A	"ever had difficulty or discomfort socializing with people you don't know?" (p.63)	N/A
9. Has your child ever had problems playing with people he or she does not know?	N/A	N/A	N/A	N/A	N/A	N/A	"ever had difficulty with socializing with people you don't know? " (p.63)	N/A
10. Has your child ever had problems with sad or depressed mood?	N/A	N/A	N/A	"ever had difficulty with down or depressed mood?" (p.283)	N/A	N/A	"ever had difficulty with down or depressed mood?" (p.63)	N/A
11. Has your child ever had problems with nervousness or anxiety?	"nervousness and/or anxiety" (p.31)	N/A	" fearfulness" (p.211)	"ever had difficulty with nervousness or anxiety?" (p.283)	N/A	N/A	"ever had difficulty with nervousness or anxiety?" (p.63)	N/A
12. Has your child ever had a problem with hurting himself or herself by head banging or biting hands, arms or other parts of their body?	N/A	" hand-biting" (p.236)	"hand-biting" (p.211)	ever had difficulty with injuring yourself?" (p.283)	N/A	"autistic-like behavior" (p.612)	"ever had difficulty with injuring yourself?"(p.63)	"hand-biting" (p.284)
13. Has your child ever picked at his or her skin or bit hands or fingers to the point of injuring self?	N/A	N/A	"hand biting" (p.211)	ever had difficulty with injuring yourself?" (p.283)	N/A	"autistic-like behavior" (p.612)	"ever had difficulty with injuring yourself?" (p.63)	hand-biting" (p.284)

BIPSSI-FX	Bailey et al., (2001)	Lachiewicz et al., (2000)	Maes et al., (2000)	Teisl et al., (1999)	de Vries et al., (1997)	Giangreco et al., (1996)	Reiss et al., (1992)	Hagerman et al., (1991)
Social and Behavioral	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**	**Social and Behavioral**
14. Does your child make the same movements over and over, such as rocking, twirling around, or clapping hands or has your child done this in the past?	N/A	"hand flapping"(p.236)	a." stereotypic hand movements" (p.211) b. "flapping hands and arms" (p.211)	"ever had difficulty with making the same movements over and over?" (p.283)	N/A	"autistic-like behavior" (p.612)	"ever had difficulty with making the same movements over and over? (p.63)"	"hyperactivity" (p..284)
15. Has your child ever had problems with saying the same word or phrase over and over?	N/A	"perseverative speech"(p.236)	"perseveratio n" (p.211)	"ever had difficulty with saying the same word or phrase over and over?" (p.283)	"Initial shyness and lack eye contact followed by friendliness and verbosity with echolalic speech"(p.661)	" autistic-like behavior" (p.612)	"ever had difficulty with saying the same word or phrase over and over?" (p.63)	"perseverative speech"(p.284)
16. Has your child talked about the same subject over and over to the point of making it hard to hold a conversation with him or her?	N/A	N/A	"being talkative" (p.211)	"ever had difficulty talking about the same subject over and over?" (p.283)	N/A	" autistic-like behavior" (p.612)	"ever had difficulty talking about the same subject over and over?" (p.63)	N/A
17. Has your child ever had problems falling asleep or staying asleep?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
18. Has your child ever had an upset or disturbed response to soft or light touch or attempted to cover himself or herself with heavy objects such as sofa cushions, a mattress, blankets, beanbag chairs, etc.?	"tactile defensiveness" (p.31)	" adverse response to touch on the skin (tactile defensiveness) (p.236) "	N/A	N/A	N/A	N/A	N/A	"tactilely defensive" (p.284)

BIPSSI-FX	**Bailey et al., 2001**	**Lachiewicz et al., (2000)**	**Maes et al., (2000)**	**Teisl et al., (1999)**	**de Vries et al., (1997)**	**Giangreco et al., (1996)**	**Reiss et al., (1992)**	**Hagerman et al., (1991)**
Biological parents	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**
1. Have you or your mother, sisters or aunts had early menopause ("going through the change of life") or premature ovarian failure?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2. Have any women in the birth father's blood family had early menopause ("going through the change of life") or premature ovarian failure?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3. Have any women in the birth mother's blood family or the birth father's family, had cysts on the ovaries, cysts removed from the ovaries, or hysterectomy (removal of the uterus)?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4. Did the mother (child's mother) ever have problems with feeling depressed or nervous **before** becoming a parent?	N/A	N/A	N/A	N/A	N/A	"Maternal female with psychiatric disorder"(p.612)	N/A	N/A
5. Did the father (child's father) ever have problems with feeling depressed or nervous **before** becoming a parent?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

BIPSSI-FX	Bailey et al., 2001	Lachiewicz et al., (2000)	Maes et al., (2000)	Teisl et al., (1999)	de Vries et al., (1997)	Giangreco et al., (1996)	Reiss et al (1992)	Hagerman et al., (1991)
Biological parents	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**	**Biological parents**
6. Is it or has it been hard for anyone in birth mother's blood family or birth father's blood family to stop activities (such as, hand washing, checking locks, worrying, refusing to throw items away, computer use, watching television) or insist on doing things or having things done perfectly or exactly a certain way?	N/A	N/A	N/A	N/A	N/A	"Family history- Maternal female with psychiatric disorder"(p.612)	N/A	N/A
7. Has the birth mother or the birth father, now (or in the past) drank too much alcohol, used too many drugs, or used drugs too often, either those prescribed by a health care worker or those not prescribed?	N/A	N/A	N/A	N/A	N/A	"Family history- Maternal female with psychiatric disorder" (p.612)	N/A	N/A
8. Has anyone in the birth mother's blood family or the birth father's blood family had mental retardation/ developmental disabilities, autism, Asperger Syndrome or FXS?	" family history of mental retardation, autism, learning problems, or special education service" (p.31)	"positive family history of developmental disabilities" (p.236)	N/A	N/A	"family history of mental retardation" (p.661)	"Family history- maternal history of x-linked mental retardation" (p.612)	N/A	"Family history of mental retardation"(p. 284)
9. Has the birth mother (child's mother) or birth father (child's father) had problems doing math?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Development of the BIPSSI-FX

No parent response tools were found in the literature, which is surprising, given parents are usually the first to recognize developmental problems in their child (Bailey et al., 2004; Bailey et al., 2001b; Mirrett, Bailey, Roberts, & Hatton, 2004; Squires et al., 2001). This becomes still more surprising when considering the fact that Bailey's (2003) study of parents' experience with early intervention found that parents had concerns about their child's development much earlier than the diagnosis of FraX was made. Forness et al. (1996) found that parents are typically first to recognize their child's social-emotional problem. This recognition typically occurs by the age of 3 years.

Given the lack of such a tool, early intervention has not been implemented for many children with the FMR-1 gene mutation during crucial early brain maturation (Grossman et al., 2003; Mirrett et al., 2004). The *BIPSSI-FX,* a parent response tool, is a conduit by which the "frontline" assessors, primary caregivers, may contribute to the earlier diagnosis. The *BIPSSI-FX* is the only parent response tool designed to tap the wealth of knowledge that parents possess about subtle characteristics of the development of very young children who have FraX to have been identified in recent studies. Based on a study of infants and toddlers with FraX in which repeated measures were obtained, Mirrett et al. concluded that systematic screening for developmental delays is a crucial aspect of decreasing the amount of time between initial parental concerns and accurate professional determination of the status of the child's development.

Squires et al. (2001) provide provocative arguments from a review of the literature for and against the use of parents as first-line screeners to identify developmental problems within the child. Furthermore, Squires et al., tested the premise

that parents were effective first-line screeners of their children's social-emotional challenges by developing and utilizing a parent response tool, *The Ages and Stages Questionnaire: Social-Emotional (ASQ: SE*), in a geographical, economical, and racially diverse sample. The *ASQ: SE* was developed to augment the *Ages and Stages Questionnaires (ASQ)***,** which is a general development screening tool for children from 4 months to 5 years of age (Squires et al. 2001)

The *ASQ* is a set of 19 parent-completed questionnaires that are designed to identify infants and young children in various aspects of development. Although the tool assesses various developmental problems, specific social and emotional aspects were not originally included, and personnel from various early intervention programs such as Head Start have expressed a desire to have an instrument by which they may easily screen for social and emotional competence in young children. Although this need is quite great, few reliable and valid screening tools have been developed for the 0- to 5-year population that can be easily used by parents. Therefore, Squires et al. developed the *ASQ: SE* to identify infants and young children whose social and emotional development requires further evaluations to determine if referral for intervention services is necessary. The purpose of the *ASQ: SE* is similar to those of the aforementioned checklists for FraX. However, the *ASQ: SE*, unlike the checklists for FraX, capitalizes on the following two unique ingredients for early identification: 1) parents/primary caregivers as front-line screeners and 2) numerous assessment intervals within infancy, toddler, and preschool ages.

The *ASQ: SE*, which spans the 3 to 63 months age period, focuses on the child's social and emotional behavior in the areas of *self-regulation, compliance,*

communication, adaptive behaviors, autonomies, affect, and interaction with people. Items of the questionnaire target the following age intervals: 6, 12, 18, 24, 30, 36, 48, and 60 months, with the number of questions per age interval varying from 19, for the youngest group, to 33 for the oldest age group. The *ASQ: SE* was tested for reliability, validity, and utility, using a field study research design. The *BIPSSI-FX*, a parent response tool to assess for FMR-1 gene mutation "at risk" status, was developed similarly to the *ASQ: SE* because the tool is a parent response tool designed to specifically address the social and emotional aspects o infant and toddler development. Social and emotional challenges are often present in individuals with FraX who have typical cognitive development and who manifest none of the physiological dysmorphology of FraX (Hagerman, 2002).

Not only is the *BIPSSI-FX* the only parent response screening instrument for FraX, no other checklists or psychometric screening instruments for FraX include an assessment for possible developmental delay. Furthermore, other checklists do not include an assessment of characteristics of the biological parents and extended relatives, despite the fact that researchers such as, Chinnery, Cartlidge, Tennant, Birchall, & Stenhouse (2004) have proposed the benefit of utilizing frequently manifested characteristics of premutation carriers to facilitate the identification of risk for FMR-1 gene mutation in a younger generation and vice versa.

Although various assessment tools have been utilized to describe characteristics of young children who have been diagnosed to have FraX, currently used psychometric screening tools fail to detect FMR-1 gene mutation "at risk" status both in children who have subtle symptoms of FraX and in children who are younger than 24-36 months of age

(Hagerman, 2002). The *BIPSSI-FX* incorporates the most frequently identified characteristics of FraX, along with an assessment of attributes cited as disproportionately higher within premutation carriers of the FMR-1 gene. The inclusion of those aspects facilitates the specificity of a tool to screen for FraX. **Thus, it was hypothesized that children with FraX will score higher on the *BIPSSI-FX* than children with other developmental disabilities (Hypothesis 4 – see end of chapter 2).** Furthermore, it was **hypothesized that the *BIPSSI-FX* would demonstrate test-retest reliability (Hypothesis 2 – see end of chapter 2) and internal consistency (Hypothesis 2).**

Screening tools and psychometric measures designed to facilitate early identification of autism continue to proliferate (Baird et al., 2000; Baron-Cohen et al., 1992; Baron-Cohen et al., 2000; Maestro, 2002; Robins, Fein, Barton, & Green, 2001a). *The M-CHAT* (Robins et al., 2001a), a parent response checklist, is an extension of the *Checklist for Autism in Toddlers (CHAT*, Baron-Cohen et al., 1992), which was established to detect autism at 18 months of age. The *M-CHAT* diagnoses autism early, but most tools developed to screen for FraX have not focused on children younger than 24 months of age. Furthermore, to justify the need for the *BIPSSI-FX,* it is necessary to see if the *BIPSSI-FX* can detect FMR-1 "at risk" status more often than the *M-CHAT.* **Therefore, it was hypothesized that the *BIPSSI-FX* would differntiate FraX from autistic children - no FraX more accurately than the *M-CHAT*. That is, it was anticipated that the *BIPSSI-FX* would predict FMR-1 gene status versus autism -no FraX status better than the *M-CHAT* (Hypothesis 6 – see end of chapter 2).**

The *BIPSSI-FX* is designed to identify characteristics of children who are "at risk" for having gene changes that are responsible for FraX. The five subscales of the

BIPSSI-FX and the items therein are supported by an exhaustive review of the literature summarized in the paragraphs that follow.

Developmental Subscale

Significant developmental delays are often evident in the early years of children who have FraX (Bailey, Hatton, Skinner, & Mesibov, 2001b; Hagerman et al., 2002; Heverly, 2000-2001; Lachiewicz et al., Keysor, Mazzocco, McLeod, & Hoehn-Saric, 2002, p. 179) in a review of the literature regarding females with FraX - full mutation, emphasize the "logic" of a "developmental approach" to frame the various aspects of FraX, such as cognitive, social, emotional, and behavioral functioning. Furthermore, Keysor et al., (2002) note that "only recently have efforts begun to identify the developmental trajectory of FraX in infants and toddlers (p. 179)." Consequently, limited data are available regarding the achievement of early developmental milestones in individuals with FraX.

Bailey et al. (2001a), in a study to distinguish differences between children with FraX and those who have autism - no FraX found developmental delay to be one of the earliest indicators of both FraX and autism. Bailey and colleagues used various diagnostic and screening inventories such as the *Battelle Developmental Inventory (BDI)* to help to differentiate characteristics of FraX and autism. The *BDI,* which spans the age range from birth to 96 months of age and measures development in five areas, namely, personal-social, adaptive, cognitive, motor, and communication, was used to compare the overall delay and to determine a pattern of delay in both children with FraX and those with autism. The study showed that having both the FraX and autism might cause a more significant developmental delay than FraX without the diagnosis of autism. The Bailey et

al. (2001b) study heavily supports the inclusion of the *Developmental Subscale* within the *BIPSSI-FX*.

Physical Subscale

The literature identifies physical manifestations, which are likely to be seen in children with FraX. The common findings assessed in the *BIPSSI-FX* include seizure activity, frequent ear infections, frequent colds and nasal infections, low muscle tone or muscle weakness, and strabismus or vision problems in general. Seizure activity is evident in about 20% of the children with FraX (Hagerman, 1997; Incorpora, Sorge, Sorge & Pavone, 2002). The American Academy of Pediatrics recommends guidelines to assist pediatricians caring for children with FraX (Desposito et al., 1996). Those guidelines include obtaining an electroencephalogram and assessing the seizure history of children ages one through 5 years (Desposito et al., 1996).

Another health concern commonly encountered in children with FraX is frequent middle ear infection (Desposito et al., 1996; Hagerman, 1987; Hagerman, 1997; Turk& Patton, 2000; Zissel & Roberts, 2003). Frequent ear infections which occur in approximately 60% of children with the disorder (Turk & Patton, 2000), directly affect speech and language development. Oftentimes children with FraX also suffer from frequent sinus infections as well (Hagerman, 2002). Low muscle tone or connective tissue defects or disorders are responsible for many of the physical characteristics of children with FraX (Lachiewicz et al., 2000). A study by Hjalgrim, Hansen, Brondum-Nielsen, Nolting, & Kjaer (2000) suggested that there is a malfunction in the supporting tissue during fetal development. Finally, strabismus and visual problems in general are seen frequently in children with FraX (Desposito et al., 1996; Hagerman, 1997; Hatton,

Buckley, Lachiewicz, & Roberts, 1998; Lachiewicz et al., 2000; Turk & Patton, 2000). Of even greater cause for alarm is Desposito et al.'s (1996) recommendation of vision exams as early as 6 to 12 months of age for children who have FraX, based upon their finding that strabismus occurs in nearly 40% of children who have FraX.

FraX occurs relatively equally in all racial and ethnic groups (Crawford et al., 1999). It is a condition of major epidemiological importance among mentally handicapped males and "must be considered in the differential diagnoses of a child with developmental delay, mental retardation, or learning disability" (Pimentel, 1999, 639).

Cognitive Subscale

Approximately 85% of boys with FraX have mental retardation (Hagerman, 1997). Among children with FraX, boys are more likely to have mental retardation whereas girls are more likely to have a learning disability with normal intelligence (Hagerman et al., 1996). According to Dyer-Friedman, et al. (2002), girls with FraX had somewhat higher cognitive abilities than did boys with FraX. Females with FraX tend to struggle with math, but may perform exceptionally well in reading and spelling; in contrast, reading often poses problems for boys (Hagerman, 1997; Mazzocco, & Myers, 2003). Additionally, speech and language present special difficulties, more often affecting boys than girls. Around 10% of children with FraX have severe delays in language development and remain nonverbal for the first 6-8 years of life, and possibly even longer (Hagerman, 1997). When speech develops, rapid speech associated with mumbling and echolalia is common in children with FraX especially in boys. Perseveration is exhibited when a question is asked repeatedly, even after an answer has

been given (Hagerman, 1997). Inappropriate outbursts and tantrums are also common in FraX, but are manifested more often in boys.

Speech and language delays lead to underdeveloped or slow learning. A common means for determining intellectual and cognitive functioning is IQ testing. The average score for any person on a standardized IQ test is 100. According to Hagerman (2002), approximately 50-70% of girls with the full mutation have an intellectual deficit with an IQ under 85, and when mental retardation occurs, it is usually mild (IQ 50-70), whereas the IQ of boys with a FraX-full mutation is in the 40s. The majority of children with FraX score below average on IQ tests. Limited FMR-1 protein production caused by a person having some cells with the premutation and other cells with the full mutation can cause higher intellectual functioning (Hagerman, 1997). These children may still face learning obstacles, but can excel in some areas of cognitive functioning particularly with individualized special education services. Due to the delayed and underdeveloped cognitive functioning of children with FraX, they are typically eligible for special education services, and cognitive outcomes become enhanced with individualized special education (Bailey et al., 2001; Braden, 2002; Hagerman, 1997; Hodapp, 1999).

Social/Behavioral Subscale

The *Social /Behavioral Subscale* is an adaptation of the 11 emotional/behavioral items of the *Consensus Group Screening Checklist for FraX* (Reiss et al., 1992). Behavioral symptoms associated with FraX tend to be both the most endearing traits as well as the most challenging ones. For example, deVries et al (1997) included a personality trait characterized by shyness and poor eye contact, including friendliness, excessive conversation, and perseverative speech. This duality, poses difficulties for

those involved in the care and education of those affected with FraX. While males tend to be very socially engaging, they may alternately and sometimes simultaneously exhibit signs of social anxiety. They tend to avoid eye contact during conversations and to speak in imitative, rapid, or perseverative ways. Other autistic-like behaviors are also frequently exhibited, such as withdrawal from others and self-stimulatory behaviors. Individuals with FraX frequently have problems with hyperactivity, short attention spans, difficulty with concentrating, and aggressive behaviors (Baumgardner, Reiss, Freund, & Abrams, 1995; Hagerman, 2002). Reports of the incidence of FraX among those diagnosed with autism vary (Blomquist, Bohman, Edvinsson, & Gillberg, 1985; Fisch, Cohen, Jenkins, & Brown, 1988). However, it is widely accepted that using DSM-IV-TR criteria, 16 to 17 % of those identified as autistic also have FraX (Hagerman, 2002). The majority of males who have the FraX - full-mutation exhibit autistic-like behaviors (Hagerman, 2002).

Furthermore, a study (Teisl et al., 1999) of 55 preschool and school-aged children with FraX, full mutation found that children with the full-mutation were more likely than the controls to be described as nervous or anxious, and to regularly engage in perseverative speech and /or other challenging behaviors. The intense reactions to auditory, tactile, visual, and olfactory stimuli in persons with the FraX mutation have been associated with anxiety, aggression, hyperactivity, and hyperactive arousal (Hagerman, 2002). Miller et al.'s (1999) study of 25 individuals with FraX (16 full-mutations) found that individuals with FraX have a physiologically based enhancement of reactions to sensory stimuli.

Roberts, Hennon, and Anderson's (2003) review of the literature reveals support for Items 1, 2, 3, and 4 of the *Social Behavioral Subscale* of the *BIPSSI-FX* which relate

to avoiding looking others in the eye, problems at school or home, emotional problems, and behavioral problems. Furthermore, Roberts and colleagues' (2003) study of 43 males with FraX, full-mutation between the ages of 2 to 7 years, showed that eight of the children exhibited characteristics of autism. Additionally, they found that the children had delayed language development with the expressive language skills developing more slowly than the receptive language skills over time. The boys with FraX showed considerable delay in receptive language development in that they developed receptive language at about one-half the rate expected for typically developing children and they developed expressive language at about one-third the rate. Roberts et al., (2003) linked cognitive and developmental characteristics to the receptive and expressive language development delay.

Richdale (2003) found that children with FraX express significantly greater difficulty fall asleep. Furthermore, Hessl et al.(2001) in their study of 120 children (80 boys and 40 girls) with the FraX - full mutation and their unaffected siblings, between the ages of 6 to 17 years, reported group differences that lend credence to the inclusion of the following items in the *Social Behavioral Subscale*: 2) "problems at home or school," 3) "emotional problems," 4) "behavioral problems," 5) "treatment for emotional or behavioral problems," 7) "difficulty keeping focus," 10) "sad or depressed mood," 11) "nervousness or anxiety," 17) "problems falling asleep or staying asleep. The variables measured in the study were behavioral problems, somatic complaints, delinquent behavior, aggressive behavior, anxiety/depression, social problems, attention problems, thought problems, and environmental problems. The children with FraX had significantly higher scores on the *CBCL* than their non-affected siblings. Thus, in the

current study **it was hypothesized that the *BIPSSI-FX* would demonstrate concurrent validity with the *CBCL* and the *Consensus Group Questionnaire for Fragile X* (Hypothesis 1 – see end of chapter 2).** Furthermore, **it was hypothesized that children with FraX would score higher on the *BIPSSI-FX* than children who do not have the FMR-1 gene mutation (Hypothesis 3).**

In addition to an assessment of developmental milestones, physical development, cognitive development, and social/emotional behaviors commonly exhibited by children with FraX, the *BIPSSI-FX* uniquely includes an assessment of characteristics that have been associated with carriers of FraX in either the premutation or the full-mutation state.

Biological Parent Subscale

FMR-1 gene alterations are transmitted in an X-linked manner and thus may be passed to offspring by the mother or father. Therefore, the inclusion of key characteristics of males and females with FraX is logical to facilitate early identification of infants and toddlers "at risk" for FraX.

A mother has a 50% chance of transmitting FraX to a male or female child because a female typically has two X chromosomes on the 23rd pair, which is responsible for determining gender. The mother contributes an X chromosome to each child she conceives. On the other hand, a male's 23rd chromosome pair consists of an X and a Y chromosome. Therefore, a man contributes an X chromosome to combine with the woman's X chromosome to reproduce a female. Thus a father who has FraX, premutation, has a 100% chance of transmitting the FraX - premutation to each of his daughters. On the contrary, since a father contributes a Y chromosome to a male child, he has a 0% chance of transmitting FraX to a son.

Not only does the prevalence of FraX necessitate focus on diagnosing and therapeutic interventions, but also the emerging data regarding the atypical transmission and phenotypic expression warrants close focus on this syndrome (Shapiro, 1997; Sherman, Jacobs, & Morton, 1985). The genetic expression of FraX is atypical in that some female carriers may have clinical symptoms of the disorder and some males who inherited the gene may not be affected clinically (Braat, Smits, & Thomas, 1999; Franke et al., 1996; Hagerman et al., 1992; Sherman et al., 1985). This phenomenon is of significance, especially in light of the increased number of individuals who may possibly experience behavioral or physiological maladies because of being a premutation-state carrier of the FMR-1 gene (Dorn, Mazzocco & Hagerman, 1994; Franke et al., 1996).

Premature Ovarian Failure, Ovarian Cysts, and Hysterectomy. Premature ovarian failure (POF), a cessation of ovarian function at the age of less than 40 years after normal development, is characterized by the occurrence of amenorrhea (absence of menstruation) with low estrogen levels (Laml, Preyer, Umek, Hengstschlager, & Hanzal, 2002). Allingham-Hawkins et al. (1999) conducted an international collaborative study examining premature menopause in FraX carriers in which 760 women with a family history of FraX were surveyed about their FraX status and menstrual and reproductive histories. Hawkins and colleagues found a significant association between FraX premutation status and premature menopause. Similarly, Giovannucci - Uzielli et al., (1999) in their study of 108 women with POF, found 6.5% of the subjects had FraX premutation. However, contrary to these findings, Kenneson, Cramer & Warren (1997) screened 216 women who had experienced early menopause at <40 years, but no FraX premutation alleles were found. Based on these findings, Kenneson et al. (1997)

concluded that FraX premutation is not a major risk factor for early menopause. It is plausible that Kenneson and colleagues' divergent findings are due to a lack of control for other causes of POF. As menopause may vary from person to person with a slight difference of a couple of years from the normal age, studies show that females with FraX, premutation experience menopause much earlier than the general population of women. Giovannucci-Uzielli et al. found that 13 to 25% of FraX carriers experienced premature ovarian failure before the age of 40 years.

A preponderance of empirical data addressing a greater incidence of irregularities of hormone functions manifested by POF, ovarian cysts, and hysterectomy in women, who are premutation carriers of the FMR-1 gene, supports the appropriateness of the inclusions of the assessment of these attributes in biological female relatives of a child for whom a psychometric screening inventory is completed. Therefore screening for FraX - premutation of women with premature ovarian failure, cysts on the ovaries, and hysterectomy, will be helpful in effective screening of young children who may be "at risk" for FraX.

Depression, Anxiety, and Attention Difficulties. A study of female carriers of the FMR-1 gene found a statistically significant behavioral phenotype (depression and anxiety) in intellectually normal and above normal females (Franke et al., 1996). Additionally, a study of male premutation carriers showed a higher incidence of behaviors related to adult Attention Deficit Hyperactivity Disorder, alcohol abuse, and dependence and obsessive-compulsive disorders (Dorn et al., 1994). Similarly, Tamm, Menon, Johnston, Hessl, & Reiss (2002), reported that females with FraX demonstrate impulsivity or problems with inhibition of behavior, which manifest as difficulties

focusing and organizing tasks. Einfeld, Tonge, and Turner's (1999) longitudinal study (7 years) of behavioral and emotional problems in young people with FraX found substantial persistence of an overall level of behavioral and emotional problems. Furthermore, Einfeld and colleagues (1999) found children with FraX could be distinguished from other children with intellectual disability by greater levels of shyness, gaze avoidance, and speech peculiarities on *Developmental Behavior Checklist (DBC*). However, the FraX group scored significantly lower on the "antisocial" subscale of the *DBC* (Einfeld et al., 1999), indicating a desire to interact with others despite having concurrent behaviors which inhibit social interaction.

Difficulties with Math. Math skills go hand in hand with reading, spelling, and writing; therefore, a math disability can be correlated with lack of reading and writing skills but may also hinder academic performance in and of themselves. Mazzocco (2001) defined math difficulty as a weakness in arithmetic performance relative to performance in other academic or cognitive domains, with particular attention given to participants whose scores fell within the range of the bottom 10th percentile of a normative sample. Significant deficits in arithmetic skills were demonstrated in females with FraX - full mutation. Similarly, Tamm et al. (2002) in a study of cognitive processing in females with FraX - full mutation found short-term memory deficits, higher verbal than performance IQ scores, and poor arithmetic performance on neuropsychological tests. Thus, the inclusion of an assessment of math abilities in the *Biological Parent Subscale* is supported by scientific evidence.

The aforementioned characteristics in biological parents, siblings, and extended relatives are frequently expressed and may be diagnosed, while the relative

simultaneously deals with stressful multi-systemic challenges of caring for the child with FraX. Often, the primary caregiver of a child who has FraX, concurrently has the dual challenge of coping with the challenges of the child as well as his or her own physical anomalies such as: a) POF, which often results in bone density loss and emotional challenges due to hormonal imbalances(Allingham-Hawkins et al.,1999; Giovannucci-Uzielli et al.,1999; Laml et al., 2002; Murray et al., 2000; Sherman, 2000); b)connective tissue weaknesses and visual problems (Amin & Maino,1995; Hagerman, 2002; Steyaert, Legius, Borghgraef, & Fryns, 2002); and c) possibly degenerative neurological changes such as those manifested in Fragile X Associated Tremors and Ataxia Syndrome (FXTAS - Hagerman et al., 2004). Therefore, **it was hypothesized that scores on the *Biological Parent Subscale* would differ between parents of children with FraX and parents of children without the FMR-1 gene mutation, including children who have developmental delays of other origins (Hypothesis 5).**

Comparison of Autism and Fragile X Syndrome

An association between autism and FraX has been described, although a diagnosis of FraX does not implicate autism, or vice versa (Mazzocco, 2000). Autism and FraX are two distinctly different disorders. Autism is a developmental disorder characterized by social and communicative abnormalities typically displayed within the first three years of life and is diagnosed by clinical interviews, direct assessment and behavioral ratings (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000). Autism is believed to have multiple causes, including genetics; however, most persons with autism have some form of mental retardation. Because the majority of males with FraX - full mutation exhibit autistic features and approximately 15 % meet the *Diagnostic and Statistical Manual-Text*

Revision (DSM IV-TR) criteria for autism, symptomatic behaviors of autism were included in the *BIPSSI-FX* to differentiate children with FraX and autism from those only with autism.

FraX is present at birth and is diagnosed definitively with 99% accuracy by genetic testing (Crawford et al., 2001). Like autism, FraX is characterized by communication delays and mental retardation. There has been a considerable amount of research comparing FraX and autism as two distinct disorders, but a differentiation of the autistic-like behaviors of FraX and the DSM-IV TR diagnosis of autism is emerging. Bailey et al. (2001a) applied various diagnostic and screening inventories to help differentiate characteristics of FraX and autism. The *Battelle Developmental Inventory (BDI),* which spans the age range from birth to 96 months of age and measures the cognitive development in five areas namely: *personal-social, adaptive, cognitive, motor*, and *communication*, was used to compare the overall delay and to determine a pattern of delay in both children with FraX and those with autism. Additionally, the *ABILITIES Index* was used to assess functional impairment of the two groups; and temperament was assessed using the *Behavioral-Style Questionnaire (BSQ),* which is a 100-item parent report scale in which scores in nine different areas of temperament are obtained. The Bailey et al. study showed that having both FraX and autism might cause a more significant developmental delay than FraX without the diagnosis of autism. The overall difference in the development of children with FraX without autism compared with the development of children who have autism - no FraX, was not significant. However, children with FraX and autism had greater impairment in behavior, social skills, and temperament than the children with FraX without autism. These findings suggest the

behavior of children with FraX and autistic are affected more severely than children with FraX alone or autism alone. **Therefore, children with FraX will differ from those with Autism, PDD-NOS, and Asperger Syndrome more on the *BIPSSI-FX* than on the *M-CHAT* (Hypothesis 6 – Study II).**

Summary of Hypotheses

In summary, the following hypotheses emanate from the review of the literature and were tested:

Hypothesis 1 - The *BIPSSI-FX* will measure FMR-1 gene mutation "at risk" status in young children validly, as indicated by concurrent validity with the *CBCL* and the Consensus Questionnaire for Fragile X (Study I).

Hypothesis 2 - The *BIPSSI-FX* will measure FMR-1 gene mutation "at risk" status in young children reliably as indicated by test-retest reliability (Study 1) and internal consistency (Study I, Study II);

Hypothesis 3 - Children with FMR-1 gene mutation will score significantly higher on the *BIPSSI-FX* than children without the gene mutation (Study II).

Hypothesis 4 - Children with FMR-1 full mutation will score higher on the *BIPSSI-FX* than children who have other types of developmental disabilities (Study II).

Hypothesis 5 – Parents of children with the FMR-1 gene mutation will score higher on the *BIPSSI-FX Biological Parent Subscale* than parents of children without the gene mutation (Study II).

Hypothesis 6 - Children with FraX will differ from those with autism, PDD-NOS, and Asperger syndrome more on the *BIPSSI - FX* than on the *M-CHAT* (Study II).

CHAPTER THREE

METHOD

Research Approach and Design

This research study featured a comparative exploratory field study design (Polit & Hungler, 1991). The comparative exploratory design was appropriate for use in the study because of the continued need for a cost-effective screening tool by which young children positive for the FMR-1 gene mutation may be identified(Teisl et al., 1999). The *BIPSSI-FX* was designed to address the special challenges of assessing very young children by way of a screening instrument that may be appropriately used in both clinical and in non-clinical settings. The tool was designed to screen for FMR-1 gene alteration "risk" in children 12 months through 84 months of age.

The reliability and validity of the original *BIPSSI-FX* was evaluated with a small sample of extended family members of individuals diagnosed with FraX. The results of this first study were used to revise the *BIPPSI-FX*. The revised *BIPSSI-FX* was further tested with a sample of parents of culturally, geographically, ethnically, and socioeconomically diverse children.

Study Samples

Study I. A pilot study of 27 children between the ages of 12 months to 18 years of age and their primary caregiver in a large extended family in which there is a relative diagnosed with FraX was conducted. The sample consisted of 15 males and 12 females, having a mean age of 9.67 years. Twenty-one children in the sample were between the ages of 6-18 years and the remaining six were between 12 months to 84 months of age. All of the children were African-American and most resided in the delta region of a

southern portion of the United States. The primary care givers of the children consisted of 13 mothers, 2 fathers, and 1 grandmother, between 31 years to 42 years of age, with a mean age of 39 years. Six parents did not provide information regarding their age. The educational attainment ranged from some college to doctorate. Seventy-nine percent (n=11)of the parents held a bachelor's degree or higher. However, two parents did not list a level of educational attainment. Specific data regarding income were not gathered due to participants' concerns for anonymity and privacy.

Study II. The small sample size of the pilot study along with the absence of geographical and ethnic diversity necessitated further testing of the *BIPSSI-FX*. Thus, a convenience sample of 359 primary caregivers of children ages 12 months to 84 months of age participated in study II. The primary caregivers' children had been previously diagnosed, using blood DNA analysis, to have FraX in the full mutation state (>200 CGG repeats) or the FMR-1 gene in the premutation state (50-200 CGG repeats). Also included for comparison were groups of primary caregivers of children who had been diagnosed to have autism, Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) or Asperger Syndrome, but had not received a diagnosis of FraX. Furthermore, a group of parents of typically developing children who had no diagnoses of learning disorders and/or behavioral disorders and did not have other biological children diagnosed with FraX.

A majority of the participants was Caucasian (84.68 %), but more than five racial or ethnic groups constituted the sample. The caregiver's relationship to the focal child was primarily “mother” (85%); 3.1 percent of the respondents were fathers. Most of the primary caregivers were married, remarried or partnered (n = 325, 90.53%). Less than ten

percent described themselves as single, divorce, separated or widowed. Educational attainment was generally high, with 208 (57.94%) having attained bachelors, masters, or doctoral degrees. Two-hundred-seventy (75.21%) primary caregivers had an annual household income of greater than $35,000. The median income of the respondents was $50,001 to $75,000 per year. The average age of the parent was 35.13 years and the children ranged in age from 11 months 20 days to 7 years and 4 days with the average age being 4.07 years. Most of the parents endorsed their religious preference as Christian (Protestant 52%, Catholic 25%). The sample consisted of participants from thirty-eight states, with no state representing more than 8.08% of the sample and most were from the United States (n = 87.47%). However, 14 countries from four continents (Europe, Australia, Asia, and Africa) were represented, in addition to North America. Table 2 provides a summary of key demographic data.

Table 2

Demographic Information: Study II

A. Gender, Age, and Relationship

Variable	Mean	(+ SD)	Frequency	%
Child age	4.07 years	(1.55)		
Child gender				
Male			166	46.24
Female			48	13.37
No gender noted by caregiver			145	40.39
Primary caregiver's gender				
Male			16	4.46
Female			343	95.54
Caregiver relationship				
Mother			304	84.68
Father			11	3.06
Grandmother			3	.84
Adoptive mom			12	3.34
Foster parent			2	0.56
Relationship not provided			29	8.08
Primary Caregivers' Age	35.13	(6.54)		

B. Family Income Level Per Year

	Frequency	%
Other	12	3.34
Less than 10,000	1	.28
10,001 - 20,000	28	7.79
20,001 - 25,000	17	4.73
25,001 - 35,000	31	8.64
35,001 - 50,000	62	17.27
50,001 - 75,000	86	23.96
75,001 - 100,000	56	15.6
100,001 and Up	66	18.38
Total	359	100.0

(1.90)

C. Primary Caregivers' Educational Attainment

Attainment	Frequency	%
Other	3	0.83
Grammar school	2	0.55
High school	41	11.36
Some college	107	29.64
College degree	133	36.84
Masters degree	64	17.73
Doctorate	11	3.05

D. Primary Caregivers' Marital Status		
Married	308	85.79
Single	12	3.34
Divorced	12	3.34
Separated	7	1.95
Remarried	2	.56
Partnered	15	4.18
Widowed	3	.84
E. Primary Caregivers' Ethnic Background		
Caucasian	304	84.68
African-American	7	1.95
Hispanic	17	4.74
Native American	4	1.11
Asian/Pacific Islander	17	4.74
Biracial	1	.28
Other	9	2.51
Total	359	100.00

Procedure

Study I

The researcher completed a small pilot study of 27 children between the ages of 12 months to 18 years of age and their primary caregiver in a large extended family in

which there was a relative diagnosed with FraX, before the larger internet-facilitated study. Prior to the initiation of the study, the researcher obtained the approval of the Oklahoma State University Institutional Review Board to conduct the research (see Appendix C). Additionally, each primary caregiver signed an Informed Consent Form and each child who was able to write gave informed Assent (See Appendix D). The primary caregiver of each child completed the *BIPSSI-FX* twice, one month apart, to assess test-retest reliability. Additionally, to facilitate the assessment of concurrent validity the primary caregivers completed the following: 1) The *Child Behavior Checklist (CBCL)* and 2) the Consensus Group Screening Questionnaire for Fragile X (*CGSQ-FX*). Furthermore, the primary caregivers collected a buccal (cheek) cell swab sample from their child, which is comparable to brushing the child's teeth. The extracted DNA was analyzed for FMR-1 gene to determine carrier status. The swab was placed in the container provided by the researcher, labeled with the last four digits of the child's social security number, and mailed by the parent in the prepaid and addressed priority mail envelope to the research assistant. The research assistant immediately (within 24 hours) took the samples to a local medical genetics laboratory for safe storage in a temperature controlled (non-cycling) freezer to preserve the integrity of the DNA and thus facilitate accurate analysis. The samples were kept in the freezer until most of the specimens were received. Additionally the assistant organized the completed research paper and pencil measures, charted the forms as received and the date. The assistant also verified that the forms were void of identifying information such as primary caregiver and child's name. Additionally the assistant insured that each form was coded appropriately. The researcher retrieved the coded swabs from the laboratory; separated the swabs into two packages,

each consisting of one of each child's swabs; and wrapped the swabs in bubble wrap and mailed packages via Express mail to the research laboratory responsible for DNA analysis.

The DNA analyses were completed in a research laboratory in which this method of screening for FMR-1 gene changes is conducted on an ongoing basis. Results from the biological analyses were correlated with the results of the psychometric measures. However, the lack of amplification of DNA in several of the specimens, despite repeated collection of the buccal cell swabs along with serendipitous findings rendered the results inconclusive. The buccal swab method of collecting DNA for analysis of the FMR -1 gene is a relatively new process and is conducted in only a few research laboratories in the United States. However, the reliability and validity of the analysis of DNA for the FMR-1 gene mutation from buccal cell swab samples is reported in the literature (Hagerman, Wilson, Staley, Lang, Fan, Ulhorn et al., 1994). Nonetheless, this DNA collection method is not used in any clinical laboratories for the purpose of FMR-1 gene mutation analysis. It is highly plausible, that the validity of the FMR-1 gene mutation analyses is questionable because of the great difficulty in collecting sufficient amounts of DNA by the buccal cell swab method.

Study II

Prior to the initiation of the study, application to conduct the research was made with the institutional review board of Oklahoma State University. After permission to conduct the research was obtained (Appendix E), primary caregivers of children from one of seven groups were recruited to participate in the study. Each parent or primary caregiver completed and submitted, via Internet, the revised *BIPSSI-FX*, the *M-CHAT*, a

Primary Caregiver Information Profile, a *Diagnosis Information* form and acknowledged a statement of informed consent contained in the *How to Participate* information sheet (see Appendix F). Instructions for completion of the study were clearly delineated on the recruitment website, http://langston.osu-tulsa.okstate.edu/vthomas (see Appendix K).

Recruitment of Subjects

The samples of parents were recruited from child-oriented Internet listserv groups and organizations. Additionally, after obtaining permission from various listserv masters, the principal investigator posted a notice recruiting parents of children diagnosed to have a developmental disability or of typically developing children (see Appendix J). A website (http://langston.osu-tulsa.okstate.edu/vthomas) specifically designed for the study provided a mechanism by which the primary caregivers completed the questionnaires online and returned the surveys by way of encrypted automated return submission, in an Access database, to the computer server of the university, which developed and sponsored the website. The researcher received approval from the Oklahoma State University Institutional Review Board to alter the inclusion criteria for the study to allow children in the comparison diagnosis groups for whom FraX had not been ruled out by DNA testing. The website and the recruitment letter reflected this change. The recruitment website remained active for 3 months for data collection and the website remained active for an additional 9 months following data collection, for purposes of disseminating aggregate data from the study, thanking parents for participating, and providing links to related websites likely to provide helpful information to parents. Confidentiality was maintained and anonymity was protected in all situations. Results of the aggregate data analyses and interpretations were provided at the conclusion

of the study by a statement posted to each of the aforementioned Listserv groups and by way of a link to the research study website.

Rationale for Internet Data Collection Method

The Internet has become an important communication tool in modern society (Frankel & Sanyin, 1999). Potentially, the Internet may change the way we conduct scholarly research (Harris & Dersch, 1999). The Internet can be very beneficial in the areas of participant recruitment and data collection. Internet sites that house questionnaires or other forms of survey instruments are not significantly different from other research involving questionnaires. Researchers to ensure results that are both reliable and valid must adhere to specific guidelines and protocols. Despite the similarities between traditional (pen and paper) and Internet conducted research, there are differences that must be addressed (Harris & Dersch; see Appendix L for more information). In order to address these problems the principal investigator invited participants to add comments or clarify their responses at the end of all questionnaires.

Inclusion Criteria for Study II

Diagnosis Groups

Fragile X - Full Mutation Group. This group included males and females aged 12 months through 84 months of age. By parent report, the children must have results of DNA testing that indicate more than 200 CGG repeats on the FMR-1 gene in cells analyzed and have been diagnosed by a qualified health-care professional or geneticist to have FraX. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Autism with no FraX, nor Asperger. This group included males and females aged 12 months through 84 months of age. By primary caregiver report, a qualified health-care professional has made the diagnosis of autism, but there is no diagnosis of FraX nor Asperger Syndrome. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Pervasive Developmental Disability Not Otherwise Specified (PDD-NOS). This group included males and females aged 12 months through 84 months of age. By primary caregiver report, a qualified health-care professional had made the diagnosis of *PDD-NOS*, but there is no diagnosis of FraX nor Asperger Syndrome. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Asperger with no FraX. This group included males and females aged 12 months through 84 months of age. By primary caregiver report, a qualified health-care professional has made the diagnosis of Asperger Syndrome, but there is no diagnosis of FraX. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Down Syndrome Group. This group included males and females aged 12 months through 84 months. By primary caregiver report, children have been diagnosed by a qualified health-care professional to have Down Syndrome (Trisomy 21). Children had not received a diagnosis of autism, nor a diagnosis of FraX or Asperger Syndrome. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Typically Developing Group (No diagnosis). This group included males and females aged12 months through 84 months of age. By primary caregiver report, the child exhibits typical growth and development, is free of chronic or terminal illnesses, and has

no known physical, cognitive, or behavioral impairments. The primary caregiver of the child had to be able to read and typewrite in English or Spanish.

Measures

Study I

Each parent or legal guardian (the primary caregiver) completed the *BIPSSI-FX*, the *Consensus Group State Screening Questionnaire for Fragile X*, the *Child Behavioral Checklist(CBCL)*, a family background information background form and a loosely structure questionnaire, while keeping in mind his or her child who was participating in the research study. Furthermore, each parent collected a sample of his or her child's DNA.

Biopsychosocial Screening Inventory for Fragile X

The researcher designed the *BIPSSI-FX* to be completed by a child's primary caregiver (see Appendix A). This 35-item Likert scale-type instrument, consists of the following five subscales: *Developmental Milestones, Physical, Social and Behavioral, Cognitive*, and *Biological Parent*. The *Social/Behavioral Subscale* was adapted from the social/emotional items of the *Consensus Group Screening Questionnaire for Fragile X – CGSQ-FX* (Reiss et al, 1992).

Consensus Group Screening Questionnaire for Fragile X

The *CGSQ-FX* (Reiss et al., 1992) is a 19 item, 3-point scale ("yes" "no" "no information") screening questionnaire designed for use by clinicians interviewing patients themselves or parents, guardians or other caregivers (see Appendix B). A group of experts in diagnosing and treating individuals with FraX developed this tool. Reliability and validity data have not been reported for the complete *CGSQ-FX*.

However, Teisl et al., 1999 presented reliability and validity data for the 11 items of the more sensitive abridged version of this instrument. Teisl and colleagues reported a 100% level of sensitivity and specificity of the sensitized screening tool for FraX, among preschoolers, in a matched sample of 110 children. A detailed report of the study was presented in Chapter 2.

Child Behavior Checklist

The *CBCL - Ages 1-1/2 years to 5 years* (Achenbach, 2001) was completed for children aged 25-71 months, whereas the *CBCL - Ages 6-18* (Achenbach, 2001) was completed for children older than 71 months. The *CBCL* was designed to facilitate the ability to empirically address child behavior problems. The *CBCL/6-18* checklist consists of 118 items related to child behavior, on a 3-point scale: "0= Not True; 1 = Somewhat or Sometimes True; 2 = Very True or Often True." The *CBCL* has been used in more than 1,000 research studies (Achenbach, 2001). Test-retest reliability was .93; inter-parent agreement was .76 (Achenbach, 2001). The *CBCL/6-18* scoring profile provides raw scores, *T* scores, and percentiles for three competence scales (*Activities, Social, and School*), Total Competence, eight cross-informant syndromes, and Internalizing, Externalizing, and Total Problems. Internal consistency for the Internalizing, Externalizing, and Total Problems scales was .80, .94, and .94, respectively (Achenbach, 2001).

Family Background Information Form

Key demographic data were collected with the *Family Background Information Form*. The researcher requested information about age, gender, marital status, level of

educational attainment, and total number of children to facilitate interpretation of the data analyzed.

Buccal Cell Swabs

Parents collected *buccal (cheek) cell swab samples* for his or her child so that DNA might be extracted for the analysis of the FMR-1 gene, using a polymerase chain reaction procedure.

Study II

Revised Biopsychosocial Screening Inventory for Fragile X (RBIPSSI-FX)

The *RBIPSSI-FX* is a computerized 49-Item Likert scale-like instrument, consisting of five subscales: *Developmental milestones*, *Physical, Social /Behavioral*, *Cognitive*, and *Biological Parent* (see Appendix G). The principal investigator revised the *BIPSSI-FX* in accordance with the outcomes of Study I and the recommendations of expert reviewers (Lachiewicz, 2003; Mazzocco, 2003; Scambler, 2003). These revisions are discussed in Chapter 4, following the results of the data analyses of Study I.

Modified Checklist for Autism in Toddlers *(M-CHAT)*

The M-CHAT (Robins et al., 2001a), a parent response checklist screening for maladaptive behaviors in toddlers, is an extension of the *Checklist for Autism in Toddlers (CHAT*, Baron-Cohen, Allen, and Gillberg, 1992), which was established to detect autism at 18 months of age (see Appendix I). The *CHAT* consists of nine items requiring parent response and five items which require a health professional's observation. Baron et al randomly selected a group of 18 month olds (n = 50) and group of younger siblings of children with autism (n = 41). The following nine areas commonly identified in children with autism comprised the questionnaire: play, socialization, motor development, social

interest, pretend play, protoimperative pointing, protodeclarative pointing, functional play, and joint-attention. The study revealed that key psychological predictors of autism at 30 months are evident at 18 months of age. The sensitivity of the *CHAT* to correctly identify autism was 38% and the specificity for identifying childhood autism was 98%. Similar findings of the efficacy of the *CHAT* have been demonstrated in studies of more than 16,000 toddlers. (American Academy of Pediatrics Committee on Disabilities, 2001; Baird et al., 2000; Baron-Cohen et al., 1996). Furthermore, the *CHAT* is widely endorsed as an entity of screening protocols for toddlers suspected of having developmental delay (American Academy of Pediatrics Committee on Disabilities, 2000; Bailey et al., 2001; Filipek et al., 2000).

A major limitation of the *CHAT* is the required observation of a health care professional or human development specialist. The literature is replete with references of the pivotal role that parents play in diagnosing developmental disabilities in their child. Parents identify key concerns in the child's development several months to years before a developmental specialist or health care professional diagnoses the child to have a developmental disability (Bailey, 2000; DeGiacomo, & Fombonne, 1998; Siegel et al., 1988; Young, Brewer, & Pattison, 2003). Consequently, Robins, et al. (2001a) developed a parent-completed instrument to screen for autism.

The *M-CHAT* (Robins et al., 2001a), consists of 23 yes/no items and was designed to evaluate the 9 parent-response items of the *CHAT* and 21 new items added to broaden the symptoms and to identify additional pervasive developmental delays. In an initial study, the *M-CHAT* was used to screen 1,293 children of ages 18 to 30 months. Fifty-eight were later given a diagnostic developmental evaluation and 39 were diagnosed with

a disorder on the autism spectrum. Reliability was determined by computing Cronbach's alpha for the 22-item checklist as well as for the subset of the six most discriminating items. Internal consistency was $\alpha = .85$ for the entire checklist and $\alpha = .83$ for the six critical items that discriminate autistic from non-autistic children. A follow-up study found a slightly lower level of internal consistency for the total checklist and the six critical items, .76 and .74, respectively (Robins, 2003).

Criterion validity of the *M-CHAT* was demonstrated by a Discriminant Function Analysis (DFA) of nonautistic and autistic children. The DFA correctly classified 33 out of the 38 children with autism and misclassified as autistic 8 of the 1196 children who had not received a diagnosis of autism. Sensitivity, specificity, positive and negative predictive power were calculated as .87, .99, .80 and .90, respectively. Longitudinal studies are being conducted to further evaluate criterion validity of the *M-CHAT* (Robins, 2003). The primary investigator obtained permission from the authors to use the *M-CHAT* in this study (see Appendix H).

Primary Caregiver Information Form

This form requested the following demographic information from parents: race or ethnic group, gender, age, relationship to the child, state or province, country, level of educational attainment, annual household income, religious affiliations, and source of support. The data collected are consistent with those collected in Squire and colleagues' (2001) study of the efficacy of a parent-completed tool to identify social and emotional problems in young children.

Diagnosis Information Form

This form was used to facilitate placement of the respondent information in the most appropriate diagnostic group as well as appropriate exclusion of those who do not meet the inclusion criteria of the study (see appendix K).

Data Analysis Plan

The six hypotheses were analyzed as follows:

Hypothesis 1, that the *BIPSSI-FX* measured FMR-1 gene mutation "at risk" status in young children validly, as indicated by concurrent validity with the *CBCL* and the *CGSQ-FX* (Study I), was evaluated by *Pearson's r*.

Hypothesis 2, that the *BIPSSI-FX* measured FMR-1 gene mutation "at risk" status in young children reliably, as indicated by test-retest reliability (Study 1) and internal consistency (Study I, Study II), was tested by *Pearson's r* and *Cronbach's alpha*, respectively;

Hypothesis 3, that children with FMR-1 gene mutation scored significantly higher on the *BIPSSI-FX* than children without the gene mutation (Study II), was evaluated by a *t-Test*. The t-test is an appropriate test to answer this hypothesis in that the independent variable (presence versus absence of FraX) has only two levels.

Hypothesis 4, that children with FMR-1 full mutation scored higher on the *BIPSSI-FX* than children who have other types of developmental disabilities (Study II), was evaluated using a *one-way ANOVA*. Although the *one-Way ANOVA* provides the same information as the *t-Test*, *ANOVA* is the appropriate statistical test in that this study only investigates one independent variable, but more than two group means were analyzed. This study used a fixed-effect between-subject design. The level of significance

selected for this study is $p < .05$. This level of significance was deemed appropriate because of the cognitive/behavioral nature of the data collected. Because the means of three groups were compared in this study, *Scheffé* post-hoc tests were used for comparisons for which samples met the assumption of homogeneity of variance. *Tamhane* post-hoc tests were used in comparisons of samples for which Levine's test for homogeneity of variance revealed significant differences in variance between samples.

Hypothesis 5, that parents of children with the FMR-1 gene mutation scored higher on the *BIPSSI-FX Biological Parent Subscale* than parents of children without the gene mutation (Study II), was evaluated using a *t-Test.*

Hypothesis 6, that children with FraX differed from those with autism, PDD, and Asperger syndrome more on the *BIPSSI - FX* than on the *M-CHAT* (Study II), was answered using *two independent one-way ANOVAs.*

CHAPTER FOUR

RESULTS

Frequencies and means for the demographic data for Study I and Study II were presented in Chapter 3. Presented in this chapter are data analyses and interpretations to address each of the six hypotheses.

Hypothesis One

The *BIPSSI-FX* will measure FMR-1 gene mutation "at risk" status in young children validly, as indicated by concurrent validity with the *CBCL* and the Consensus Questionnaire for Fragile X.

Study I. The concurrent validity of the *original BIPSSI-FX* was assessed by comparing the results with those obtained on the *Child Behavior Checklist (CBCL)* and the *CGSQ-FX*. The validity of the *Original BIPSSI-FX* was assessed by comparing the results with those obtained on the *CBCL* (Achenbach, 2001*).* An acceptable level for Pearson's r correlations was set a priori at .70.

Each subscale of the *BIPSSI-FX* significantly correlated with the total scale score of the *CGSQ – FX*; however only one subscale, the *Social and Behavioral Subscale* was correlated highly, $r = .93$, $p < .0001$. The finding was anticipated in that the *Social and Behavioral Subscale* is an adaptation of the 11 social and emotional items of the *CGSQ – FX* (see Table 4). The *BIPSSI-FX* however, includes descriptors of the scoring continuum. The *Developmental Subscale* showed a moderate correlation of $r = .51$ and the *Cognitive Subscale* showed a moderate correlation ($r = .53$). The construction of the *BIPSSI-FX* is more parallel to the C*BCL* in consideration of the *Social and Behavioral*

aspects of FX than other subscales of the *BIPSSI-FX*. This point could account for the lack of correlation of the other four subscales of the *BIPSSI-FX* to the *CBCL*.

Table 3

Correlations between BIPSSI-FX Time 1, CGSQ-FX, and CBCL

Variables	*CGSQ* Total	*CBCL* Internal T Score	*CBCL* External T-Score	*CBCL* Total T
BIPSSI Developmental	.51*	.18	.36	.31
BIPSSI Physical	.19	.25	.14	.18
BIPSSI Social and Behavioral	.93**	.73**	.83**	.84**
BIPSSI Cognitive	.52**	.2	.4*	.24
BIPSSI Biological Parent	.19	.48*	.31	.42*
BIPSSI-FX Total	.90**	.71**	.76**	.77**

*p<.01 **p<.001

Hypothesis Two

The *BIPSSI-FX* will measure FMR-1 gene mutation "at risk" status in young children reliably as indicated by test-retest reliability (Study 1) and internal consistency.

Study I. Data collected from the repeated administration of *the BIPSSI-FX* in Study I were evaluated for *test-retest reliability* by use of the *Pearson's r* correlation coefficient with levels set at .70.

Table 4

Test-Retest Reliability Original BIPSSI-FX

Time 2 ⟶ / Time 1 ↓	*Developmental*	*Physical*	*Social Behavioral*	*Cognitive*	*Biological Parent*
Developmental	.68**	.52**	.60**	.54**	.18**
Physical	.58**	.69**	.38	.33	.10
Social/Behavioral	.49*	.47*	.93**	.68**	.11
Cognitive	.66**	.36	.46*	.62**	.18
Biological Parent	-.30**	-.26	.08	-.06	.76***

Note: N=27 at Time 1 and N=24 at Time1. *p < .05 ** p< .001

The highest degree of stability over time was manifested in responses to the *Social and Behavioral Subscale*, r= .93, p<. 0001. A high level of stability was also seen in the *Biological Parent Subscale*, in that the responses from the first testing were highly correlated with those of the second testing, r= .76, P. < .0001.

Reliability of the *Original BIPSSI-FX* was further appraised by analyzing the total scale and each subscale for internal consistency by the computation of *Cronbach's alpha,* as is shown below in Table 5 for time 1 and Table 6 for time 2.

Table 5

Cronbach's Alpha for the Five Subscales of the Original BIPSSI-FX – Time 1 (N=27)

Subscale	Alpha	Standardized Item Alpha
Developmental	.81	.82
Physical	.28	.36
Social- Behavioral	.95	.95
Cognitive	.89	.91
Biological Parent	.61	.62
Total Scale	.91	.92

The *Cognitive Subscale* revealed a high level of internal consistency, alpha = .89. However, the elimination of item number one ("has your child ever had placement in "gifted" class programs or received information that he or she is unusually bright?") would increase the overall scale alpha to .98. None of the other items, if deleted, would enhance the overall alpha. The items of the *Biological Parent* Subscale revealed a moderate level of internal consistency, $\alpha = .61$. Eliminating item 10 ("has anyone in the father's family had mental retardation") would enhance the alpha to .68.

Table 6

Cronbach's Alpha for the Five Subscales of the Original BIPSSI-FX – Time 2 (N=23)

Subscale	Alpha	Standardized Item Alpha
Developmental	.78	.78
Physical	.29	.34
Social- Behavioral	.91	.95
Cognitive	.83	.89
Biological Parent	.44	.39
Total Scale	.94	.94

Disclosing the presence of mental retardation in ones' family tends to be difficult, therefore it is highly plausible that item number 10 had an associated social desirability aspect. Therefore, the researcher combined items 9 and 10 to address both the mother and the father in the revised tool to decrease reluctance of a parent to respond accurately. Additionally, items 11 and 12; 6 and 7; along with items 3 and 4 were combined in the revised *BIPSSI-FX* to eliminate the aforementioned social desirability factors. Combining these items reduced the problem of social desirability because the respondent may respond honestly without having to specifically acknowledge challenges in the respondent's own biological family. The respondent is aware that an honest response could be interpreted as reflective of either biological parent's blood family. Additionally, the researcher reworded item 5 in a manner in which both the biological mother and the

biological father are addressed. These changes could possibly decrease social desirability factors and thereby increase the accuracy of the internal consistency of the *Biological Parent Subscale*.

Study Two. *D*ata obtained by the *Revised BIPSSI-FX* were analyzed and evaluated for aspects of internal consistency by conducting a Cronbach's alpha (see Table 7). The internal consistency for the *Developmental Subscale*, *Social-Behavioral* and *Cognitive Subscales* were acceptable. However, the internal consistency of the *Biological Parent Subscale* was lower than desired. In the SPSS output for *Reliability Analysis*, the *Alpha If Item Deleted Scale* revealed that deleting item 3 would enhance the *Biological Parent Subscale* internal consistency to .60, which is acceptable. Therefore item 3 "Have any women in the birth mother's blood family or the birth father's blood family, had cysts on the ovaries, cysts removed from the ovaries, or hysterectomy (removal of the uterus)?" was deleted from the Biological Parent Subscale of the *Revised BIPSSI-FX*. However, the internal consistency of the *Physical Subscale* was .43, which is not acceptable. Furthermore, the elimination of no item would increase the level of internal consistency of the subscale. The researcher considered the level unacceptable; therefore, she eliminated the *Physical Subscale* from the *Revised BIPSSI-FX* in subsequent analyses.

Table 7

Cronbach's Alpha for the Five Subscales of the Revised BIPSSI-FX

Subscale	Alpha	Standardized Item Alpha
Developmental	.67	.67
Physical	.43	.42
Social- Behavioral	.89	.89
Cognitive	.84	.84
Biological Parent	.60	.58
Total Scale	.90	.88

Hypothesis 3

Children with FMR-1 gene mutation will score significantly higher on the *BIPSSI-FX* than children without the gene mutation.

Study Two was conducted to address hypotheses three through six as well as some aspects of hypothesis two. A t-Test of the mean scores of children who have the FMR-1 gene mutation compared to those who do not, revealed a highly significant difference as is depicted in Table 8 below.

Table 8

t-Test of BIPSSI-FXby FMR-1 Gene Status

Gene Status	*n*	*M*	*SD*	*t*	*df*	*p*
FraX-FM	43	78	12.17			
Non-FraX-FM	282	69.35	14.55			
				3.7	323	.000

The differences between the mean scores of the children with FMR-1 gene full-mutation and the children without the gene changes were further analyzed by t-Tests on the four subscales of the *BIPSSI-FX* as is shown in Table 9. *Levene's* test for equality of variances showed that in two subscales the assumption of homogeneity of variance was violated. Therefore, the SPSS computer program adjusted the results shown below to account for the lack of homogeneity of variance, as is designated by a superscript.

Table 9

t-Test of BIPSSI-FX Subscales by FMR-1 Gene Status

	t	*df*	*p*	Mean difference
Cognitive Subscale [a]	2.87	69.11	.005	2.02*
Developmental Subscale	4.55	343	.000	2.16**
Biological Parent [a]	-.67	69.59	.505	-.24
Social Behavioral Subscale	3.12	330	.002	4.72*

[a] Equal variances not assumed * p< .001 **p<. 0001.

The t-Tests revealed that significant differences exist among the children with the FMR-1 gene changes, from those without the gene changes. However, this analysis did not compare subgroups of children without the FMR-1 gene (e.g., autistic children, children with PDD-NOS). Therefore, analyses to detect these differences are addressed in the report of results in Hypothesis 4.

Hypothesis 4

Children with FMR-1 full mutation will score higher on the *BIPSSI-FX* than children who have other types of developmental disabilities.

The scores of children with FMR-1 full mutation on the *BIPSSI-FX* were compared with those of children who have Down syndrome, autism, PDD-NOS, Asperger, and children who have no diagnosed disability (Study II), using a *one-way ANOVA* as is depicted in Table 10 and Figure 1. The dependent variable was total score on the *BIPSSI - FX* and the independent variable was diagnostic group with six levels: FraX full mutation, Down syndrome, autism, PDD-NOS, Asperger, and no diagnoses.

Since the means of six groups were compared in this study, *Scheffe' post-hoc* comparisons were conducted to determine differences among groups when the *Levene* test not significant. However, when the *Levene* test revealed heterogeneity of variance, a *Tamhane* post hoc test was conducted, as this test adjusts for inequality of variance among groups. Additionally, the *Tamhane* post hoc is a more conservative test compared to the *Dunnett*, thus decreasing the likelihood of a Type I error.

Table 10

ANOVA on BIPSSI-FX Full Scale Scores by Diagnosis Group

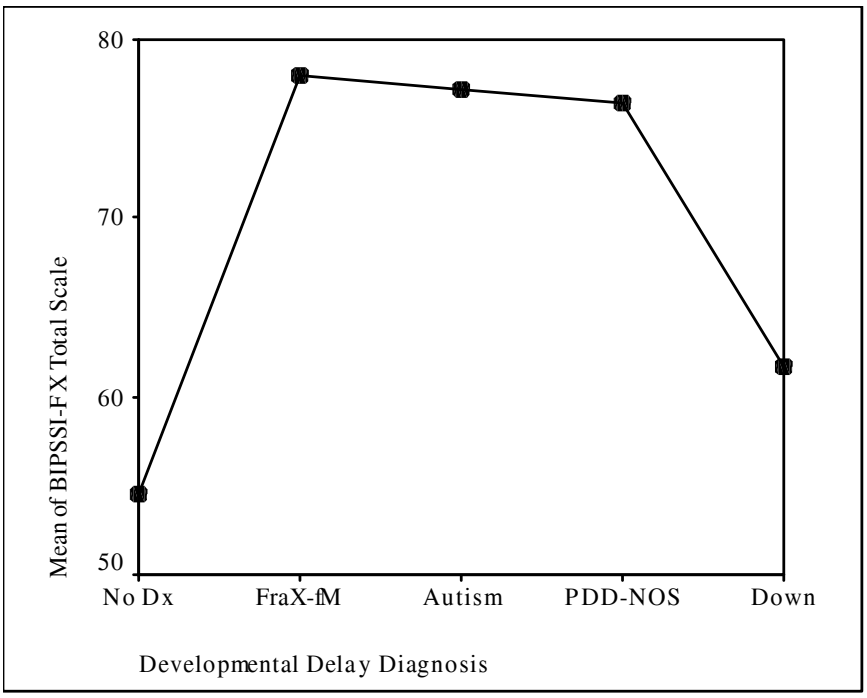
Diagnostic Group	N	M	Mean Difference	SD	F
No diagnosis	33	54.52	23.48***	11.14	
FraX - full mutation	43	78.00	_____	12.17	
Autism	84	77.26	.74	9.73	
PDD-NOS	63	76.38	1.62	10.81	
Down	90	61.72	16.28***	14.15	
Total		70.32			42.49***

[a]Scheffe, [b]Tamhane, *p < .05, ** p < .001, *** p < .0001

The mean total scores on the *BIPSSI-FX* were higher for FraX-FM than those of each of the other groups. However, post hoc tests elucidated that *BIPSSI-FX* scores of the FraX-FM group were significantly different only from the normative group and the children with Down syndrome. There was no significant difference in overall scores between the FraX-FM group and autistic or PDD-NOS groups. The mean *BIPSSI-FX* total scores of the five groups of children are depicted in Figure 1 below.

Figure 1

Graph of BIPSSI-FX Full Scale Mean Scores



The children with FraX had the highest mean score followed by children with autism. Post hoc analyses indicated that the scores were significantly different only with the Down Syndrome group and the group of children with no diagnosed developmental delay.

The difference in the mean *BIPSSI-FX* scores of the children with FraX-FM from children without the gene changes were further analyzed by *ANOVA* on the four subscales of the *BIPSSI-FX* as is shown below in Tables 11-14 and Figures 2-5. The *Levene's* test for equality of variances showed that in two subscales the samples significantly violated the assumption of homogeneity of variance. *Tamhane* post hoc tests were conducted in those situations to adjust for the lack of homogeneity of variance and as is designated by a superscript.

Table 11

ANOVA on BIPSSI-FX Developmental Subscale by Diagnosis Group Compared with FraX Full Mutation

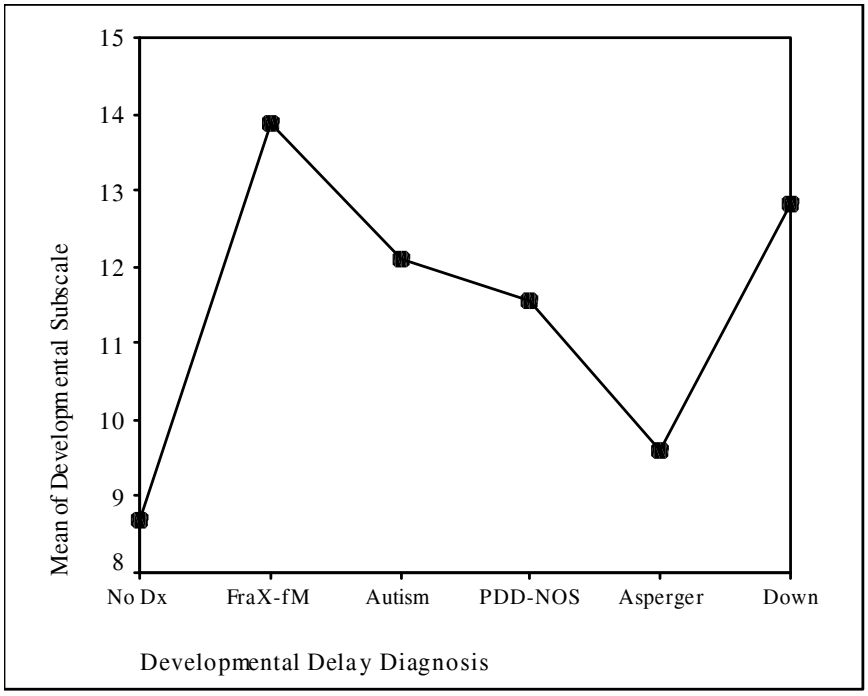
Diagnosis group	*n*	*M*	Mean Difference	*SD*	*F*	*P*
No Diagnosis[b]	34	8.76	5.19***	2.74		.000
FraX-FM	46	13.89	___	2.86		
Autism [a]	90	12.1	1.79*	2.77		.027
PDD-NOS [a]	65	11.57	2.32**	2.78		.002
Asperger [a]	12	9.58	4.31**	3.09		.007
Down [b]	78	12.19	1.08	2.65		.448
Total	345	12.02		3.08	17.92	.000

[a]Scheffe, [b]Tamhane,*p < .05, ** p < .001, *** p < .0001

The mean *BIPSSI-FX Developmental Subscale* scores of the five groups of children depicted in Figure 2 shows that the children with FraX experienced greater delays in achieving developmental milestones than any of the other groups of children. Children with no diagnosed disabilities scored lower on the *Developmental Subscale* than any of the other groups of children.

Figure 2

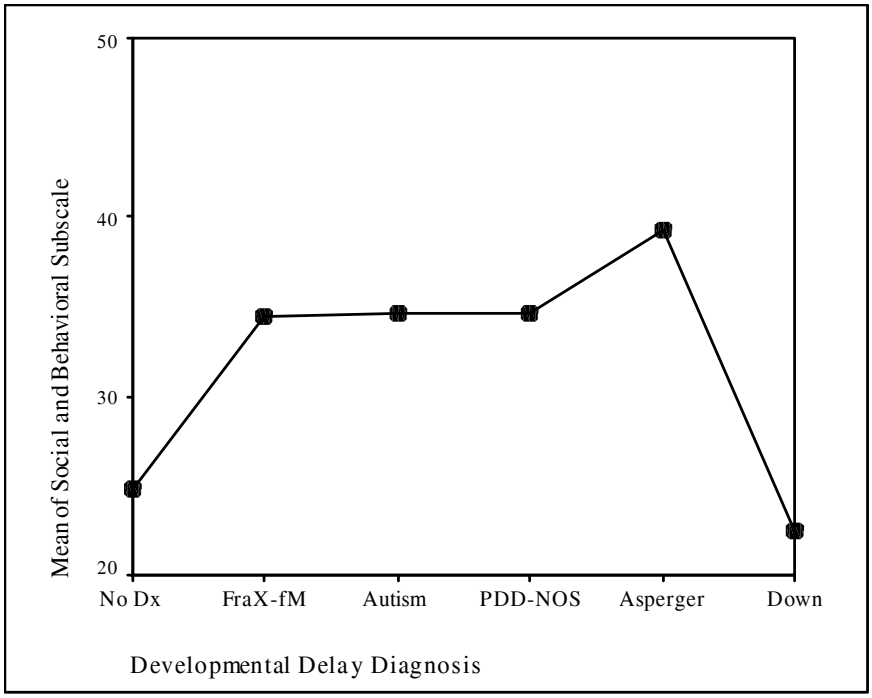
Graph of BIPSSI-FX Developmental Subscale Mean Scores by Diagnosis Group



The mean *BIPSSI-FX Social and Behavioral Subscale* scores of the five groups of children depicted in Figure 3 shows that the children with Asperger experienced greater social and behavioral challenges than any of the other groups of children. However, the mean scores of children with FraX were the next highest.

Figure 3

Graph of BIPSSI-FX Social Behavioral Subscale by Diagnosis Group



The difference in the mean *Social and Behavioral* scores of the children with FraX-full mutation from the groups of children without the gene changes were further analyzed by *ANOVA* as is shown below in Table 12. Post hoc analyses revealed that the parents of a child with FraX-full mutation reported significantly greater social and behavioral challenges in their affected child than did the parents of children with Down syndrome and those of children with no diagnosed disability. Although the parents of children with Asperger appraised their child's social and behavioral challenges as greater than those of the parents of children with FraX-full mutation, the difference was not significant.

Table 12

ANOVA on BIPSSI-FX Social Behavioral Subscale by Diagnosis Group Compared with FraX-Full Mutation

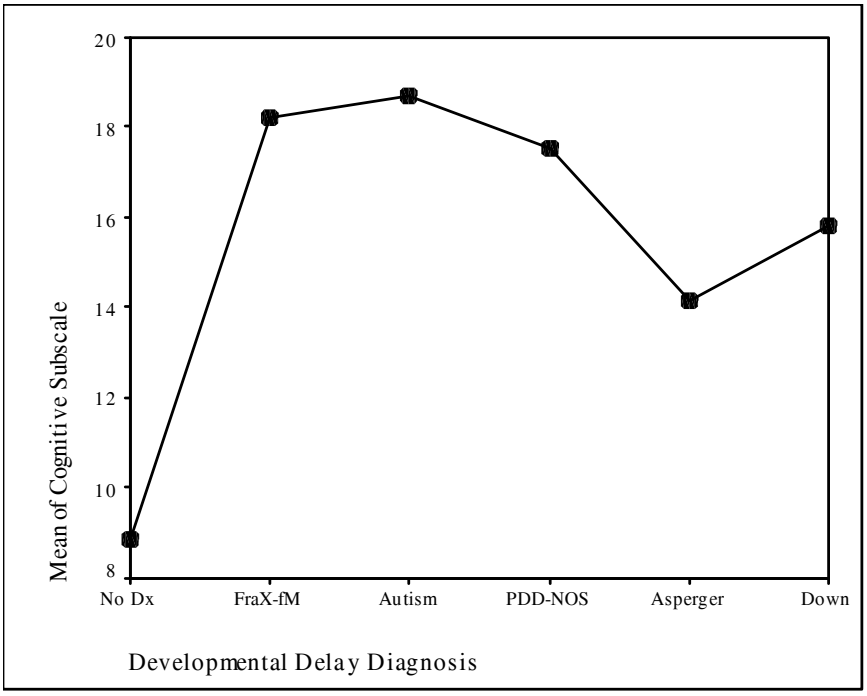
Diagnosis group	*N*	*M*	Mean Difference	*SD*	*F*	*P*
No diagnosis [a]	33	24.81	9.65***	6.24		.00
FX-FM	43	34.47	____	8.32		____
Autism	87	34.67	-.20	6.42		1.00
PDD-NOS	63	34.54	-.08	7.99		1.00
Asperger	12	39.25	-4.79	9.55		.57
Down [a]	94	22.49	11.98***	7.55		.00
Total	332	30.36		9.40	40.71	.00

[a]Scheffe, * $p < .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$

The mean *BIPSSI-FX Cognitive Subscale* scores of the five groups of children depicted in Figure 4 shows that children with autism experienced greater cognitive challenges in comparison with children with FraX-full mutation. The scores of children with no diagnosed disability were lower than the scores for all other groups of children with disabilities.

Figure 4

Graph of BIPSSI-FX Cognitive Subscale Mean Scores by Diagnosis Group



The results of post hoc analyses shown in Table 13 revealed that the mean *Cognitive Subscale* scores of the children with FraX-full mutation differed significantly from those of children with no diagnosed disability. Additionally, the group of children with Asperger showed significantly stronger cognitive abilities than the children with FraX-full mutation.

Table 13

ANOVA on BIPSSI-FX Cognitive Subscale by Diagnosis Group Compared with FraX–Full Mutation

Diagnosis group	*N*	*M*	*Mean Difference*	*SD*	*F*	*p*
No diagnosis [b]	33	8.85	9.40***	4.55		.000
FraX full mutation	45	18.24	_____	4.21		_____
Autism	89	18.89	-.44	3.87		1.00
PDD-NOS	65	17.55	.69	3.54		.999
Asperger [b]	12	14.17	4.08*	3.49		.037
Down Syndrome	97	15.83	2.41	6.02		.098
Total	341	16.49		5.38	24.98	.000

[b]Tamhane,
* $p < .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$

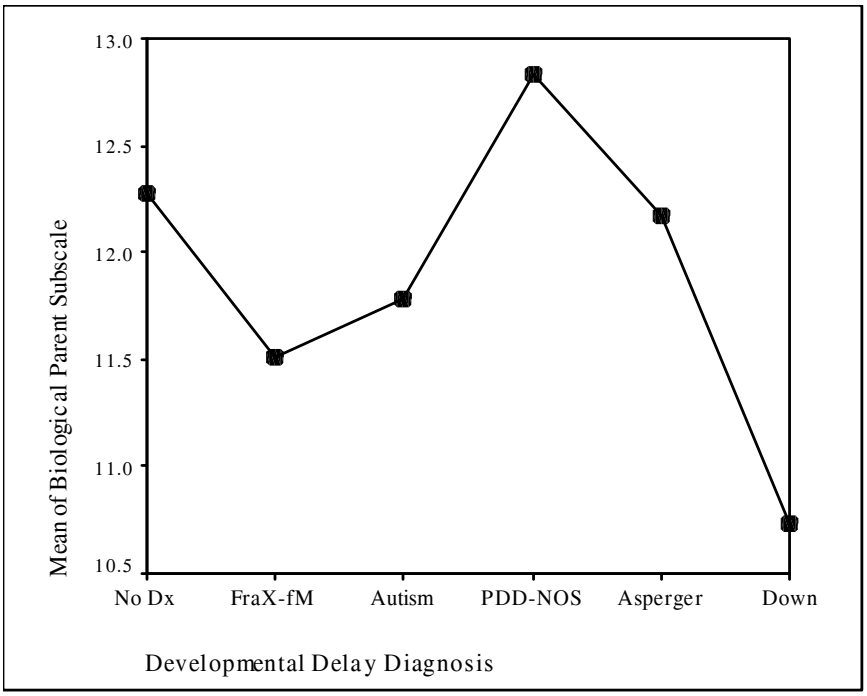
Hypothesis 5

Parents of children with the FMR-1 gene mutation will score higher on the *BIPSSI-FX Biological Parent Subscale* than parents of children without the gene mutation.

BIPSSI-FX Biological Parent Subscale scores of parents of children with the FMR-1 gene mutation were compared with those of parents of children without the gene mutation by conducting a *t-Test* as is shown in Figure 5 and Tables 14 and 15.

Figure 5

Graph of BIPSSI-FX Biological Parent Subscale Mean Scores by Diagnosis Group



Surprisingly the parents of children with FraX scored lower on the *Biological Parent Subscale* than the parents of children in each of the autism spectrum disorders. Furthermore, the scores of the parents of children with no diagnosed disabilities were higher than those of the parents of children with FraX. Foster parents were eliminated from the study in an effort to prevent the challenge of non-biological primary caregivers trying to address questions without adequate knowledge of the child's biological family, but adoptive parents were retained.

Table 14

t-Test on BIPSSI-FX Biological Parent Subscale by FMR-1 Gene Status

Gene Status	*N*	*M*	*SD*	*t*		*p*
FraX-FM	43	78	12.17			
Non-FraX-FM	282	69.35	14.55			
				-.67	69.59	.505

Table 15

ANOVA on BIPSSI-FX Biological Parent Subscale by Diagnosis Group Compared with FraX Full Mutation

Diagnosis group	*n*	*M*	Mean Difference	*SD*	*F*	*p*
No diagnosis	33	12.27	-.76	3.57		.989
FraX full mutation	43	11.51	_____	2.07		
Autism	85	11.78	-.27	2.88		1.00
PDD-NOS	63	12.83	-1.31	2.79		.093
Asperger	12	12.17	-.66	3.35		1.00
Down	90	10.73	.78	2.30		.55
Total	326	11.72		2.80	4.85	.000

**** $p < .0001$

There were no significant differences on the mean *BIPSSI-FX Biological Parent Subscale* score*s* between the parents of children with the FMR-1 gene mutation and those of the parents of the children without the FMR-1 gene mutation.

Hypothesis 6

Children with FraX will differ from those with autism, PDD, and Asperger syndrome more on the *BIPSSI - FX* than on the *M-CHAT*. The group of children with Asperger Syndrome was excluded from the analyses due to a sample size of only n=12.

Two independent *One Way ANOVA*'s were conducted to compare the ability of the *BIPSSI - FX* and the *M-CHAT* to differentiate children with FraX from those with autism, and PDD-NOS as is shown below in Table 16. The mean group *M-CHAT* scores are depicted by Figure 6. Total *M-CHAT* scores are inversely related to the risk for autism, whereas *BIPSSI-FX* scores were designed to be positively related to FraX "risk."

Figure 6

Graph of M-CHAT Mean Scores by Diagnosis Group

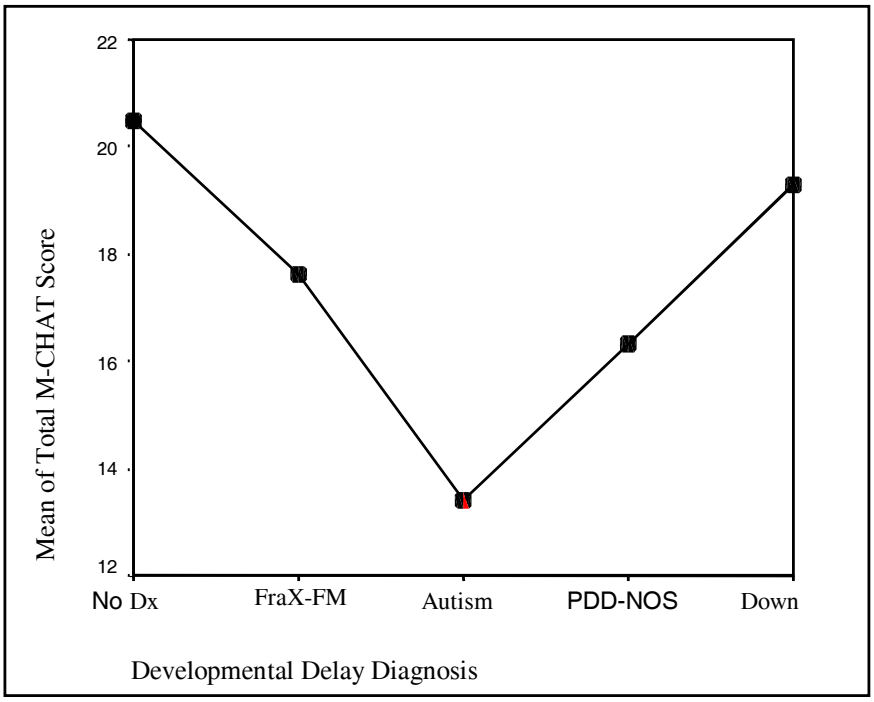


Table 16

ANOVA on M-CHAT by Diagnosis Group Compared to ANOVA on BIPSSI-FX by Diagnosis Group

Diagnosis group	*n*	*M*		SD		Mean Difference	
		M-CHAT	*BIPSSI-FX*	*M-CHAT*	*BIPSSI-FX*	*M-CHAT*	*BIPSSI-FX*
No DX	33	20.52	54.52	4.05	11.14	-2.88*	23.48***
FX-FM	43	17.63	78.00	3.38	12.18	___	___
Autism	83	13.39	77.26	3.38	12.17	4.23***	.738
PDD-NOS	61	16.33	76.38	4.16	9.73	1.3	1.62
Down	90	19.28	61.72	4.35	10.81	-1.65	16.28***
Total	310	17.03	70.32	4.62	14.65	____	____
						F=33.11*** df 4;304	F=42.48** df=4;308

The FraX group *M-CHAT* mean scores differed significantly from those of the Autism group. However, although the FraX group scored higher on the *BIPSSI-FX* than the Autism group the differences were not significant. The scores of the No diagnosis group on the *M-CHAT* differed significantly from those of the FraX group, however, the magnitude of the differences between these groups was greater on the *BIPSSI-FX*. Furthermore, the mean *BIPSSI-FX* scores of children with Down Syndrome differed

significantly from those of the children with FraX, whereas, this difference was not manifested by the *M-CHAT* mean score.

CHAPTER FIVE

DISCUSSION

A discussion of the results of the reliability and validity testing of the *BIPSSI-FX* and the ability of the *BIPSSI-FX* to differentiate among children with FraX from children with other developmental disabilities and children with no diagnosed disability is presented in this chapter. The findings of the current study are compared and contrasted with previous findings, which are presented under each hypothesis. Explanations of unexpected findings as well as limitations of the study are presented. Finally presented are research implications.

Interpretation of Findings

Hypothesis One

Hypothesis 1 stated that the *BIPSSI-FX* would measure FMR-1 gene mutation "at risk" status in young children validly, as indicated by concurrent validity with the *CBCL* and the *CGSQ-FX*. The findings generally supported the potential of the *BIPSSI-FX* to be a reliable and valid screening tool for FraX at risk status. However, the small sample small size and the homogeneity of the sampling inhibited the appraisal of the efficacy of the tool. This hypothesis was confirmed in that each subscale of the *BIPSSI-FX* was significantly correlated with the total scale score of the *CGSQ-FX*. However only one subscale, the *Social and Behavioral Subscale* was correlated highly. The researcher

anticipated this result, in that the 19-item *Social and Behavioral Subscale* is an adaptation of the 11-item social and emotional subscale of the *CGSQ-FX*. The *BIPSSI-FX* however, includes descriptors of the scoring continuum to facilitate clarity and consistency in the respondents' interpretation of what constitutes "A little," "A lot," or "Not at all."

The *Social and Behavioral Subscale* of the *BIPSSI-FX* correlated with the *CGSQ-FX* and with each *CBCL* subscale, except for the *Externalizing T score* of the *CBCL.* This *BIPPSI-FX* subscale measures behavior associated with children with FraX, which includes social withdrawal, anxiety, and depression. These findings concur with those of Hessl and colleagues (2001) in that girls with FraX exhibited internalizing behaviors (social withdrawal, anxious, and depressed behavior) when they used the *CBCL* to assess internalizing behavior.

The *Biological Parent Subscale* of the *BIPSSI-FX,* which is a measure of the parents' psychological functioning, was moderately correlated with both the internalizing T score and the total score for their children on the *CBCL.* This indicates that the *Biological Parent* Subscale is a potential useful diagnostic tool in the early identification of children with FraX. This result is congruent with the results of Hessl et al.'s (2001) study of the influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with FraX. In their investigation of 80 boys and 40 girls with FraX full mutation and their unaffected siblings, they found that parental psychological problems correlated with the *Internalizing* and *Externalizing Scales* of the *CBCL* for boys with FraX.

The *BIPSSI-FX Full Scale* was highly correlated with the *CGSQ* and moderately correlated with both the *Internalizing Scale* and the *Externalizing Scale* of the *CBCL* as

well as the total *CBCL* score. According to Carter's (2003) meta-analytic review of various types of reliability coefficients and test types and the recommended standards (Pearson's *r* Coefficient of .70) the coefficients for the *BIPSSI-FX* were acceptable, therefore, hypothesis one was confirmed.

Hypothesis Two

Hypothesis 2 stated the *BIPSSI-FX* would measure FMR-1 gene mutation "at risk" status in young children reliably, as indicated by test-retest reliability and internal consistency. The researcher recruited an international sampling of parents from racially, geographically, and socioeconomically diverse backgrounds by using a unique sampling scheme during the second study. In this study, data were collected by Internet and automatically received into an Access database, which resulted in a larger and more representative sample in comparison to the sample of the first study. See the detailed sample description in Chapter 3.

A moderate correlation was shown on the *Cognitive Subscale* of the *BIPSSI-FX* at test retest while the *Developmental* and the *Physical Subscale* of the *BIPSSI-FX* were highly correlated at test retest. The correlation between the *Physical Subscale* of the *BIPSSI-FX* on test retest reliability revealed a slightly higher correlation than the correlation *on the Developmental Subscale*. The correlation of the *Biological Parent Subscale* of the *BIPSSI-FX* was slightly higher than the previous subscales. Finally, the highest degree of stability was manifested in the *Social and Behavioral Subscale* of the *BIPSSI-FX*.

These results support hypothesis two in that the scale is stable over time. Test retest reliabilities were not conducted on other FraX screening tools, by Teisl and

colleagues (1999), Lachiewicz and colleagues (2000), and de Vries and colleagues (1996), therefore comparison data are unavailable. However, the reliability of the current study is comparable to the test retest reliability of associated parental response tools such as the *CBCL* and *M-CHAT*, .80 and .76-.72, respectively.

The reliability of the *BIPSSI-FX* was further appraised by analyzing each subscale and the total score at both the first and repeat administration during Study I and initial testing during study II. The level of internal consistency was acceptable both overtime within the same sample (Study I) and between samples (Study 1 and Study II). Furthermore, the reliability of the current study is comparable to the test retest reliability of other checklists for FraX, such as, Maes et al.(2000) .84 for the total checklist and .82 for the behavioral features.Therefore, hypothesis 2 was confirmed.

The *Social Behavioral Subscale* and the *Cognitive Subscale*s of the *BIPSSI-FX* revealed a high level of internal consistency while the Developmental Subscale showed an acceptable level of internal consistency. However, the internal consistency of the Biological Parent Subscale was questionable and the Physical Subscale had an unacceptably low level.

Perhaps, the subtlety of the physical features of FraX, which has been widely reported (Lachiewicz et al., 2000; Bailey, et al., 2002; Hagerman, 2002) contributed to the low internality consistency of the Physical Subscale. In boys, specific physical characteristics such as an elongated face, large head, and prominent ears are typically present by age 8 (Stoll, 2001). The physical characteristics of girls are generally normal, although some girls share some of the features with boys, such as a long face and prominent ears (Butler, Pratesi, Watson, Breg, & Singh, 1993; Hagerman, 2002).

Nonetheless, this researcher, like other researchers attempted to elucidate these subtleties in an attempt to facilitate early identification of children with FraX (Lachiewicz et al, 2000; Hagerman, 2002). Although, physical characteristics are variable in females and in prepubertal males (Reiss & Dant, 2003) recent studies have increasingly revealed distinguishing physical characteristics of FraX in toddlers (Lachiewicz et al., 2000).

Hypothesis Three

Hypothesis 3 stated children with FMR-1 gene mutation would score significantly higher on the *BIPSSI-FX* than children without the gene mutation (Study II). The children with the FMR-1 gene mutation scored significantly higher on the *BIPSSI-FX* Full Scale than children without the FMR-1 gene changes; therefore, Hypothesis 3 was confirmed. A detailed discussion of the interpretation of these findings is presented in the discussion of hypothesis 4.

Hypothesis Four

Hypothesis 4 stated that children with FMR-1 full mutation would score higher on the *BIPSSI-FX* than children who have other types of developmental disabilities. Children with the FMR-1 full mutation (FraX-fM) scored higher on the *BIPSSI-FX* than the groups of children with other developmental disabilities. The children with FraX had the highest mean score followed by children with autism spectrum disorders. The mean *BIPSSI-FX Full Scale* score for the group of children with Down syndrome was the lowest of each of the groups of children with diagnosed developmental delay. A Post Hoc test elucidated that mean *BIPSSI-FX Full Scale* score of the FraX-FM group were significantly different from only the mean *BIPSSI-FX Full Scale* scores of the normative group and the group of children with Down syndrome. There was no significant difference in overall scores

between the FraX-fM group and autism, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), or Asperger groups. Therefore, the *BIPSSI-FX* correlated with Down syndrome, but not with PDD-NOS, autism, or Asperger. This finding is consistent with those of other research studies (Rogers,Wehner, & Hagerman, 2001) in that it is challenging to differentiate the clinical features of young children who have diverse autism spectrum disorders.

However, post hoc analysis revealed the specific subscales of the *BIPSSI - FX* for which the scores indeed differed among children with FraX and those with other autism spectrum disorders. The *Developmental Subscale* score differentiated the children with FraX from each of the other autism spectrum groups. The Down Syndrome group was the only group of children with diagnosed delays from whom the means scores of the children with FraX did not significantly differ. As was depicted in Table 1 in Chapter Two, developmental milestones have just begun to emerge in checklists for FraX (Bailey, 2003). The finding in this study supports the potential benefit of the inclusion of an assessment of developmental milestones as a mechanism of differentiating children with FraX from children with other autism spectrum disorders.

In contrast, the *Social and Behavioral* Subscales did not differentiate the children with FraX from those with autism, Asperger, PDD-NOS, but it did differentiate the children with FraX from those with Down Syndrome. The literature is replete with examples of the similarities in social, emotional, and behavioral attributes of children diagnosed with FraX and those with other autism spectrum disorders (Bailey et al., 2000; Bailey et al., 2001a; Denmark et al., 2003; Kau et al., 2004; Rogers, Wehner, & Hagerman, 2001). Therefore, the finding of this study concurs with previous studies.

Furthermore, mean *Cognitive Subscale s*cores differentiated children with FraX only from the children with Asperger. This finding was expected as most children with Asperger have normal cognitive development as opposed to children with Down Syndrome and other developmental disabilities. For example, male and female children with Down Syndrome and girls and boys with autism have mental retardation, whereas, 95 percent of males with FraX have mental retardation, but only 50% of females with FraX-full mutation have intellectual impairment. However, children with FraX did score higher on the *Cognitive Subscale* than those with Down Syndrome and slightly higher than those with PDD-NOS, thus indicating a greater amount of cognitive challenges. It is possible that the *Cognitive Subscale* scores of the children with FraX were influenced by the concurrent emotional and social challenges such as attention deficits and anxiety.

Hypothesis Five

Hypothesis 5 stated that parents of children with the FMR-1 gene mutation would score higher on the *BIPSSI-FX Biological Parent Subscale* than parents of children without the gene mutation (Study II). The scores of parents of children with the FMR-1 gene mutation were surprisingly lower than the mean score of the parents of each of the other groups of parents, with the exception of the parents of children with Down Syndrome. This finding is truly serendipitous in that the literature strongly supports the items of the *Biological Parent Subscale* as characteristics seen more commonly in biological relatives of children with FraX. Although some parents completed surveys for children who were members of diverse diagnosis groups, the researcher took steps as are described in Chapters 3 and 4, to ensure that the groups were mutually exclusive.

A possible explanation for the unexpected result could be that the parents of

children with FraX have adapted to a life of chronic stress, thereby minimizing the reporting of symptoms. It is also plausible that the responses of parents of children with FraX were influenced by a social desirability factor, in that FraX is the only diagnosis of those included in this study for which an exact genetic mode of transmission is known, except for the rare cases (less than 5 %)of Robertsonian Translocation Down Syndrome (Bandyopadhyay, et al., 2003). Having a knowledge that one has transmitted the gene responsible for mental retardation in one's child may engender a feeling of guilt in the parent responsible for transmitting the FMR1 gene mutation to the child affected with FraX. This phenomenon has been documented in the literature (Braden, 1996) and several parents of children with FraX, wrote of feelings of guilt in the comments section of the survey.

Another plausible explanation for the lower scores on the *Biological Parent Subscale* among parents of children with FraX is that it is possible that some of the parents were FraX-full mutation carriers and have mental retardation. Previous literature has documented the greater tendency of individuals with mental retardation to respond in ways which the individuals believe others would desire. According to (Finlay & Lyons, 2001) self-response questionnaires completed by individuals with developmental disabilities are especially vulnerable to contamination of social desirability. Furthermore, researchers (Sobesky, Hull & Hagerman, 1992; Sobesky, Pennington, Porter, Hull & Hagerman, 1994) have described a tendency among females who have the FraX-FM to deny problems even when significant others have documented that the problems actually exist. Sobesky et al. (1992), who termed the phenomenon a *blinders effect*, found in their study of females with FraX-FM that these women present their current situations in

simplistic ways and tend to discount previous experiences. According to these researchers, this tendency for denial measured by the Lie Scale of the *Minnesota Multiphasic Personality Inventory (MMPI)*, makes it difficult to document anxiety or depression in women with FraX-FM (Sobesky et al., 1992).

Hypothesis Six

Hypothesis 6 stated that children with FraX would differ from those with autism, PDD-NOS, and Asperger syndrome more on the *BIPSSI - FX* than on the *M-CHAT* (Study II). Although the *M-CHAT* detects children with FraX as well as autism, PDD-NOS and Asperger, the BIPSSI FX did a better job differentiating the children who had no diagnoses and those with Down Syndrome from those with FraX than children with autism spectrum disorders. The two independent *one-Way ANOVA*s indicated that the *BIPSSI FX* in conjunction with the *M-CHAT* may provide a stronger measure of FraX "at risk" than the *BIPSSI-FX* alone. Therefore, hypothesis 6 is confirmed.

Limitations

The potential challenges of the use of parent response measures exclusively for screening has limitations, as have been well documented (Squires, et al., 2001). This aspect is of particular importance in that the researcher did not control for mental retardation in the parents who participated in the study.

Additionally, the use of Internet as the only data collection medium poses several potential threats to external validity (Harris & Dersch, 1999). The use of the Internet limited the researcher's ability to control for situational contaminants such as; environmental factors (temperature, lighting, time of day) or fatigue of the respondents. Furthermore, each of the following factors could have influenced the primary caregiver's

responses: response set-bias, transitory personal factors, lack of instrument clarity, and the formatting of the instruments. It is possible that extreme responses, such as consistently assigning the most severe or the least severe rating to an item without considering the question, influenced the self-reported data in this study. However, it is unlikely because the parents volunteer to complete the survey with compensation.

Transitory personal states such as the caregiver's fatigue, hunger, anxiety, fluctuations in mood, or even the trials of the siblings' mood state may have influenced the manner in which the primary caregivers responded. Families of children who have developmental delays or disabilities are especially subject to temporary states. The literature is replete with information regarding how the various bidirectional effects may influence transitory or permanent states of individuals within families in which there is a child who has a developmental disability (Burton, 1992; Casper & Bryson, 1998; Dowdell, 1995; Gardner, Scherman, Mobley, Brown, & Schutter1994; Schilmoeller & Baranowski, 1998; Seamon, 1992; Seligman, 1991). Living with a disabled child permanently changes the life of each family member causing transitorily personal states or permanent personal changes. Sometimes, the process of the family's adjustment to a child with a disability is very strenuous, long, and difficult. As Perske (1981) posits:

> When a new youngster has a handicap, the family often expends energy beyond ordinary. An increased sharpening of wits and widening of hearts becomes necessary so that the one with the handicap can be understood, loved, and accepted as a member of a close-knit family circle. On the other hand, some households become cold towards such a child, and more families change for the worse (p. 14).

Instrument clarity. The researcher received e-mail messages from participants requesting clarification of the instrument. Additionally, two international participants commented in the open-ended sections of the survey that some cultural variants made

some sections of the surveys challenging to decipher. Their comments indicate that some respondents possibly misinterpreted the directions for the accurate completion of the research instruments. Finally, some respondents expressed difficulty in using the calendar (formatting issues) to enter the completion date and child's date of birth. However, many respondents rectified this problem by typing the intended information in the open-end comments section of the survey.

Recommendations

Research Implications

This researcher recommends the following to further develop the *BIPSSI-FX* and to evaluate its psychometric properties. 1) Conduct factor analysis of the tool to illuminate which items tend to cluster. 2) Collect data on more children with FraX-pM and conduct discriminate function analysis to determine which items of the *BIPSSI-FX* best predict FraX – FM and FraX –pM. 3) Analyze the subscales in predicting membership in a FraX – FM and FraX - pM group to determine if a combination of subscale scores instead of one total scale score is a more valid measure of FraX "at risk" status.

In addition to further analysis of the psychometric properties, the *BIPSSI-FX* should be revised to enhance the clarity of the items and the descriptors by conducting a focus group with parents of children with FraX. Furthermore, the *Physical Subscale* should be revised to include only items that have been found to highly discriminate toddlers with FraX from children who do not have the FMR-1 gene mutation when analyzing the data for children younger than 84 months of age. This may be accomplished by scoring in accordance with age intervals such as accomplished in the

ASQ: SE (Squires et al., 2001). Alternatively, a method such as that used by Maes et al. (2000) in their study of a phenotypic checklist to screen for FraX in males aged 3-51 years could be employed. This method consisted of adjusting the scoring in cases in which there were several responses of "Not applicable" as was found in the responses of the parent of an individual would could not speak to items about language..

In addition to changes to the *Physical Subscale*, and the fore mentioned controls for mental retardation in parent respondents, the *Biological Parent Subscale* should be expanded to include an additional item which is believed to have potential in the bidirectional identification of children with FraX and adults with FraX-premutation, the Fragile X Associated Tremors and Ataxia Syndrome (FXTAS - Greco et al.,2002; Hagerman & Hagerman, 2004; Hagerman, Leavitt et al.,2004; Leehey et al.,2003; Robinson, 2003).

Furthermore, after the revisions have been made, the *BIPSSI FX* should be tested on larger samples of children with FraX and other developmental disabilities for whom confirmatory diagnostic records are available to the researcher, either directly or through a collaborative agreement with clinicians after the revisions have been made. Finally, an assessment of an infant or toddler independent of an assessment of the child's proximal environment, the family, is incomplete (Seltzer, Abbeduto, Krauss, Greenberg, & Swe, 2004; Troost & Filsinger, 1993). Therefore, it is imperative to include a measure of the family dynamics in the process of using a screening measure to predict FMR-1 gene mutation "at risk" status in young children. The measures of family functioning may be profound covariates in the analysis of screening measures for children.

In conclusion, although the *BIPSSI-FX* cannot replace essential standardized early

assessment tests, it may effectively help parents to articulate concerns about the child's development to professionals. Additionally, the *BIPSSI-FX* may augment comprehensive assessment of infants and toddlers and facilitate the decision of whether or not testing for the FMR-1 gene mutation is indicated.

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APPENDIX A

Biopsychosocial Screening Inventory for Fragile X

Original Parent Response Version

Directions:

Please mark with an "X" the box that best describes the child, "A lot", "A little" "not at all" or "N/A if the item does not apply to child. The last part "Biological parent" should be answered with the parent of the child in mind.

Additional information is provided in some of the boxes to help to make the desired choice clear.

Number (last four digits of the Social Security Number)_____

Date of Form Completion:_____

Child's Date of Birth: _____

DEVELOPMENTAL MILESTONES				
1. How old was your child when he/she could sit without support?	Older than 9 months	Older than 7 months	Younger than 7 months	
2. How old was your child when he/she began walking well?	Older than 20 months	Older than 14 months	Younger than 14 months	
3. At what age did your child first say a first word?	Older than 18 months	Older than 12 months	Younger than 12 months	
4. At what age did your child first wave "bye-bye?"	Older than 14 months	Older than 9 months, but earlier than 14 months	Younger than 9 months	
5. At what age did your child first respond to her or his name?	Older than 10 months	Older than 7 months, less than 10 months	Younger than 7 months	
6. At what age was your child toilet trained?(urine and BM, with not more than 3 accidents while awake in one year)	5 years or older, or is not now toilet trained	Older than four years but less than five	Younger than four years	

PHYSICAL	A Lot	A Little	Not at All	N/A
1. Does your child have low muscle tone/ muscle weakness?				
2. Does your child have any seizures?	2 or more seizures and takes medicine for seizures	At least 1 seizure		
3. Has your child ever had frequent ear infections (more than 3 per year)?	More than 3 per year	At least 2 per year, but at least 1		
4. Has your child ever had frequent colds or nasal infections?	At least 3 or more per year	At least 2 per year, but at least 1		
5. Has your child ever had cleft lip, cleft palate or an arched palate (top of the inside of the mouth).				
Social / Behavioral	**A Lot**	**A Little**	**Not at All**	**N/A**
1. Has your child ever avoided looking others in the eye?				
2. Has your child had problems at home or school?				
3. Has your child had emotional problems?				
4. Has your child had behavioral problems?				
5. Has your child ever had treatment for emotional or behavioral problems?	3 or more visits, at least one hospitalization	2 visits or less, no hospitalizations		
6. Has your child ever taken medication for emotional or behavioral problems?	2 or more medicines for longer than 1 month	1 medicine or if more, for less than 1 month		
7. Has your child ever had difficulty keeping his or her attention focused?				
8. Has your child ever had problems talking with people he or she does not know?				

SOCIAL/BEHAVIORAL	A Lot	A Little	Not at All	N/A
9. Has your child ever had problems playing with people he or she does not know?				
10. Has your child ever had problems with sad or depressed mood?				
11. Has your child ever had problems with nervousness or anxiety?				
12. Has your child ever had a problem with hurting himself or herself by head banging or biting hands, arms or other parts of their body?				
13. Has your child ever had problems with picking at his or her skin or biting fingernails?				
14. Has your child ever had problems with making the same movements over and over.				
15. Has your child ever had problems with saying the same word or phrase over and over?				
16. Has your child ever had problems with talking about the same subject over and over?				
17. Has your child ever had problems falling asleep or staying asleep?	5-7 nights per week	1-4 nights per week		
18. Has your child ever had an upset or disturbed response to soft or light touch or attempted to cover himself or herself with heavy objects such as sofa cushions, a mattress, blankets, beanbag chairs, etc.?				
19. Have you every heard your child talking to him or herself or making humming sounds?	Almost daily	Less than twice a week.		

COGNITIVE	A Lot	A Little	Not at all	N/A
1. Has your child ever placement in "gifted" class programs received or received information that he or she is unusually bright?	In gifted and talented class for 1 year or more	Not in a gifted and talented program, but receives "only A's and B's on progress reports.		
2. Has your child ever had any speech problems?				
3. Has your child ever received speech therapy?				
4. Has your child ever had any language problems?				
5. Has your child ever received language therapy?				
6. Has your child ever had any learning problems?				
7. Has your child ever had problems such as a learning disability, being a slow learner, or with mental retardation?				
8. Has your child ever attended special classes or preschool or received tutoring?				

BIOLOGICAL PARENT	A Lot	A Little	Not at All	N/A
1. Have you or your mother, sisters or aunts had early menopause?	Before age 35 yrs	Before age 40 yrs; older than 35		
2. Have you or your mother, sisters or aunts had cysts on the ovaries?	Both ovaries or more than one time	One ovary, no more than one time		
3. Did the mother (child's mother) ever have problems with feeling depressed or nervous before becoming a parent?	Has received hospital treatment	Has received therapy, but not hospital treatment		
4. Did the father (child's father) ever have problems with feeling depressed or nervous before becoming a parent?	Has received hospital treatment	Has received therapy, but not hospital treatment		
5. Have you or your mother, sisters, or aunts had problems with stopping activities or insisting on doing things exactly a certain way?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems		
6. Has the mother had problems with drinking too much or problems with using other drugs, those prescribed either by a health care provider or those not prescribed?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems with others		
7. Has the father had problems with drinking too much or problems with using other drugs, either those prescribed by a health care provider or those not prescribed?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems with others		

BIOLOGICAL PARENT	A Lot	A Little	Not at All	N/A
8. Have any other family members had problems with drinking too much or problems with using other drugs, either those prescribed by a health care provider or those not prescribed?	Mother or Father	Grandparent Aunt, Uncle or cousin		
9. Has anyone in the mother's (child's mother) family had mental retardation?	Mother, father, grandparent, brother or sister	Aunt, Uncle or cousin		
10. Has anyone in the father's (child's father) family had mental retardation?	Mother, father, grandparent, brother or sister	Aunt, Uncle or cousin		
11. Has the mother (child's mother) had problems with doing math?	Influenced job choices	Did not influence job choices		
12. Has the father (child's father) had problems with doing math?	Influenced job choices	Did not influence job choices		

Scoring:

APPENDIX B

Screening Questionnaire for Fragile X Syndrome

CONSENSUS GROUP SCREENING QUESTIONNAIRE

Purpose: To increase the recognition of the affected neurobehavioral states in fragile x syndrome and other genetic conditions.

Directions: The questionnaire is designed to be given as a brief interview. The informant will usually be the patient(begin questions with "Have you…"). In the case of children or individuals with developmental disability, parent, guardian or other caregivers should provide the information (begin questions with "Has(name").

Please complete one questionnaire for each family member.
Patient Name/Number: _____Date of Birth_____
Sex_____ Date: _____

Informant(s): _____Relationship to Patient: _____
Interviewer:_____

History-Cognitive **Circle One Answer** **History-Behavior**
Circle One Answer

1) Ever had any learning, speech or language problems? Yes No No Info
If yes, describe_____
_____
_____

2) Ever attended special classes or preschool; received tutoring: had math or reading problems? Yes No No Info
If yes, describe_____
_____

3) Ever received speech or Language therapy? Yes No No Info
If yes, describe_____
_____
_____

4) Ever had problems such as a learning disability; being a slow learner, or mental retardation? Yes No No Info
If yes, describe_____
_____

5) Ever had an achievement or IQ test? Yes No No Info
If yes, brief description of reason for test And estimate date and site of testing(to Obtain records)_____
_____
_____

6) (For Adults Only) How many years of schooling (education) have you had? _____

7) Highest level of education achieved? _____

8) (For Adults Only) Occupation: _____

1) Ever had problems at home or school? Yes No No Info
If yes, describe_____
_____
_____

2) Ever had any emotional or behavioral problems? Yes No No Info
If yes, describe_____
_____

3) Ever taken medications for emotional or behavioral problems? Yes No No Info
If yes, describe_____
_____
_____

4) Ever received treatment for emotional or behavioral problems? Yes No No Info
If yes, describe_____
_____

5) Ever had difficulty with:
a) keeping attention focused? Yes No No Info
b) avoiding looking others in the eye? Yes No No Info
c)discomfort socializing with people you don't know? Yes No No Info
d) down or depressed mood? Yes No No Info
e) nervousness or anxiety? Yes No No Info
f) injuring yourself? Yes No No Info
g)making the same movements over and over? Yes No No Info
h) saying the same word or phrase over and over? Yes No No Info
i) talking about the same subject over and over again? Yes No No Info

Summary – If there is indication of cognitive/learning or behavioral/psychological problems, the following recommendations are made:

<u>Recommendations for cognitive (IQ) testing:</u> If available, obtain records of prior testing. If no prior records, referral for cognitive testing should be made for all patients whenever possible, but particularly for patients suspected of having a learning problem.

Overall Cognitive Function: Normal_____ Borderline IQ _____Mild Retardation_____Moderate Retardation _____

Severe-Profound Retardation _____ IQ_____ Name of IQ Test_____

<u>Recommendation for behavioral assessment</u>: At time of visit parent should complete the Child Behavioral Checklist (CBCL)[1] for any child ages 2 to 16 with no evidence of mental retardation. Factor scores from the CBCL will indicate level of hyperactivity, depression and social deficits. Each parent should also complete the Hopkins Symptom Checklist (HSCL)[2]

Child Behavioral Checklist available from T.M. Achenbach, Center for Children, Youth & Families, University of Vermont, 1 South Prospect St. Burlington, VT 05401: 2 HSCL available from Journal of Affective Disorders 1: 9-24. 1979

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APPENDIX C
Study I - Institutional Review Board Approval

Oklahoma State University
Institutional Review Board

Protocol Expires: 6/11/03

Date: Monday, June 17, 2002 IRB Application No HE0258

Proposal Title: PILOT STUDY OF THE EFFICACY OF SCREENING TOOL IDENTIFICATION OF THE FMR - 1 MUTATION AMONG DEVELOPMENTALLY AND BEHAVIORALLY AT RISK YOUNG CHILDREN

Principal Investigator(s):

Vanessa Thomas
224 HES
Stillwater, OK 74078

Patricia Self
226A HES
Stillwater, OK 74078

Reviewed and Processed as: Expedited (Spec Pop)

Approval Status Recommended by Reviewer(s): Approved *

Dear PI :

Your IRB application referenced above has been approved for one calendar year. Please make note of the expiration date indicated above. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

As Principal Investigator, it is your responsibility to do the following:

1. Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval.
2. Submit a request for continuation if the study extends beyond the approval period of one calendar year. This continuation must receive IRB review and approval before the research can continue.
3. Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of this research; and
4. Notify the IRB office in writing when your research project is complete.

Please note that approved projects are subject to monitoring by the IRB. If you have questions about the IRB procedures or need any assistance from the Board, please contact Sharon Bacher, the Executive Secretary to the IRB, in 203 Whitehurst (phone: 405-744-5700, sbacher@okstate.edu).

Sincerely,

Carol Olson

Carol Olson, Chair
Institutional Review Board

*NOTE: While benefits accrue to subjects in the follow-on dissertation research, testing the efficacy of an instrument may not, in and of itself, constitute a benefit.

APPENDIX D

OKLAHOMA STATE UNIVERSITY
INFORMED CONSENT FORM

Title of the Project: ***PILOT STUDY OF THE EFFICACY OF SCREENING TOOL IDENTIFICATION OF YOUNG CHILDREN AT RISK FOR THE FMR-1 GENE MUTATION***

AUTHORIZATION

I,_____, agree for my child_____ to participate as a volunteer in a study as a part of a research program of Oklahoma State University, under the supervision of the College of Human Environmental Sciences faculty members.

DESCRIPTION OF RESEARCH AND PURPOSE

I understand that the purpose of the research is to investigate the effectiveness of a screening tool to identify a gene difference in young children that sometimes causes problems with behavior and learning. I understand that the research will include my completion of brief questionnaires and the collection of a buccal (cheek) cell swab sample from my child.

PROCEDURES

As a participant in this study, I understand that the following procedures are involved:

1. Each parent or legal guardian (the primary caregiver) will complete the Consensus Group Fragile X Screening tool with this or her child who is participating in the research study in mind.

2 Each parent or legal guardian (primary caregiver) will complete The *Biopsychosocial Screening Inventory for Fragile X (BIPSSI-FX*) with the child who is participating in the research study, in mind.

3. Each parent or legal guardian (the primary caregiver) will fill-out regarding the child who is participating in the research study, *The Carey Temperament Scales Toddlers Temperament Scales(*for children 12 to 24 months) and the *Infant/Toddler Symptom Checklist* (for children 12 months to 30 months), *The Child Behavior Checklist* Ages 1-1/2 years to 5 years (for children 25-71 months) or *The Child Behavior Checklist* Ages 6-18 (for children older than 72 months).

4. Each parent or legal guardian (the primary caregiver) will complete, the *Family Background Information Form.*

5. Each parent or legal guardian (the primary caregiver) will participate in a loosely structured questionnaire concerning his or her child who is participating in the research study, family supports and stressors and access to community services.

6. Each parent or legal guardian will collect a swab (light brushing) of the inside of the child's mouth in the cheek area. This procedure should be done immediately before brushing the child's teeth. The swab used to collect the sample is similar to a Q-tip swab. This swab is longer than the usual Q-tip swab but is controlled in similar manner as a toothbrush. A child who usually brushes his or her teeth without help may collect the swab sample under the parent's supervision. The swab will be placed in the container provided by the researcher, labeled with using the last four digits of the child's social security number and mailed by the parent or the researcher in the prepaid and addressed express mail envelope to the laboratory where the sample will be tested.

7. Each parent, if desired, will be told by a research assistant or genetic counselor, by telephone and in writing of the preliminary results of the cheek cell swab samples. Referral information regarding more definitive testing and counseling will be provided by the research assistant or genetic counselor. Additionally, a summary of the findings of each of the questionnaires/assessment tools completed, will be provided to the parent, if desired. In addition, if desired, each parent will be informed in writing of the general findings of the study. The principal investigator, **Vanessa Johnson Thomas**, will remain unaware of the identity of the DNA sample results as well as the identity of the questionnaire results.

Do you want to be told the results of the genetic test?

[ ] Yes [ ]No

Additional tests: It is standard practice for laboratories to store samples that are left over after testing. The samples often can be used for up to 5 to 10 years after collection. The researchers are asking your desires concerning the results of any future genetic or medical testing. Will you allow us to test any samples left over from your buccal (cheek) cell sample?

[ ] Yes [ ]No

Do you want to be provided with a summary of the results of the questionnaires?

[ ] Yes [ ]No

Potential Risks

I understand that there are no known risks to my child or me by participating in this research. If my child is identified as possibly having the gene mutation, this information may produce unpleasant emotional responses for my family and me. I understand that genetic counseling referrals and counseling from a qualified health professional is available to me, my child and other family members, if desired. Also, information regarding appropriate community agencies will be available to me.

If you answered "yes" to any of the above questions, and important in genetic or medical information about you or your family is found, a genetic counselor will first re- inform you of the potential risks and benefits of telling you this information.

POTENTIAL RISKS

These risks include the possibility that you or your child have a genetic or medical abnormality that was previously unknown to you and that may be important to your health, or to the health of your children, future children, or extended family, and that also could impact matters such as eligibility for health and life insurance. Only after you have had a chance to review this information again, will the genetic counselor or research assistant reveal to you the preliminary results of the genetic testing.

BENEFITS

There is no direct benefit for you or your child. The possible general benefit to science resulting from participating in this study includes adding to the knowledge about ways in which potential behavioral and developmental challenges may be identified early, easily and inexpensively.

The possible benefits of participating in this research study's may be that early involvement services and programs for the child may be more easily available because of the identification of gene changes that are often associated with behavioral and developmental challenges. In addition, various related treatments are being researched nationally and internationally and progress is being made toward decreasing challenges associated with having this gene change that causes Fragile X Syndrome. Moreover, research currently supports the use of certain medications, educational strategies and other therapeutic measures that seem to work better than others do in treating the symptoms related to Fragile X Syndrome. Knowledge of your child's FMR-1 gene status may help you and your child to make important family decisions.

THE RESEARCHERS CANNOT GUARANTEE ANY BENEFIT TO YOU OR YOUR CHILD FROM PARTICIPATION IN THIS STUDY.

CONFIDENTIALITY

I understand that the information obtained from my child and me will be kept confidential, using the following methods: (1) all data collected will be identified by using a code number assigned to my child (the last four numbers of the social security number), (2) the list of the codes will be kept under lock and key, with access to no one but the research assistant and the laboratory personnel, the principal investigator,(3) Vanessa Johnson Thomas will NOT have access to the identifying code sheet (4) study findings will be reported as grouped data in a way that no individual may be identified.

I understand that my child and I are free to refuse to participate in **any** part of the study at any time without bias and unfair treatment to either of us. Additionally, the research will be explained to my child and the researchers will attempt to obtain assent (agreement to

participate) from my child. I understand that my child and I are free to stop participating in the study at any time without penalty or bad treatment. I understand that by agreeing to participate in this research and by signing this form, I do not give up any of my legal rights.

If I have any questions about the study, or need to report any unpleasant effects from the research procedures, I will contact; Patricia Self, Ph.D., the supervising professor at Oklahoma State University Department of Human Development and Family Science, at (405) 744-8348, during the workday or Vanessa Johnson Thomas, doctoral student, Oklahoma State University Department of Human Development and Family Science at (918) 295-7858 or (918) 850-5279 or vjthomasrn@aol.com during the day, evenings and weekends.

If I have questions about my rights as a research participant, I will contact: Sharon Bacher, Institutional Review Board Executive Secretary, Oklahoma State University, 203 Whitehurst, Stillwater, OK 74078. Telephone: 405- 744-5700.

I have read this consent document. I understand its contents, and I freely consent for my child to participate in this study under the conditions described here. I will receive a copy of this consent form.

Date: _____ Time: _____ (a.m./p.m.)

_____

Name (printed) Signature

_____

Signature of person authorized to sign for subject, if required

Witness(es) if required**:** _____

_____

I certify that I have personally explained all elements of this form to the subject or his/her representative before requesting the subject or his/her representative to sign it.

Signed: _____

Project director or authorized representative

OKLAHOMA STATE UNIVERSITY

INFORMED ASSENT

We want to learn how well a form can help us to find out information about the way a child acts and learns. We will ask your parent to fill out papers that ask questions about the way you do things.

The test will not hurt you. We will ask your parent to help you wipe inside your cheek with a swab. This will feel like placing a toothbrush in your mouth or rubbing your tongue against the inside your cheek.

We hope to learn a lot, about how our paper and pencil test will help us get the information that the swab gives. Taking part in this test probably will not help you directly.

If you agree to this test, please sign your name on the line below.

If you change your mind about having the test done, anytime, you may stop the test or refuse to begin. If you decide not to take part in the test, we will not treat you differently than if you had done the test.

_____ _____

Child's Name **Date**

_____ _____

Researcher **Date:**

APPENDIX E

Study II – Institutional Review Board Approval

Oklahoma State University
Institutional Review Board

Protocol Expires: 9/29/2004

Date: Tuesday, September 30, 2003 IRB Application No HE049

Proposal Title: DEVELOPMENT OF A BIOPSYCHOSOCIAL SCREENING INVENTORY FOR FMR-1 GENE MUTATION "AT RISK" STATUS IN YOUG CHILDREN

Principal Investigator(s):

Vanessa Johnson Thomas
522 E. Newton Pl
Tulsa, OK 74106

Patricia Self
226A HES
Stillwater, OK 74078

Reviewed and Processed as: Exempt

Approval Status Recommended by Reviewer(s): Approved *

Dear PI :

Your IRB application referenced above has been approved for one calendar year. Please make note of the expiration date indicated above. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

As Principal Investigator, it is your responsibility to do the following:

1. Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval.
2. Submit a request for continuation if the study extends beyond the approval period of one calendar year. This continuation must receive IRB review and approval before the research can continue.
3. Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of this research; and
4. Notify the IRB office in writing when your research project is complete.

Please note that approved projects are subject to monitoring by the IRB. If you have questions about the IRB procedures or need any assistance from the Board, please contact [redacted], the Executive Secretary to the IRB, in 415 Whitehurst (phone: 405-744-5700, sbacher@okstate.edu).

Sincerely,

Carol Olson, Chair
Institutional Review Board

*NOTE: Change IRB contact on consent form to Dr. Carol Olson, IRB Chair, 415 Whitehurst, 405-744-1676, colson@okstate.edu

APPENDIX F

Study II - Informed Consent – *How to Participate*

HOW TO PARTICIATE

Purpose of the Study

The purpose of this research is to gather information that may be helpful in developing an effective parent completed survey that may be used by parents to help check their child's development. The forms are used for research purposes only and should not be used to measure your child's development. However, research is a major step toward treatments and cures.

Please contact your physician or other child development professional if you have concerns about your child's development.

If you have one or more children between the ages of 12 months to 18 years of age whom a health care professional has diagnosed to have:

- **Autism**
- **Pervasive Developmental Disorder (PDD)**
- **Asperger Syndrome**
- **Down Syndrome**
- **Fragile X Syndrome**
- **Fragile X Premutation Carrier**
- **No disabilities DNA tests have ruled-out Fragile X Syndrome.**

We invite you to participate in our study.

Your Consent and Rights

All of your information will be kept private and information about the study will be reported only in grouped information, using computer assigned numbers and no names. E-mail addresses will not be shared with any other group or person and will NOT be stored.

If you have any questions or concerns about the surveys, or wish to report any adverse effects from the research procedures, you may contact Patricia Self, at (405) 744-8348, during the workday or Vanessa Johnson, at (918) 295-7858 or (918) 638-7858 or tveness@okstate.edu during the day, evenings and weekends.

If you have questions about your rights as a research participant, you may contact: Dr. Carol Olson, IRB, Oklahoma State University, 203 Whitehurst, Stillwater, OK 74078. Phone: 405-744-5700.

By completing the surveys and returning them, you are agreeing to participate in this research.

Instructions

The following instructions are to assist you to complete the surveys on the computer.

1. Please select the translation of the website and surveys that you wish to use by clicking the language in the translation drop box at the bottom of the first page.

2. There are four brief surveys to complete: The Primary Caregiver Background, the Diagnosis Form, The Biopsychosocial Screening (BIPSSI), and the *M-CHAT*. Please complete each survey using the scroll-down bars and checking the box(s) that indicates your selection. When you are finished with each survey click on the "next form" button and it will take you to the next survey. **By completing these surveys and electronically submitting them, you are agreeing to participate in this research**.

3. Please read each question carefully, but quickly. Do not spend too much time trying to answer one question. There are no right or wrong answers.

4 . If you have more than one child who meets the conditions for the study listed above, please complete the four surveys for the first child then return to the ***How to Participate*** page and begin the surveys for the next child and so on.

5. We appreciate you participating in this study and helping professionals working with children to gain helpful information.

Thank you very much!

Start Survey

Choose a Language

APPENDIX G

BIPSSI-FX
Revised Parent Response Version

Directions:

Please mark with an "X" the box that best describes the child, "A lot," "A little," "not at all" or "N/A" if the item does not apply to child. The last part "Biological parent" should be answered with the parent of the child in mind.

Additional information is provided in some of the boxes to help to make the desired choice clear.

Date of Form Completion:_____

Child's Date of Birth: _____

1. How old was your child when he/she could sit without support?	Older than 9 months	Older than 7 months	Younger than 7 months	
2. How old was your child when he/she began walking well?	Older than 20 months	Older than 14 months	Younger than 14 months	
3. At what age did your child first say a first word?	Older than 18 months	Older than 12 months	Younger than 12 months	
4. At what age did your child first wave "bye-bye?"	Older than 14 months	Older than 9 months, but earlier than 14 months	Younger than 9 months	
5. At what age did your child first respond to her or his name?	Older than 10 months	Older than 7 months, less than 10 months	Younger than 7 months	
6. At what age was your child toilet trained?(urine and BM, with not more than 3 accidents while awake in one year)	5 years or older, or is not now toilet trained	Older than four years but less than five	Younger than four years	

	A Lot	A Little	Not at All	N/A
1. Does your child have low muscle tone/muscle weakness?				
2. Does your child have any seizures?	2 or more seizures and takes medicine for seizures	At least 1 seizure		
3. Has your child ever had frequent colds or nasal infections?	More than 3 per year	At least 2 per year, but at least 1		
4. Has your child ever had cleft lip, cleft palate or an arched palate (top of the inside of the mouth)?	At least 3 or more per year	At least 2 per year, but at least 1		
5. Has your child ever had frequent ear infections (more than three per year)?				
6. Does your child have problems with his or her eyes?				
7. Does your child have a long face and / or long ears?				

	A LOT	A Little	Not at all	N/A
1. Has your child ever avoided looking others in the eye?				
2. Has your child had problems at home or school?				
3. Has your child had emotional problems?				
4. Has your child had behavioral problems?				
5. Has your child ever had treatment for emotional or behavioral problems? 6. Has your child ever had difficulty keeping his or her attention focused?	3 or more visits, at least one hospitalization	2 visits or less, no hospitalizations		
7. Does your child talk with people he or she does not know or has your child done this in the past?				
8. Has your child ever had problems playing with people he or she does not know?				
9. Has your child ever had problems with sad or depressed mood?				
10. Has your child ever had problems with nervousness or anxiety?				
11. Has your child ever had a problem with hurting himself or herself by head banging or biting hands, arms or other parts of their body?				
12. Has your child ever picked at his or her skin or bit hands or fingers to the point of injuring self?				
13. Does your child make the same movements over and over, such as rocking, twirling around, or clapping hands or has your child done this in the past?				

	A LOT	A Little	Not at all	N/A
14. Has your child ever had problems with saying the same word or phrase over and over?				
15. Has your child talked about the same subject over and over with, the child to the point of development making it hard to hold a conversation with him or her?				
16. Has your child ever had problems falling asleep or staying asleep?	5-7 nights per week	1-4 nights per week		
17. Has your child ever had an upset or disturbed response to soft or light touch or attempted to cover himself or herself with heavy objects such as sofa cushions, a mattress, blankets, beanbag chairs, etc.?				
18. Have you every heard your child talking to him or herself or making humming sounds?	Almost daily	Less than twice a week.		

	A LOT	A Little	Not at all	N/A
1. Has your child ever placement in "gifted" class programs received or received information that he or she is unusually bright?	In gifted and talented class for 1 year or more	Not in a gifted and talented program, but receives "only A's and B's on progress reports.		
2. Has your child ever had any speech problems?				
3. Has your child ever received speech therapy?				
4. Has your child ever had any language problems?				
5. Has your child ever received language therapy?				

6. Has your child ever had any learning problems?				
7. Has your child ever had problems such as a learning disability, being a slow learner, or with mental retardation?				
8. Has your child ever attended special classes or preschool or received tutoring?				
	A Lot	**A Little**	**Not at All**	**N/A**
1. Have you or your mother, sisters or aunts had early menopause ("going through the change of life")or premature ovarian failure?	Before age 35 yrs	Before age 40 yrs; older than 35		
2. Have any women in the birth father's blood family had early menopause ("going through the change of life") or premature ovarian failure?	Both ovaries or more than one time	One ovary, no more than one time		
3. Have any women in the birth mother's blood family or the birth father's family had cysts on the ovaries, cysts removed from the ovaries, or hysterectomy (removal of the uterus)?				
4. Did the mother (child's mother) ever have problems with feeling depressed or nervous **before** becoming a parent?	Has received hospital treatment	Has received therapy, but **not** hospital treatment		
5. Did the father (child's father) ever have problems with feeling depressed or nervous **before** becoming a parent?				
6. Is it or has it been hard for anyone in birth mother's blood family or birth father's blood family to stop activities (such as, hand washing, checking locks, worrying, refusing to throw items away, computer use, watching television) or insist on doing things or having things done perfectly or exactly a certain way?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems		
7. Has the birth mother or the birth father, now (or in the past) drank too much alcohol, used too many drugs, or used drugs too often, either those prescribed by a health care worker or those not prescribed?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems with others		

8. Has anyone in the birth mother's blood family or the birth father's blood family had mental retardation/developmental disabilities, autism, Asperger Syndrome or Fragile X Syndrome?	Has caused problems with work, family or friends	Bothersome to self, but has not caused problems with others		
9. Has the birth mother (child's mother) or birth father (child's father) had problems doing math?				

Scoring:

APPENDIX H

Permission to Use the M-CHAT

Subj:	**RE: Permission to use M-CHAT**
Date:	6/4/2003 7:02:31 PM Central Daylight Time
From:	*fein@uconnvm.uconn.edu (Dr. Deborah Fein)*
To:	*Vjthomasrn@aol.com*
CC:	*drobins@hp.ufl.edu (Diana Robins), pamdixon2001@yahoo.com (Pam Dixon)*

Dear Vanessa. Thanks for your message. I' m not sure I understand your research question #4, but it sounds like a worthwhile project. You have permission to use the M-CHAT in your project. You can reprint it yourself from the JADD article, or we can send you a hard copy, which you can then copy. If you'd like the latter, please e-mail pamdixon2001@yahoo.com and ask her for one. Thanks - Deborah Fein-----

Original Message-----
From: Vjthomasrn@aol.com [mailto:Vjthomasrn@aol.com]
Sent: Wednesday, June 04, 2003 6:45 PM
To: barton@psych.psy.uconn.edu; fein@uconnvm.uconn.edu
Subject: Permission to use *M-CHAT*

OKLAHOMA STATE UNIVERSITY

OSU

College of Human Environmental Sciences
Department of Human Development and Family Science
243 Human Environmental Sciences
Stillwater, Oklahoma 74078-6122
405-744-5057; Fax: 405-744-2800

June 3, 2003

Diana Robins
Department of Psychology
University of Connecticut
406 Babbidge Road, U-1020
Storrs, Connecticut 06269-1020

Dear Dr. Robins:
I am a doctoral candidate in the Human Development and Family Science at Oklahoma State University. My dissertation research focuses on the early identification of children who have Fragile X Syndrome. I am particularly interested in contributing to the epidemiological database regarding developmental disabilities in infants and toddlers. The need is immense for heightened awareness of Fragile X Syndrome and pivotal early interventions. As the parent of two boys who have Fragile X Syndrome (full-mutation) and as a behavioral health professional, I feel impelled to contribute significantly to the

knowledge base regarding this complex and intriguing disorder as well as other associated developmental disabilities.

I recently read your (2001) article, the Modified checklist for autism in toddlers: An initial Study investigating the early detection of autism and pervasive developmental disorders. Journal of Autism and Developmental Disorders, 31(2), 131-144. I would greatly appreciate an opportunity to review your questionnaire and request your permission to use it as a measure in my dissertation research study.

I have enclosed a copy of an abstract of my proposed research. I would appreciate your assistance immensely and I look forward to your reply.

Sincerely,

Vanessa J. Thomas, Ph.D. (C) MS, RN
Human Development and Family Science
Oklahoma State University

522 East Newton Place
Tulsa, Oklahoma 74106
E-mail address: tveness@okstate.edu
Telephone:(918)295-7858
Enclosures

APPENDIX I

M-CHAT

Please fill out the following about how your child **usually** is. Please try to answer every question. If the behavior is rare (e.g. you've seen it once or twice), please answer as if the child does not do it.

1. Does your child enjoy being swung, bounced on your knee, etc.?	Yes No
2. Does your child take an interest in other children?	Yes No
3. Does your child like climbing on things, such as up stairs?	Yes No
4. Does your child enjoy playing peek-a-boo/hide-and-seek?	Yes No
5. Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?	Yes No
6. Does your child ever use his/her index finger to point, to ask for something?	Yes No
7. Does your child ever use his/her index finger to point, to indicate interest in something?	Yes No
8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?	Yes No
9. Does your child ever bring objects over to you (parent) to show you something?	Yes No
10. Does your child look you in the eye for more than a second or two?	Yes No
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)	Yes No
12. Does your child smile in response to your face or your smile?	Yes No
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?)	Yes No
14. Does your child respond to his/her name when you call?	Yes No
15. If you point at a toy across the room, does your child look at it?	Yes No
16. Does your child walk?	Yes No
17. Does your child look at things you are looking at?	Yes No
18. Does your child make unusual finger movements near his/her face?	Yes No
19. Does your child try to attract your attention to his/her own activity?	Yes No
20. Have you ever wondered if your child is deaf?	Yes No
21. Does your child understand what people say?	Yes No
22. Does your child sometimes stare at nothing or wander with no purpose?	Yes No
23. Does your child look at your face to check your reaction when faced with something unfamiliar?	Yes No

Please refer to: Robins, D., Fein, D., Barton, M., & Green, J. (2001). The Modified Checklist for Autism in Toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 31 (2), 131-144.

APPENDIX J

OKLAHOMA STATE UNIVERSITY

OSU

College of Human Environmental Sciences
Department of Human Development and Family Science
243 Human Environmental Sciences
Stillwater, Oklahoma 74078-6122
405-744-5057; Fax: 405-744-2800

January 24, 2004

Dear Parent / Primary Caregiver:
I am Vanessa Johnson Thomas, Mom to John, 14 (DD; Sammy, 13 (DD) and Elizabeth, 19 yrs (typically developing). I am also a doctoral candidate in the Human Development and Family Science Program at Oklahoma State University. My dissertation advisors, Dr. Patricia Self, and I have are particularly interested in identifying infants and toddlers who may need early interventions. As the parent of two boys who have significant development disabilities and as a health professional, I feel driven to help, by doing research. The purpose of our research is to gather information that may help children to receive important help earlier. Research is a major step toward successful treatments.

We invite you to complete surveys online if **one or more** of your children are between the **ages of 12 months to 18 years of age** and have received a diagnosis by a health care professional of either:

No disabilities
Autism
Down Syndrome
Fragile X Syndrome
Fragile X **Premutation Carrier**
Asperger Syndrome
Pervasive Developmental Disorder (PDD-NOS)

If you want to help with our study, please click http://langston.osu-tulsa.okstate.edu/vthomas to go to the website in which English and Spanish versions of the surveys are available The English version is the default language. The "start survey" link at the bottom of the "How to Participate" page leads to the first survey. It takes about 15 minutes to finish all of the surveys online. We would appreciate your help and will send a report of the results of the study to moderators, list servs and message boards, clinics, etc. after we finish the study.

All information that you give will be kept 100% private. We will not collect ANY identifying information and will have no way of knowing who filled-out the surveys. Your help is important! We hope our research will increase awareness, research and early interventions with children.

Vanessa Johnson Thomas, Ph.D., (candidate), MS, RN, BC
Oklahoma State University Human Development and Family Science
700 N. Greenwood NCB 358
Tulsa, Oklahoma 74106
(918) 594-8082 (Office)
tveness@okstate.edu

Patricia Self, Ph.D., Professor
Oklahoma State University
Human Development and Family Sciences
HES RM 226A
Stillwater, Oklahoma 74078
(405) 744-8348 (Office)

APPENDIX K

Sample Website Pages

Cómo Participar

V. Johnson

Investigación: Un Paso más cerca a una Respuesta

Webmaster

Choose a Language

CONTACT INFORMATION

Vanessa Johnson, Ph.D (Candidate), MS(N), RN

Email Address:
Vjthomasrn@aol.com
mailto:tveness@okstate.edu

Phone Numbers:

Office:	(918) 594-8082
	(918) 295-7858
Fax:	(918) 295-7852
Langston School of Nursing Fax:	(918) 594-8357

Web Address:

http://langston.osu-tulsa.okstate.edu/vthomas/

Contact Information:

Patricia Self, Dissertation Advisor

Institutional Review Board: Oklahoma State University

CONTACT INFORMATION

Vanessa Johnson, Ph.D (El candidato), MS(N), RN

Mande correo electrónico la Dirección:
Vjthomasrn@aol.com
mailto:tveness@okstate.edu

El teléfono Numera:

La oficina:	(918) 594-8082
	(918) 295-7858
El fax:	(918) 295-7852
La Escuela de Langston de Cuidar Fax:	(918) 594-8357

Cinche la Dirección:

http://langston.osu-tulsa.okstate.edu/vthomas/

Avise Información:

Patricia Self, El Consejero de la disertación

La Tabla institucional de la Revisión: la Universidad del Estado de Oklahoma

Primary Caregiver Background

Primary Caregiver's Race or Ethnic Group

Primary Caregiver's Gender

Caregiver's Age

Caregiver's Relationship to Child

State or Province in which you reside

Country in which you reside

Primary Caregiver's Marital Status

Religious Preference

Level of Education Completed

Annual Household Income

El Fondo primario de Caregiver

La Carrera primaria de Caregiver o Grupo Etnico

el Género Primario de Caregiver

La Edad de Caregiver

Caregiver'la Relación de s al Niño

El estado o la Provincia en que usted reside

El país en que usted reside

La Posición Marital primaria de Caregiver

La Preferencia religiosa

El nivel de la Educación Completó

Los Ingresos anuales de la Casa

Continue Reset Form

Number of children / siblings with a disability

Family Composition

(Please do not include the child for whom you are completing the survey)

Other Children / Siblings	Date of Birth	Developmental Disability, Delay or other Concerns	Disability Diagnosis
Child #1	Select		
Child #2	Select		
Child #3	Select		
Child #4	Select		
Child #5	Select		
Child #6	Select		
Child #7	Select		

Continue Reset Form

La Forma del diagnóstico

La fecha

Select

La Fecha del niño del Nacimiento

Select

La Demora de desarrollo del niño/el Diagnóstico de la Incapacidad

- Síndrome X frágil (mutación Repleta, más de 200 CGG repite)
  El número de repite
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- El Portador frágil de Premutation X (50 - 199 CGG repite)
  El número de repite
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- Abajo Síndrome
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- El autismo - Sin Síndrome X Frágil
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- La Incapacidad penetrante del Desarrollo (PDD no)
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- Síndrome de Asperger
  ¿Ha recibido el niño Probar de DNA (prueba de sangre) para el Síndrome X Frágil?
- Ningún Diagnóstico de Síndrome X Frágil (fmr -1 gene normal; 40 ni menos CGG Repite), el Autismo, Abajo Síndrome, ni alguna demora de desarrollo.

El número de niños/hermanos para quien usted ha sido responsable
fpara su cuidado y la educación para por lo menos los pasados tres meses

El número de niños/hermanos sin una incapacidad

El número de niños/hermanos con una incapacidad

La Composición de la familia

(Por favor no incluye al niño para quien usted completa la inspección)

Otros Niños/Hermanos	La fecha del Nacimiento	La Incapacidad de desarrollo, la Demora u otro Concierne	El Diagnóstico de la incapacidad
El niño #1	Select		
El niño #2	Select		
El niño #3	Select		
El niño #4	Select		
El niño #5	Select		
El niño #6	Select		
El niño #7	Select		

Continue Reset Form

BIPSSI - Part 1

Directions: Please click on the selection in the drop down box that best describes your child.

1. How old was your child when he/she could sit without support?

2. How old was your child when he/she began walking?

3. At what age did your child first say a first word?

4. At what age did your child first wave "bye-bye"?

5. At what age did your child first respond to her or his name?

6. At what age was your child toilet trained? (urine and BM, with not more than 3 accidents while awake in one year)

Continue Reset Form

BIPSSI - Part 3

Directions: Please click on the selection in the drop down box that best describes your child.

1. Does your child have low muscle tone/ muscle weakness?

2. Does your child have any seizures?

3. Has your child ever had frequent colds or nasal infections?

4. Has your child ever had cleft lip, cleft palate or an arched palate (top of the inside of the mouth).

5. Has your child ever had frequent ear infections (more than three per year)?

6. Does your child have problems with his or her eyes?

7. Does your child have a long face and / or long ears?

Continue Reset Form

BIPSSI - Part 4

Directions: Please click on the selection in the drop down box that best describes your child.

1. Has your child ever avoided looking others in the eye?

2. Has your child had problems at home or school?

3. Has your child had emotional problems?

4. Has your child had behavioral problems?

5. Has your child ever had treatment for emotional or behavioral problems?

6. Has your child ever taken medication for emotional or behavioral problems?

7. Has your child ever had difficulty keeping his or her attention focused?

8. Does your child talk with people he or she does not know or has your child done this in the past?

9. Does your child play with people he or she does not know or has your child done this in the past?

10. Has your child ever had problems with sad or depressed mood?

11. Has your child ever had problems with nervousness or anxiety?

12. Has your child ever had a problem with hurting himself or herself by head banging or biting hands, arms or other parts of their body?

13. Has your child ever picked at his or her skin or bit hands or fingers to the point of injuring self?

14. Does your child make the same movements over and over, such as rocking, twirling around, or clapping hands or has your child done this in the past?

15. Has your child ever had problems with saying the same word or phrase over and over?

16. Has your child talked about the same subject over and over with, the child to the point of development making it hard to hold a conversation with him or her?

17. Has your child ever had problems falling asleep or staying asleep?

18. Has your child ever had an upset or disturbed response to soft or light touch holding, hugs or attempted to cover himself or herself with heavy objects such as sofa cushions, a mattress, blankets, beanbag chairs, etc.?

19. Have you every heard your child talking to him or herself or making humming sounds?

Continue Reset Form

BIPSSI - Part 5

Directions: The following questions should be answered with the birth mother and father of the chiild in mind. Please click on the selection in the drop down box that best describes the blood parents of the mother and father of the child.

1. Have any women in the birth mother's blood family had early menopause ("going through the change of life") or premature ovarian failure?

2. Have any women in the birth father's blood family had early menopause ("going through the change of life") or premature ovarian failure?

3. Have any women in the birth mother's blood family or the birth father's family had cysts on the ovaries, cysts removed from the ovaries, or hysterectomy (removal of the uterus)?

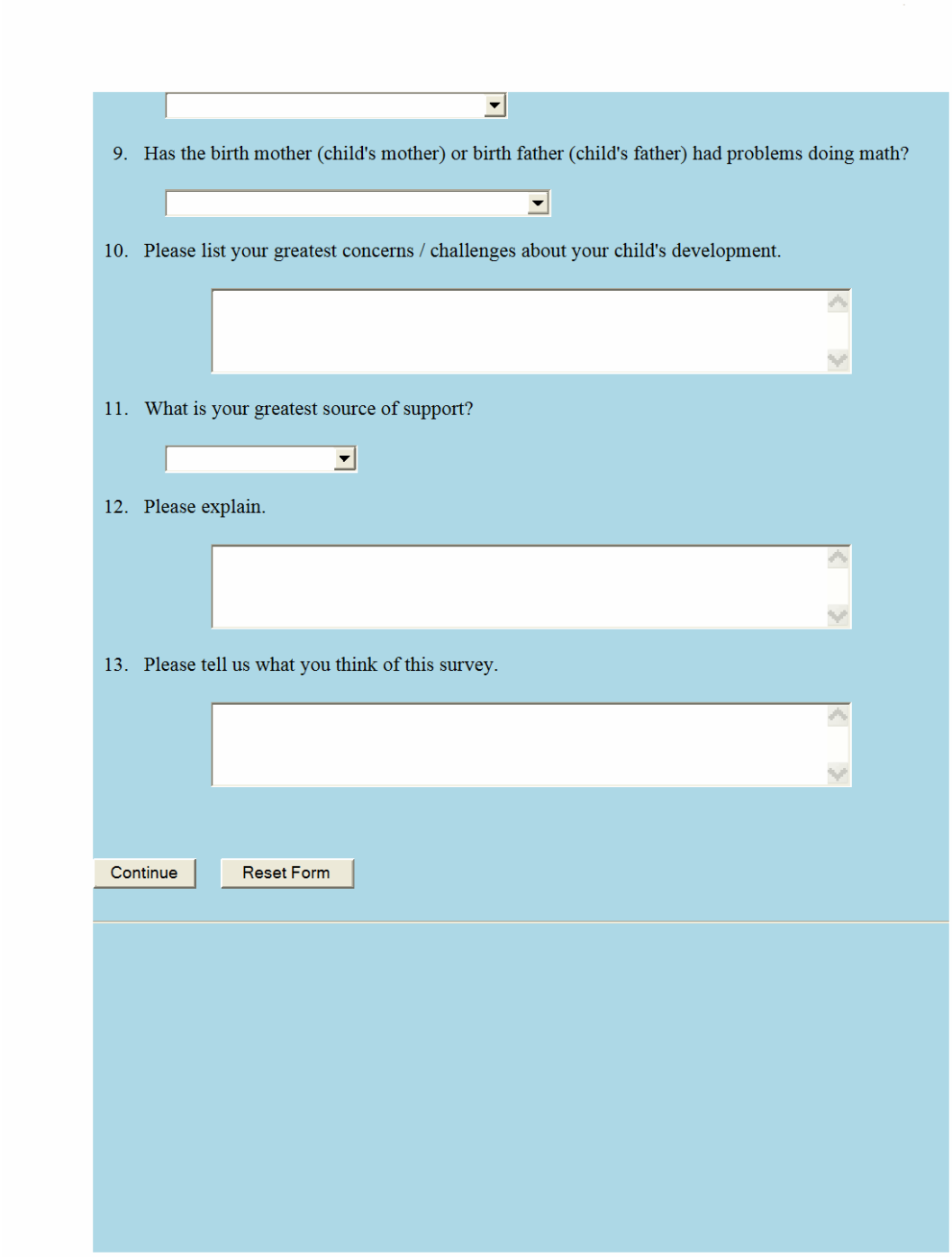
4. Did the mother (child's mother) feel depressed or nervous **before** becoming a parent?

5. Did the father(child's father) feel depressed, nervous or anxious **before** becoming a parent?

6. Is it or has it been hard for anyone in birth mother's blood family or the birth father's blood family to stop activities (such as, hand washing, checking locks, worrying, refusing to throw items away, computer use, watching television) or insist on doing things or having things done perfectly or exactly a certain way?

7. Has the birth mother or the birth father, now (or in the past) drank too much alcohol, used too many drugs, or used drugs too often, either those prescribed by a health care worker or those not prescribed?

8. Has anyone in the birth mother's blood family or the birth father's blood family had mental retardation / developmental disabilities, autism, Asperger Syndrome or Fragile X Syndrome?



9. Has the birth mother (child's mother) or birth father (child's father) had problems doing math?

10. Please list your greatest concerns / challenges about your child's development.

11. What is your greatest source of support?

12. Please explain.

13. Please tell us what you think of this survey.

Continue Reset Form

BIPSSI - Despide 1

Las direcciones: por favor chasquido en la selección en la gota hacia abajo caja que describe mejor a su niño.

1. ¿Qué edad era su niño cuando él/ella podría sentarse sin apoyo?

2. ¿Que edad era su nino cuando el/ella podria sentarse sin apoyo?

3. ¿En qué edad hizo su niño dice primero una primera palabra?

4. ¿En que edad hizo su nno primero onda “bye-bye” o “adios”?

5. ¿En qué edad hizo su niño responde primero a ella o a su nombre?

6. ¿En qué edad se entrenó su lavabo del niño? (la orina y BM, con no más de 3 los accidentes mientras se despierta en un año)

Continue Reset Form

BIPSSI - Despide 2

Las direcciones: por favor chasquido en la selección en la gota hacia abajo caja que describe mejor a su niño.

1. ¿Ha sido jamás su niño colocado en clases o programas talentosos, o en información recibida que él o ella son excepcionalmente brillantes?

2. ¿Ha tenido jamás su niño cualquier problemas de la habla?

3. ¿Ha recibido jamás su niño la terapia del habla?

4. ¿Ha tenido jamás su niño cualquier problemas del idioma?

5. ¿Ha recibido jamás su niño la terapia del idioma?

6. ¿Ha tenido jamás su niño cualquier problemas que aprenden?

7. ¿Tiene su niño una incapacidad que aprende, la demora de desarrollo (el aprendizaje lento) o la incapacidad de desarrollo?

8. ¿Ha asistido jamás su niño las clases especiales o dar clases privadas preescolar o recibido?

Continue Reset Form

BIPSSI - Despide 3

Las direcciones: por favor chasquido en la selección en la gota hacia abajo caja que describe mejor a su niño.

1. ¿Tiene su niño el tono bajo de músculo/la debilidad de músculo?

2. ¿Tiene su niño algún ataque?

3. ¿Ha tenido jamas su nino catarro o las infecciones nasals?

4. Tiene a su niño labio hendido jamás tenido, paladar hendido o un paladar arqueado (la cima del interior de la boca).

5. ¿Ha tenido jamás su niño las infecciones frecuentes de oreja (más de tres por año)?

6. ¿Tiene su niño los problemas con ojos?

7. ¿Tiene su nino una cara larga y/u orejas largas?

Continue Reset Form

BIPSSI - Despida 4

Las direcciones: por favor chasquido en la selección en la gota hacia abajo caja que describe mejor a su niño.

1. ¿Ha evitado jamás su niño los otros que miran en el ojo?
2. ¿Ha tenido su niño los problemas en casa o la escuela?
3. ¿Ha tenido su niño los problemas emocionales?
4. ¿Ha tenido su niño los problemas conductistas?
5. ¿Ha tenido jamás su niño el tratamiento para problemas emocionales o conductistas?
6. ¿Ha tomado jamás su niño la medicina para problemas emocionales o conductistas?
7. ¿Ha tenido jamás su niño mantener de dificultad su atención enfocada?
8. ¿Habla su niño con gente que no sabe o su niño ha hecho esto en el pasado?
9. ¿Juega su niño con gente que no sabe o su niño ha hecho esto en el pasado?
10. ¿Ha tenido jamás su niño los problemas con el humor triste o presionado?

11. ¿Ha tenido jamás su niño los problemas con el nerviosismo o la ansiedad?

12. ¿Ha tenido jamas su nino un problema con lastimar por pegando o golpeando de cabeza o mordendose los manos, los armamentos u otras partes de su cuerpo?

13. ¿Ha escogido jamás su niño en manos de piel o pedacito o dedos al grano de herir el ser?

14. ¿Hace su niño los mismos movimientos repetidamente, tal como meciendo, el giro alrededor, o manos que aplauden o su niño han hecho esto en el pasado?

15. ¿Ha tenido jamás su niño los problemas con decir la misma palabra o la frase repetidamente?

16. ¿Ha hablado su niño acerca del mismo sujeto repetidamente con, el niño al grano de desarrollo que hace para tener duramente una conversación con él o con ella?

17. ¿Ha tenido jamás su niño los problemas durmiendo o permaneciendo dormido?

18. ¿Ha tenido jamás su niño un contratiempo o la respuesta perturbada suaves o para encender el toque teniendo, los abrazos o procurado a la cubierta él mismo o a ella misma con objetos pesados tal como cojines de sofá, un colchón, las frazadas, sillas de bolsa de frijoles, etc..?

19. ¿Usted cada le ha oído a su niño que hablale o a ella misma o hacer tararear los sonidos?

Continue Reset Form

BIPSSI - Despida 5

Las direcciones: Las preguntas siguientes se deben contestar con la madre del nacimiento y el padre del chiild en la mente. Por favor chasquido en la selección en la gota hacia abajo caja que describe mejor a los padres de sangre de la madre y el padre del niño

1. ¿Ha tenido cualquier mujer en la familia de sangre de madre de nacimiento la menopausia temprana (" atravesar el cambio de la vida") o el fracaso ovárico prematuro?

2. ¿Ha tenido cualquier mujer en la familia de sangre de padre de nacimiento la menopausia temprana (" atravesar el cambio de la vida") o el fracaso ovárico prematuro?

3. ¿Ha tenido cualquier mujer en la familia de sangre de madre de nacimiento o la familia de padre de nacimiento quistes en los ovarios, los quistes quitados de los ovarios, o de la isterectomía (la eliminación del útero)?

4. ¿Hizo a la madre (madre de niño) se siente presionado o nervioso antes de llegar a ser a un padre?

5. ¿El padre (niño engendró) se siente presionado, nervioso o ansioso antes de llegar a ser a un padre?

6. ¿Es o ha sido duro para cualquiera en la familia de sangre de madre de nacimento o la familia de sangre de padre de nacimiento para parar las actividades (como, lavando los manos, cerraduras que verificcan, preocupado, rehusar para trirar articulos lejos, el uso de la computadora, mirando la televsion) o isite a hacer las cosas o las cosas que tienen hecho perfectamente o exactamente una cierta manera?

7. ¿Tiene la madre del nacimiento o al padre del nacimiento ahora (o en los pasados) tomaba mucho alcohol, usaba muchas drogas o usaba drogas frecuencia, o esos prescrito por un trabajador del cuidado de la salud o esos no prescrito?

8. ¿Cualquiera en la familia de sangre de madre de nacimiento o la familia de sangre de padre de nacimiento ha tenido problemas de mental (cabeza)/las incapacidades de desarrollo, el autismo, Síndrome de Asperger o Síndrome X Frágil?

9. ¿Tiene a la madre del nacimiento (madre de niño) o padre de nacimiento (padre de niño) los problemas tenidos las matemáticas que hacen?

10. Concierne de grande de más de el de su de favor de por de Liste/acerca de desafíos de Los de desarrollo de su de niño.

11. ¿Qué es su fuente el más grande de apoyo?

12. Explique por favor.

13. Diga por favor nosotros lo que usted piensa en esta inspección.

Continue Reset Form

M-CHAT

Please fill out the following about how your child usually is. Please try to answer every question. If the behavior is rare (e.g., you've seen it once or twice), please answer as if the child does not do it. For each question please chose "yes" or "no".

1. Does your child enjoy being swung, bounced, on your knee, etc.?

2. Does you child take an interest in other children?

3. Does your child like climbing on things?

4. Does your child enjoy playing peek-a-boo / hide and seek?

5. Does you child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?

6. Does your child ever use his / her index finger to point, to ask for something?

7. Does your child ever use his / her index finger to point, to indicate interest in something?

8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?

9. Does you child ever bring objects to you (parent) to show you something?

10. Does your child look you in the eye for more than a second or two?

11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)

12. Does your child ever smile in response to your face or your smile?

13. Does your child imitate you? (e.g. when you make a face will your child imitate it?)

14. Does your child respond to his / her name when you call?

15. If you point at a toy across the room, does your child look at it?

16. Does your child walk?

17. Does your child look at things you are looking at?

18. Does your child make unusual finger movements near his / her face?

19. Does your child try to attract your attention to his / her own activity?

20. Have you ever wondered if your child is deaf?

21. Does your child understand what people say?

22. Does your child sometimes stare at nothing or wander with no purpose?

23. Does your child look at your face to check your reaction when faced with something unfamiliar?

Finish Reset From

Please refer to: Robins, D., Fein, D., Barton, M. & Green, J. (2001). The Modified Checklist for Autism in Toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. Journal of Autism and Developmental Disorders, 31(2), 131-144. Used with permission of the authors.

M-CHAT

Llene por favor el siguiente acerca de cómo su niño es generalmente. Por favor prueba para contestar cada pregunta. Si la conducta es rara (por ejemplo, usted lo ha visto un par de veces), por favor respuesta como si el niño no lo hecho. Para cada pregunta escogió por favor "sí" o "no".

1. ¿Goza su niño es columpiado, botado, en la rodilla, etc..?

2. ¿Usted niño toma un interés en otros niños?

3. ¿Su nino le gusta subir en
cosas?

4. ¿Su nino le gusta jugar, la Mirada un se mofa/el cuero y
busca?

5. ¿Usted niño finge jamás, por ejemplo, para hablar en el teléfono o cuidar de muñecas, o fingir otras cosas?

6. ¿Usa jamás su niño el dedo del índice para señalar, pedir algo?

7. ¿Usa jamás su niño el dedo del índice para señalar, indicar el interés en algo?

8. ¿Puede jugar su niño apropiadamente con juguetes pequeños (E. G. coches o ladrillos) sin apenas mouthing, jugetear, o dejar caerlos?

9. ¿Usted niño jamás le trae objetos a usted (padre) para mostrarlo algo?

10. ¿Lo mira su niño en el ojo para más que un segundo o dos?

11. ¿Parece jamás su niño oversensitive al ruido? (por ejemplo, orejas que tapan)

12. ¿Sonríe jamás su niño en la respuesta a su cara o su sonrisa?

13. ¿Lo imita su niño? ¿ (E. G. cuando usted hace muecas la voluntad que su niño imita?)

14. ¿Responde su niño su nombre cuando usted llama?

15. ¿Si usted señala en un juguete a través de la habitación, su niño lo mira?

16. ¿Camina su niño?

17. ¿Mira su niño las cosas que usted miran?

18.¿Hace su niño los movimientos excepcionales de dedo cerca de su cara?

19. ¿Trata su niño de atraer su atención a su propia actividad?

20. ¿Se ha preguntado jamás usted si su niño es sordo?

21. ¿Entiende su niño que qué gente dice?

22. ¿Mira fijamente a veces su niño en nada o vaga sin propósito?

23. ¿Mira su niño su cara para verificar su reacción cuando encaró con algo no familiarizado?

Finish Reset From

Refiérase por favor a: los Petirrojos, D., Fein, D., Barton, M. & Verde, J. (2001). La Lista de verificación Modificada para el Autismo en Pequeñines: Un estudio inicial investigando el descubrimiento temprano de autismo y desórdenes de desarrollo penetrantes. El diario de Autismo y Desórdenes de desarrollo, 31(2), 131-144. Usado con el permiso de los autores.

APPENDIX L

Rationale for Internet Data Collection Method

Internet

The Internet has become an important communication tool in modern society (Frankel & Sanyin, 1999). Potentially, the Internet may change the way we conduct scholarly research (Harris & Dersch, 1999). The Internet can be very beneficial in the areas of participant recruitment and data collection. Internet sites that house questionnaires or other forms of survey instruments are not significantly different from other research involving questionnaires. Researchers to ensure results that are both reliable and valid must adhere to specific guidelines and protocols. Despite the similarities between traditional (pen and paper) and Internet conducted research, there are differences that must be addressed (Harris & Dersch, 1999).

World Wide Web (WWW) technology is affording opportunities for research never before possible. For instance, a study of cholangiocarcinoma, a rare cancer of the bile ducts, was possible when a computerized disease tracing system was developed that could then access a database using the Web. Data were gathered from patients diagnosed with cholangiocarcinoma at the Mayo Clinic and Foundation outpatient clinics and hospitals. Permission was obtained from the institutional review board, the security committee, the clinical practice committee, and the legal department (de Groen, Barry, & Schaller, 1998).

There are many benefits of conducting research online including data collection from widely dispersed populations with lower cost (Frankel & Sanyin, 1999). Internet research may provide certain individuals or populations with the opportunity to be involved in research of which they may otherwise be unaware. According to Currie

(1999), recruiting subjects from the web is no different than soliciting using consumer groups' newsletters. Subject recruitment via the Internet is bound by the same ethical principles that bind conventional subject recruitment.

Lenert et al. (2002) tested the validity of data collected via the Internet by conducting a study to determine if subjects who participated in migraine research on the Internet actually had the disorder. The subjects were screened using various methods including a comparison of their reported symptoms with the International Headache Society's criteria for diagnosis of migraines. Of the 45 participants who consented for physician verification of their Internet-derived diagnosis, 44 (97.6%) were confirmed by their physicians, and one had another primary diagnosis of cluster headaches. Lenert et al. (2002) concluded, "the validity of self-reported diagnosis of migraine does not appear to be an obstacle to conduction research in subject populations on the Internet" (p. 200).

Although there are many advantages to conducting Internet research, there are ethical and scientific concerns as well (Currie, 1999). Internet researchers must address potential breaches of privacy and confidentiality related to technology in order to minimize any potential risks (Frankel & Sanyin, 1999). Raw data cannot be locked in a file cabinet when conducting Internet research, so ensuring data is encrypted and behind firewalls is essential (Lutz & Henkind, 2000). In addition, participants need to know how the information they are providing will be used both now and in the future.

Informed consent has also been a topic that needs special consideration. Safeguards need to be built in that would ensure the participant fully understands what they have read. For example, Lutz, and Henkind suggest asking participants to read pertinent information about the study and be quizzed afterward. In addition, Currie

(1999), suggests giving potential participants the opportunity to ask the researcher questions via interactive e-mail or telephone contact. One drawback of Internet research in general is that it excludes anyone who does not have Internet access. For people with few economic resources this can be a barrier to their participation (Harris & Dersch, 1999).

Although Internet research is creating some exciting opportunities for scientific research, it is not without potential problems. Internet recruitment and data collection are becoming well accepted and researchers must be willing to educate themselves regarding the above-mentioned unique differences inherent to Internet research so reliability and validity can be maintained.

VITA

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