The Dissertation Committee for Andrea Lynn Hester Certifies that this is the approved version of the following dissertation:

Evaluation of Psychological Functioning and Neuroanatomy in Children with 18q- Following Growth Hormone Treatment

Committee:

Margaret Semrud-Clikeman, Supervisor

Timothy Keith

William Koch

Timothy Schallert

Jannine Cody

Evaluation of Psychological Functioning and Neuroanatomy in Children with 18q- Following Growth Hormone Treatment

by

Andrea Lynn Hester, B.A., M.A.

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DEDICATION

This dissertation is dedicated to the strength, spirit, and memory of my beautiful sister, Shauna Jacobson.

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Evaluation of Psychological Functioning and Neuroanatomy in Children with 18q- Following Growth Hormone Treatment

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Supervisor: Margaret Semrud-Clikeman

This study investigates psychological functioning and neuroanatomical underpinnings in children with 18q- before and after growth hormone (GH) treatment. Children with 18q- were referred for participation in this study by the Chromosome 18 Clinical Research Center. Overall, children with 18q- scored lower across composite measures of cognitive and adaptive behavior functioning, and higher on a measure of behavioral symptoms when compared to controls, both before and after GH treatment. Analyses of brain regions revealed neuroanatomical abnormalities in children with 18q-, including smaller midsagittal corpus callosum area, larger lateral ventricle volume, and reversed cerebral hemisphere asymmetry when compared to controls. Contrary to expectations, control participants did not have larger right than left cerebral hemispheres, and instead exhibited overall symmetrical hemispheres. Total cerebral volume was found to not significantly differ in participants with 18q- and controls. Post GH treatment, there was

significant growth in children with 18q- in regard to head circumference and midsagittal corpus callosum area, and a trend towards greater right hemispheric volume, particularly in female participants. The neuroanatomical abnormalities associated with 18q- suggest that there is significant and pervasive neural system disruption, likely associated with global dysmyelination previously documented in these individuals. It probable that the neuroanatomical abnormalities associated with 18q- have various functional implications in addition to those found in the comparatively impaired levels of functioning across psychological measures. It is hoped that the results of this study will expand knowledge regarding the relationship of neurological underpinnings with psychological functioning in individuals with 18q-, and ultimately, help inform medical professionals, parents, and educators regarding the unique needs that children with this disorder present.

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CHAPTER 1: INTRODUCTION

Overview

With the recent technological breakthroughs in chromosome mapping techniques, geneticists are able to identify chromosome abnormalities associated with various diseases, disorders, and syndromes. Chromosome abnormalities can involve the duplication, translocation, or deletion of genetic material from chromosomes. One of the most common chromosome deletions occurs with the 18th chromosome (e.g., 18q-) (Cody et al., 1999a; Kline et al., 1993). People with deletions of 18q have missing genetic material from the long ("q") arm from one copy of the 18th chromosome. While the clinical manifestations of 18q- are variable, typical associated characteristics include mental retardation, microcephaly, central nervous system (CNS) dysmyelination (i.e., decreased myelination in the brain), delayed growth, hypotonia, hearing impairment, and dysmorphic features (Kline et al., 1993; Loevner et al., 1996; Ono, 1994; Strathdee et al., 1995). Delays in growth have been linked to growth hormone (GH) deficiency (Cody et al., 1997a; Ghidoni et al., 1997). The majority of research regarding 18q- has focused on describing the various physiological aspects of the disorder or associated cognitive deficits, such as mental retardation (Cody et al., 1997a; Mahr et al., 1996). Less is understood regarding behavioral aspects associated with 18q-, such as adaptive and emotional/behavioral functioning. However, behavioral difficulties such as hyperactivity, aggression, and autism have been documented (Mahr et al, 1996; Philippe et al, 1999; Semrud-Clikeman et al, 1999). Additionally, decreased

adaptive behavior skills were also noted in individuals with 18q- (Semrud-Clikeman, et al., 2005).

The Link between Growth Hormone Deficiency and Neuroanatomy

As previously mentioned, a commonly associated feature of 18q- is growth hormone (GH) deficiency. Individuals with 18q- who are GH deficient have been noted to have CNS dysmyelination which is believed to be associated with the absence of crucial genes that are implicated in the formation of myelin (Cody et al, 1997a). The cognitive and behavioral implications of dysmyelination are not fully understood, although children who have incomplete CNS myelination generally exhibit impairment in cognitive functioning and delayed acquisition of developmental milestones (Ono et al., 1994). In individuals with 18q-, dysmyelination has been noted throughout the brain, indicating global volumetric deficits in white matter (Hardies et al., 2000; Miller et al., 1990; Ono et al., 1994). It follows that such dysmyelination in individuals with 18q- would be associated with cognitive impairment.

One of the major myelinated structures in the brain is the corpus callosum. The corpus callosum plays an important role in cognitive functioning, as it is generally believed that it serves to segregate and integrate brain functions that are lateralized to one hemisphere or the other, essentially allowing for interhemispheric transmission of information (Gazzaniga, 1998; Peterson, et al., 1994). The corpus callosum has also been implicated in information processing speed (Rao et al., 1989). Abnormal corpus callosum have been reported individuals with 18q- (Bekiesinska-Figatowska & Walecki, 2001; Gay et al., 1997; Kochunov et al.,

2005). This finding is somewhat controversial, as the corpus callosum has also been reported to be normal in some children with 18q- (Loevner, 1997; Mahr et al., 1996; Miller et al., 1990). Agenesis or underdevelopment of the corpus callosum, as well as global dysmyelination in individuals with 18q-, could conceivably greatly impact cognitive, adaptive, and behavioral functioning due to inhibition of both neural connectivity and interhemispheric transfer of information. Equivocal findings support the need for further study in this area.

Implications for Growth Hormone Treatment in 18q-

It is well documented that growth hormone (GH) treatment increases linear growth and improves muscle tone (Eiholzer, Bachmann & I'Allemand, 2000; Laron & Galatzer, 1980; Strobl & Thomas, 1994). However, the effects of GH treatment now extend beyond improving physical growth to address cognitive functioning delays (Anneren, Tuvemo, & Gustafsson, 2000; Laron & Galatzer, 1980; Sartorio et al., 1996). Recent findings by the research team at the University of Texas Health Science Center in San Antonio indicate that GH administration to individuals with 18q- who are GH deficient have increased psychometric intelligence scores on intellectual testing (i.e., the Wechsler Intelligence Scales-Third Edition (WISC-III) (Cody et al., 1999; Cody et al., 2005; Semrud-Clikeman et al., 2005). The exact neurophysiological mechanism behind increased IQ scores post GH treatment is not fully understood at this time, but it may be implicated in increased levels of CNS myelination that has been reported in individuals with 18q- after treatment with GH (Hardies et al., 2001). Such an increase in myelination may allow faster neural conduction of information (Churchland, 1995). It is unclear as to whether similar

improvements in speed of information processing are present post GH treatment in individuals with 18q-.

Less is understood about the potential benefits of GH on improving behavioral difficulties associated with 18q-, such as with adaptive behavior functioning (e.g., the ability to function independently in one's environment) or with emotional and behavioral aspects such as hyperactivity or aggression. It is possible that improved levels of intellectual functioning in individuals with 18q- who are administered GH treatment may likewise be associated with improvement in emotional/behavioral functioning and adaptive behavior. GH treatment has been implicated in improving emotional and behavioral functioning in individuals with other disorders, such as Turner's syndrome (Lagrou et al., 1998), intrauterine growth retardation (Van der Reijden-Lakeman et al., 1997), and isolated growth hormone insufficiency (Laron & Galatzer, 1980).

Description of Current Study

This study investigates the cognitive, adaptive, and behavioral implications of short-term growth hormone (GH) treatment in individuals with 18q- who are GH deficient. This study will further explore whether such improvements post GH treatment are also reflected in changes in neuroanatomy. Preliminary review of participant Magnetic Resonance (MR) images revealed that direct volumetric analyses of white/gray matter change in individuals with 18q- are not feasible due to poor boundary demarcation between the matter boundaries on MR images. Therefore, MR image analyses of total cerebral volume, left/right cerebral volume asymmetry, and increase in corpus callosum area change post GH treatment may

provide indirect structural correlates for increased myelination. A relative increase in overall cerebral volume may be related to increases in IQ post GH treatment, as brain volume has shown to be positively correlated with IQ (Reiss et al, 1996). Comparisons between the right and left hemispheric volume pre and post GH treatment may provide clues as to changes in myelination, as greater ratios of white matter to gray matter have been reported in the right hemisphere in normally developing children (Teeter & Semrud-Clikeman, 1997). Possible growth in corpus callosum area post GH treatment might also be related to improved interhemispheric transfer of information, and thus, improved cognitive performance and information processing speed. However, it should be noted that change in CNS white matter may be due to a number of factors, including total number of fibers, thickness of axons, or the myelin content of the axons or fibers per unit area (Woiciechowsky, Vogel, Myer, & Lehmann, 1997) and, therefore, distinct cerebral changes (i.e., increased myelination) associated with any volume change would be unknown.

This study is part of an ongoing research project at the University of Texas Health and Science Center in San Antonio, in conjunction with the University of Texas at Austin. Participants with 18q- were recruited from the Chromosome 18 Clinical Research Center. Psychological measures used to assess participants were selected prior to the current analysis. Participants ranged from 2 years to 14 years of age. Comparisons were made between participants with 18q- prior to and after receiving GH treatment, as well as with normal controls.

It is hoped that results from this study will further the applicability of GH treatment for individuals with chromosome disorders in not only improving

cognitive ability but adaptive and emotional/behavioral functioning as well and potentially aid in diagnosis and treatment planning for individuals with 18q-. It is also hoped that findings will support the applicability of utilizing brain imaging as a further means of establishing the impact of GH treatment on the brain in individuals who are GH deficient.

CHAPTER 2: LITERATURE REVIEW

Historical Context

In 1964, De Grouchy first described the existence of a terminal deletion on the long arm of the 18th chromosome in a 1-year-old child. Although genetic testing and understanding of phenotypic expressions associated with genetic disorders was in its infancy at that time, De Grouchy was able to document physical phenotypes associated with a deletion on the 18th chromosome. He reported characteristics such as psychomotor retardation, microcephaly, short stature, malformation of the palate, atresia of the middle ear, kidney malformation and abnormalities in finger whorls and palmar fold (De Grouchy et al., 1964). Such physical characteristics have now been determined to be commonly associated with 18q- (Cody et al, 1997; Strathdee et al, 1996)

Identification of 18q-

Chromosome disorders can manifest in various ways, such as having added, translocated, or deleted genetic material. Most chromosome deletions are terminal, meaning that the missing piece is from a break point to the end of the chromosome. Some deletions are interstitial, which means that the missing piece is between two break points. Each chromosome has a short and a long arm (e.g., p and q, respectively) that are separated by the centromere. Common areas of deletions on the q arm occur from 18q21.1 to 18q23 (see Figure 1, below), although deletions can occur in other regions of the chromosome (Cody et al., 1997b).

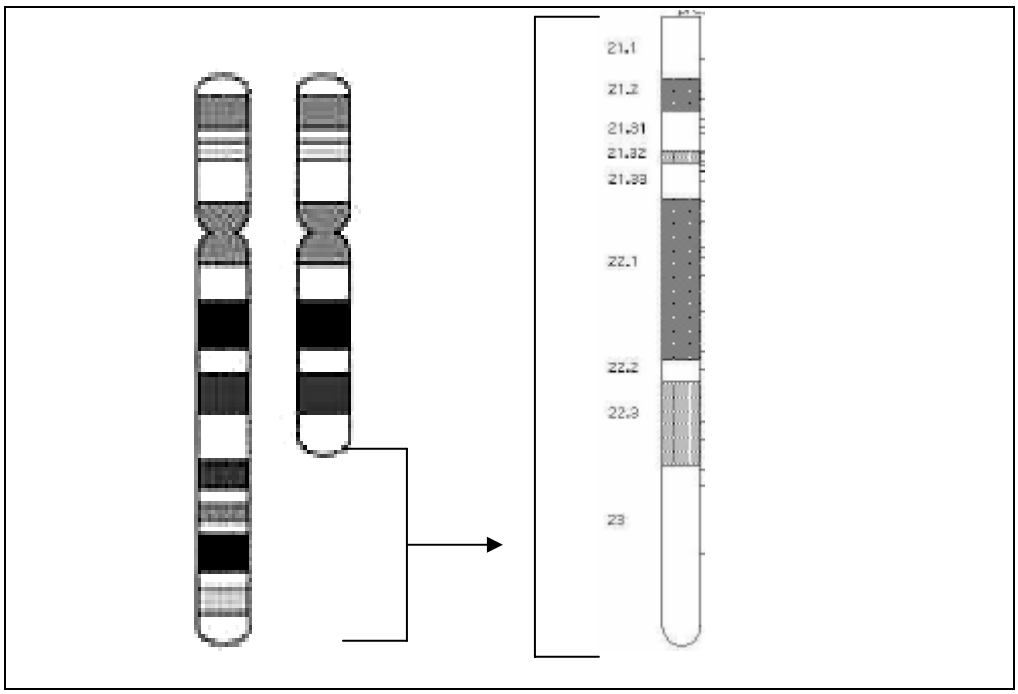

Figure 1. Areas of deletion from the "q" arm of one copy of chromosome 18.

Adapted from the Chromosome 18 Registry website (www.chromosome18.org.) & Coriell Institute for Medical Research website (http://locus.umdnj.edu/nigms/ideograms/18q.html)

Each chromosome arm has numbered bands that indicate the distance from the centromere (i.e., the higher the band number, the further away from the centromere). The micrograph of the chromosomes provides a diagnosis of 18q- when a deletion from the long arm of one of the two copies of the 18th chromosome is of sufficient size to be visible on a high-resolution karyotype.

Etiology of 18q-

The majority of chromosome deletions arise as de novo events, meaning that the deletion is a new one and occurred during the formation of the sperm or egg or very early in embryonic development. Parents who have normal chromosomes have

a low probability of having a child with a chromosome abnormality. Some cases of 18q- result from a balanced translocation, meaning one parent has a deletion on one chromosome, but the deleted piece is attached to another chromosome. Usually such parents have no symptoms, but have a significant chance of having a child with an unbalanced translocation (i.e., missing or extra chromosome material). There appears to be a prevalence of paternally derived deletions, presumably due to increased number of cell divisons in sperm cells (Cody, et. al., 1997b). Advanced parental age does not appear to be a risk factor associated with 18q- (Cody et al, 1997b), unlike other chromosome disorders such as Trisomy 21 (Moldavsky et al., 2001). There is no reported evidence at this time that 18q- is caused by exposure to environmental agents such as medicine, toxins, or radiation. There is also no current evidence that one ethnic group or geographic area is at increased risk.

Deletions of chromosome 18 (18q-, 18p-, and ring 18) occur in approximately 1 in every 40,000 births (the Chromosome 18 Registry and Research Society, 1991). The incidence of 18q- is higher in females, with the female to male ratio at 1.7/1. Birth weight for individuals with 18q- averages 6 lb 2 oz., which is below average but is still considered to fall within the normal range for infant birth weight.

Characteristics and Symptoms of 18q-

Disorders involving chromosome deletions are characterized by a karyotype revealing missing pieces of chromosome. The exact size and placement of deletion sites vary, so the clinical presentation of symptoms is likewise variable. However, in general, individuals with 18q- exhibit often exhibit poor growth due to growth

hormone (GH) deficiency, cognitive deficits, speech difficulties, microcephaly, CNS dysmyelination, hypotonia, and hearing impairment (Cody et al, 1997a; Hale et al., 2000; Kline et al., 1993; Ono et al., 1994; Strathdee et al., 1996). Many of these individuals also exhibit behavioral difficulties such as hyperactivity and aggression, as well as autistic features (Mahr et al, 1996; Philippe et al, 1999; Semrud-Clikeman et al, 1999). While there is overlap in both physiological and behavioral phenotypes, there is still wide variability in the number and severity of symptoms. (See Table 1 for major clinical features of 18q-).

Table 1

Major Clinical Features Associated with 18q- (N = 42)

Characteristic	Percent
CNS Dysmyelination	97
Speech failure	91
Hypotonia	79
Decreased or absent deep tendon reflexes	76
Foot deformities	74
Hearing Loss	70
Mental Retardation (e.g., IQ <70)	68
Gait abnormalities	68
Growth hormone deficiency	68
Proximally placed thumbs	65
Atretic/Stenotic canals	64
Tremor	62
Short stature	61
Microcephaly	53
Optic nerve hypoplasia	23
Autistic features	20
Nystagmus	14

Note. From the Chromosome 18 Clinical Research Center at the University of Texas Health Science Center at San Antonio, 2000.

Prognosis

The prognosis for individuals with 18q- varies, but their life span is presumed to be typically normal (Kline et al, 1993; Strathdee, et al., 1995). As the majority of individuals are identified with some degree of mental retardation, many have delays in adaptive behavior skill levels that significantly limit their ability to live independently. Some individuals with 18q- are reported to have delayed puberty, which presumably is associated with endocrine dysfunction. Development of progressive tremors has been reported as individuals reach adulthood (Mahr et al., 1996; Miller, et al., 1990). Emotional and behavioral dysfunction often increases in severity with onset of puberty, therefore early intervention services are recommended to improve quality of life for themselves and their caretakers (Semrud-Clikeman, et al., 1999).

The Role of Gene Deletion Size and Sites in Phenotype

It has been hypothesized that the severity of the symptoms associated with 18q- is related with the size of the chromosome deletion, since it was assumed that more missing genetic material would result in increased overall impairment. Conflicting research regarding the impact of gene deletion size on physical and behavioral impairment has been reported, making definitive links between size of the deletion and phenotype initially difficult to determine. Some studies have posited that symptom severity is not associated with deletion size, specifically in regards to IQ, adaptive functioning, behavioral difficulties, or MRI abnormalities (Mahr et. al., 1996; Strathdee et al., 1995). However, other studies involving molecular analysis of breakpoint sites, such as reported by Kline et al (1993),

supported this assertion, correlating deletion size with the severity of the phenotype. Indeed, recent findings support the argument that symptom severity and variability within individuals with 18q- is associated to the size of the deleted chromosome region (Cody et al., 1997; Semrud-Clikeman et al., 2005). It should be noted that the field of genetics is rapidly progressing, and new evidence may yield new insight regarding the relationship between missing genes of the 18th chromosome and specific phenotypic expression.

In addition to deletion size, the site of deleted genes on the long arm of the 18th chromosome can also impact phenotype, as certain regions have been associated in specific clinical manifestations. Commonly reported areas of deletion sites in 18q- are located from 18q21.1 to 18q23 (Cody et al., 1997a; Kline et al., 1993; Mahr, et al., 1996; Ono et al., 1994; Strathdee et al., 1995). Strathdee et al. (1995) mapped clinical features such as microcephaly and genitourinary malformations to a deletion proximal to 18q23, although microcephaly has also been reported in cases with deleted sites at 18q21 (Kline et al., 1993; Miller et al., 1990; Wilson, 1979). One such deleted site that is of particular interest to this study is the localization of a gene associated with growth hormone deficiency to a deletion at 18q23. This region is also implicated in CNS dysmyelination, cognitive dysfunction, and possibly in behavioral difficulties in individuals with 18q- (Cody et al., 1997a; Gay et al., 1997).

Cognitive Functioning in 18q-

Definition of Mental Retardation

The American Psychiatric Association (APA) (1994) and the American Association on Mental Deficiency (AAMD) (Grossman, 1983) define the term mental retardation as involving two key components: 1) significantly delayed intellectual functioning that exists concurrently with, 2) deficits in adaptive behavior (the latter of which includes difficulties with personal and social responsibility) (Sattler, 1992). However, this definition of mental retardation has been criticized for inclusion of the social responsibility component, which is argued as difficult to define and measure (Zigler, Balla, & Hodapp, 1984). Therefore, alternate definitions of mental retardation have been conceptualized in terms of cognitive performance on standardized intelligence tests (e.g., more than 2 *SD* below the mean) without evaluation of an adaptive behavior component. For example, an IQ standard score of 69 or below on the Wechsler Intelligence Scales would be considered to fall in the mentally retarded range (Sattler, 1992) without using adaptive behavior skills for the determination of mental retardation. Sattler (1992) uses the term "mental retardation" to describe children who are functioning two standard deviations or more below the mean for IQ. This study will utilize both IQ and adaptive behavior functioning as variables of interest.

Etiology of Mental Retardation

Mental retardation (MR) affects approximately 3% of the general population, yet a diagnosis is obtained in only a third of all cases (Flint, et al., 1995; Knight, et al., 1999; Singh, Oswald, & Ellis, 1998). Several factors impact the identification of MR, as individuals with MR do not compose a homogeneous group and differences in etiologies, clinical presentations, and levels of impairment are

commonly reported (Singh et al., 1998). However, more severe levels of MR are generally associated with a responsible etiological agent (Singh et al., 1998). Etiological determinants of mental retardation that can occur both prenatally and postnatally include genetic abnormalities, exposure to teratogens (e.g., alcohol, narcotics, etc.), nutritional deficiency, birth complications, neglect, abuse, and exposure to toxins such as lead (Hart et al., 1996; Teeter & Semrud-Clikeman, 1997). Etiology associated with chromosome abnormalities account for approximately 30-40% of identified cases of MR (Knight et al., 1999). Studies investigating intellectual functioning in 18q- have reported a wide range of IQ scores on standardized tests (i.e., < 40 to 120) (Cody, personal communication; Mahr et al., 1996). However, despite variability in IQ scores, most children with 18q- have some degree of mental retardation.

Familial versus Organic Mental Retardation

Sattler (1992) discusses how the etiology of mental retardation can affect clinical manifestation and prognosis. He refers to two primary etiological groups: familial and organic. The familial group describes the majority of mentally retarded individuals (i.e., 85%) and involves mild levels of mental retardation that arises as a result of subclinical organic brain damage or a combined effect of genetic factors and below average environment (i.e., extreme poverty). These individuals are generally capable of improving their adaptive skills over time and tend to be more receptive to social reinforcement than non-retarded peers. Further, individuals with familial retardation may display improvements in IQ during adolescence or early adult years. Factors such as environmental stimulation and social interaction can

improve aspects of cognitive functioning in such individuals in regard to language development and intellectual capacity, as well as behavioral functioning. Conversely, the organic group is more rare (e.g., 15%) and generally involves more severe intellectual deficits. The etiology of the organic group includes individuals with genetic defects (e.g., chromosome abnormalities) that significantly affect prenatal brain development. Such individuals exhibit diffuse effects from abnormal brain development, such as significantly delayed language and motor milestones, low IQ, and marked impairment in behavioral development. Based on these two etiological groupings, individuals with 18q- meet criteria for categorization in the organic group due to the genetic component associated with abnormalities in prenatal brain development, cognitive impairment and developmental delays.

Stability of IQ in Individuals with Mental Retardation

Sattler (1992) asserted that individuals with the mildest form of mental retardation (e.g. from familial group vs. organic group etiology) may show a small increase in IQ scores due to environmental influences during adolescence or early adulthood. However, the majority of mentally retarded individuals have been shown to exhibit less change in IQ when retested than non-retarded individuals, particularly in children with moderate to severe retardation (Naglieri & Pfeiffer, 1983; Sattler, 1992; Silverstein, 1982). There have also been studies that report decreases in intellectual and adaptive functioning in mentally retarded individuals with genetic disorders such as fragile X, Down syndrome, and autism spectrum disorders upon subsequent examination (Fisch, Simensen, & Schroer, 2002; Wishart, 1993), particularly on tasks requiring inferential reasoning and abstract

thought. Several factors can impact variability of IQ test scores in the same individual with MR. Intervals between assessments and type of IQ test used can impact IQ scores, as shorter testing intervals and use of the same test often results in more similar IQ scores (Sattler, 1992). Also, declines in norm referenced cognitive and adaptive behavior scores may reflect slower skill acquisition when compared to normal children instead of an actual regression of ability. Sattler (1992) suggests clinical comparison of raw scores as well as the use of standard scores, which may avoid potential problems when using norm-referenced scores to assess mentally retarded individuals.

Mental Retardation in 18q-

Mental retardation is one of the most commonly noted characteristics in individuals with 18q- (Cody et al., 1999b; Mahr et al., 1996). The severity of cognitive delay varies in these individuals, with reported IQ scores ranging from severely delayed (< 40) to superior (120) on standardized intellectual tests such as the Wechsler Intelligence Scale for Children (Chromosome 18 Registry and Research Society, 1991; Mahr et. al, 1996; Wechsler, 1991). Performances on neuropsychological measures of attention, novel problem solving, memory, language, visuomotor integration, and fine motor dexterity have been reported to be in the moderately to severely impaired range in individuals with 18q- (Mahr et al., 1996). Mahr et al. (1996) further concluded that executive functioning tasks requiring mediation by the frontal lobes (i.e., problem solving, cognitive flexibility, and motor control) were most notably impaired in individuals with 18q-. However, this study included a wide age range (e.g., from 2 to 47 years of age), which makes

it unclear whether conclusions drawn from his sample regarding neuropsychological performance is generalizable to children with 18q-. In addition, many of the participants included in the study were unable to complete many of the neuropsychological measures used due to age inappropriateness, thus further limiting the generalizability of these findings to children.

Processing Speed and Attention

One of the components involved in cognitive ability involves speed of information processing. Information processing speed refers to the ability to rapidly scan an array of information, a skill that involves a high degree of concentration and attention (Sattler, 1992). While attention deficits alone have not been shown to be associated with lower IQ (Sattler, 1992), attentional deficits have been associated with problems with information processing and speed of cognitive processing (Elliott, 1990; Teeter & Semrud-Clikeman, 1997). Widely used intelligence tests such as the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991) and the Differential Ability Scales (DAS) (Elliott, 1991) include processing speed tasks as part of the testing battery. The degree to which processing speed is related to IQ is controversial, as some studies have reported that it accounts for only 10-20% of the variance in IQ, indicating that processing speed is a construct with a high level of specificity independent of intelligence (e.g., overall cognitive ability) (Elliott, 1990; Posthuma et al., 2001; Spearman, 1923). However, processing speed (i.e., "inspection time") has been reported to correlate with IQ, and highest with Performance IQ (r = -0.54), indicating that individuals with higher IQ's tend to have

shorter processing speed times (Kranzler & Jensen, 1989; Posthuma, De Geus, & Boomsma, 2001).

Despite equivocal findings regarding the degree to which processing speed relates to IQ, it is cautioned that processing speed indices are not to be interpreted as sole indicators of overall cognitive functioning (Sattler, 1992; Wechsler, 1991), as other factors such as motor difficulties, attention deficits, short-term numerical memory, and visual impairment can also affect performance (Elliott, 1990; Sattler, 1992; Teeter & Semrud-Clikeman, 1997; Wechsler, 1991). Although no research to date has examined information processing speed in individuals with 18q-, it is likely that deficits exist in this domain that are comparable to delays in overall cognitive ability and may also be associated with attention deficits, short-term memory impairment, or visual tracking difficulties.

Adaptive Functioning and Cognitive Dysfunction

As previously discussed, while assessment of cognitive functioning level is important in determining intellectual ability in delayed individuals, it is also important to determine adaptive behavior functioning. Assessment of adaptive behavior provides an index for how well an individual can perform and navigate the demands of their everyday environment expected of their age and social group. As argued by Liss et al. (2001), adaptive skill level rather than cognitive ability is the determining factor in whether individuals require constant supervision or are able to function more independently. A common measure used to determine adaptive functioning is the Vineland Adaptive Behavior Scales (VABS) (Grossman, 1983; Sparrow, Balla, & Cicchetti, 1984). The VABS includes components believed to be

involved in adaptive functioning, such as daily living skills, communication skills, socialization, and motor skills. While the VABS is widely utilized for assessment of mental retardation (based on APA and AAMD criteria), accurate assessment of adaptive skills is dependent on the reliability of respondent answers on the questionnaire (Sattler, 1992).

Adaptive functioning in individuals with 18q- has been reported to be variable, but generally is delayed. Vineland Adaptive Behavior Composite scores for individuals with 18q- have been reported to range from severely impaired to normal (Mahr et al., 1996), reflecting the variability in symptoms that can associated with this disorder. Adaptive functioning has also been found to be delayed and generally commensurate with intellectual functioning in individuals with 18q- who have been identified as GH deficient (More et al., 2001). More et al. (2001) suggested that Vineland adaptive ratings may be negatively impacted by the high prevalence of behavioral difficulties represented in this population. Specifically, respondent perceptions of behavioral difficulties could impact item ratings that involve behavioral components such as social reciprocity, willingness to comply with caregiver rules or limits, or ability to display emotional control (Sparrow et al., 1984).

Behavioral Difficulties Related to Cognitive Dysfunction

Individuals with 18q- have been noted to exhibit behavioral difficulties such as attentional deficits, hyperactivity, low frustration tolerance, aggression, obsessive-compulsive disorder, and autism (Mahr et al, 1996, Philippe et al, 1999; Semrud-Clikeman et al, 1999). Mahr et al. (1996) reported that the most common

behavioral difficulties exhibited in 18q- include externalizing behaviors such as impulsivity, temper, and aggression. This study did not directly address the relationship between behavioral difficulties and intellectual ability in individuals with 18q-. However, it is likely that maladaptive behavior symptoms exhibited in 18q- is related to some degree with associated cognitive deficits. Behavioral difficulties similar to those noted in 18q-, such as hyperaggression, low frustration tolerance, and impulsivity, have been frequently reported in children with mental retardation associated with varied etiologies (Bihm, Poindexter, & Warren, 1998; Franzen & Berg, 1989; Singh, et al., 1998). Indeed, the prevalence of behavioral difficulties is up to five times higher in individuals with MR than in the general population (Singh et al., 1998). Individuals with genetic disorders such as 15q- (e.g. Prader-Willi), Phenylketonuria (PKU) and severe autism (Franzen & Berg, 1989; Liss et al, 2001) have been reported to have severe cognitive delays associated with behavioral dysfunction. Individuals with frontal lobe dysfunction associated with executive functioning deficits (which is involved in more advanced mental processes such as planning and organization of information) have been reported to have behavioral and social difficulties due to impulsivity, lack of insight, and deficits in complex reasoning (Kolb & Whishaw, 1996). Executive functioning difficulties are also closely interrelated with attentional deficits, the latter of which has been noted to occur more frequently in children with 18q- (24%) (Semrud-Clikeman, 1999) than in the general population (3-5%) (APA,1994). While the link between cognitive deficits and behavioral disorders is not well understood in 18q-,

there appears to be consensus as to the existence of behavioral difficulties in this population. Therefore, further study in this area is needed.

Social Interaction: Implications for Cognition and Behavior

It is important to consider how the interaction between a child's genotype and their environment can differentially affect the ways in which individuals respond to them. Children who are physically different or cognitively impaired may not receive the same quality or amount of interaction with others in their environment, thus potentially hindering their neurodevelopment. Therefore, it is important that children with cognitive and physical challenges receive rehabilitative services, as well as family and peer interaction to assist in realizing their full potential (Greenough et al., 1987; Park & Peterson, 2003). Given the numerous physical, cognitive, and behavioral difficulties, as well as potential lack of social interaction that can be associated with children identified with disorders such as 18q-, it is imperative that such services and considerations be given to improve overall functioning across various domains.

Neuroanatomical Implications of 18q-

To date, investigations as to how neurophysiological components are linked to cognitive and behavioral functioning in 18q- are in their preliminary stages. While some of the findings regarding brain development have been equivocal, there has been general agreement regarding findings of global levels of white matter CNS dysmyelination in children with 18q- (Gay et al., 1997; Lancaster et al., 2001; Mahr et al., 1996; Miller et al., 1990; Ono et al., 1994). Less is understood regarding the impact of brain dysmyelination on cognition and behavior in 18q-, and whether

reported change in cognition following growth hormone treatment (Cody et al., 2005) will also be reflected in other domains of functioning (e.g., adaptive behavior and behavioral functioning).

Myelination and Growth Hormone

As previously mentioned, common characteristics in individuals with 18q- include GH deficiency and decreased white matter (e.g., dysmyelination). Such factors are believed to play a central role in impaired cognitive, adaptive, and behavioral functioning in these individuals, presumably due to decreased neural connectivity. In individuals with 18q-, dysmyelination of white matter has been reported throughout much of the brain. Conflicting findings have been reported for the corpus callosum in individuals with 18q-, as some studies have reported normally myelinated corpus callosum (Mahr et al., 1996; Miller et al., 1990; Ono et al., 1994) and other studies have reported abnormal size of the corpus callosum (Bekiesinska-Figatowska & Walecki, 2001; Gay et al., 1997). Abnormalities of the corpus callosum are of interest to this study, as this region contains a high concentration of myelinated fibers which are implicated in interhemispheric transmission of information and a component of cognitive ability (Posthuma et al., 2001; Preis et al., 2000). The volume of the cerebral and existence of cerebral asymmetry may also provide indirect indices of white matter content and overall relative brain growth. This study will examine possible implications of dysmyelination on CNS development by examining specific brain structures such as the corpus callosum, left and right cerebral volume, and total cerebral volume.

The role of Myelination in Information Processing Speed. Myelinated axons serve to connect neurons in the cerebral cortex to other locations in the brain. Myelin is composed of protein and lipid layers that provide axonal insulation, enabling faster conduction of neuronal impulses, propagating signals within neurons. Conduction velocity of neurons depends on the fiber diameter of neurons, the number and form of ion channels contained in axons, and thickness of the myelin sheath (Posthuma et al., 2001). It is estimated that a well myelinated motor neuron in a human brain can conduct a neuronal impulse up to 130 meters per second, whereas an unmyelinated axon sends impulses at only approximately 0.5 meters per second (Churchland, 1995). Myelination is therefore implicated in the speed in which an individual is able to process information, as visual scanning and accurate perceptual discrimination of stimuli requires efficiency of synaptic neurotransmission (Posthuma et al., 2001).

Development of Myelin. Growth of myelin follows a developmental trajectory that can be observed via MR imaging. At birth, MR images typically reveal myelination in the posterior limb of the internal capsule, the cerebellar peduncle, and the corona radiata (Barkovich, 2000; Loevner et al., 1996). By 8 months of age, the splenium of the corpus callosum is typically recognizable in normally developing children (Miller et al., 1990). The progression of myelination rapidly continues during early infancy and by the age of two years typically shows patterns of myelination similar to that of adults (Loevner, et al., 1996; Ono, 1994). By 3 years of age, all the major fiber tracts are identifiable (Matsuzawa, 2001) and stabilization of myelin growth occurs by 5 years of age (Lancaster, 2001), although the process of myelination

continues through early adulthood (Churchland, 1995). During infant brain development, delays in myelination can result in difficulties in achieving developmental milestones (i.e., lack of myelination in the motor cortex results in delayed acquisition of motor milestones) (De Haan & Johnson, 2003; Kandel, et al, 2000).

Definitive detection of genes or combination of genes that are responsible for abnormal myelination is still subject to further study. However, the absence of the myelin basic protein gene (MBP), which is expressed in myelinating cells of the CNS, has been implicated in developmental abnormalities of white matter (dysmyelination) in individuals with 18q-. The location of the MBP gene is on the distal portion of chromosome 18q. It is speculated that the loss of one of the MBP genes in individuals with 18q-, possibly in association with other genes on 18q, may result in dysmyelination.

Demyelinating and Dysmyelinating Disorders. Disease models involving lack of CNS myelin allow for examination of its varied effects in individual functioning and correlations between brain imaging and myelin levels. Demyelinating diseases such as Multiple Sclerosis (MS), adrenoleukodystrophy (ALD), and metachromatic leukodystropy (MLD) involve actual loss of previously myelinated axons. These diseases can be detected and tracked via MR imaging (Barkovich, 2000) and all have varied physical and behavioral sequelae and pathological manifestations depending on the degree of demyelination and locations of CNS lesioning (Demyer, 1988). Dysmyelinating disorders, such as 18q-, differ from demyelinating diseases due to the failure of initial axonal myelin growth versus loss of existing myelin.

Both demyelinating and dysmyelinating disorders involve the prevention of nerve cells from transmitting impulses down their axons (Andreasen, 2001). The effects from inhibited neural transmission are diffuse, resulting in a wide variety of deficits depending on location, as with motor, language, memory impairment and emotional and behavioral difficulties (Pelletier et al., 2001). In children with 18q-, dysmyelination is believed to be related to a number of factors, including delayed developmental milestones (Ono et al., 1994) and mental retardation (Cody et al., 1999a; Hardies et al., 2001; Mahr et al., 1996) and may be implicated in behavioral difficulties (Loevner et al., 1996; Mahr et al., 1996).

Magnetic Resonance Imaging of Myelination. Through MR imaging, brain maturation (i.e., myelination) can be assessed through analysis of various components, including shortening of T1 and T2 relaxation times, reduced water diffusion, increased diffusion anisotropy, and increased magnetization transfer (Barkovich, 2000). In MR imaging and MRI relaxometry analyses in individuals with 18q-, central white matter tract abnormalities (e.g., dysmyelination) have been noted for both T1 and T2 values (Gay et al., 1997; Mahr et al., 1996). While global dysmyelination throughout the brain has been reported individuals with 18q-, normal patterns of myelination have been reported in the corpus callosum (Barkovich, 2000; Hardies et al., 2000; Loevner et al., 1996; Miller et al., 1990), although abnormalities in corpus callosum size have also been reported (Bekiesinska-Figatowska & Walecki, 2001; Gay et al., 1997; Kochunov et al., 2005).

Brain Volume

Cerebral Spinal Fluid and the Lateral Ventricles. Brain volume consists of cerebral spinal fluid (CSF) and both gray (neuronal) and white (myelinated) matter (Andreasen, 2001). The primary function of CSF is twofold: 1. to essentially act as a "shock absorber" for the brain, and 2., to mediate between blood vessels and brain tissue in the exchange of materials, such as nutrients. The choroid plexus, a highly vascular portion of the lining of the ventricular system, secretes CSF, the largest area of which is contained in the lateral ventricles. Morphometric and volumetric brain studies often include analysis of the lateral ventricles, as the presence of enlarged or misshapen lateral ventricles is often associated with disorders considered to be neurodevelopmental in origin, such as autism, idiopathic mental retardation, fragile X syndrome, Nijmegen breakage syndrome (NBS) and schizophrenia (Bekiesinska-Figatowska et al., 2004; Gilmore et al., 2001;Teeter & Semrud-Clikeman, 1997). Further, ventriculomegaly (enlarged ventricles) have also been associated with children with developmental delays and learning disabilities (Gilmore et al., 2001).

Developmental of White Matter (Myelination). White matter is so called due to the white-colored myelin sheaths that cover axons. In gray matter, CNS signals originate in neurons that travel down myelinated axons that compose white matter. White matter includes the major commissural tracts, cortical association fibers, and cortical afferent/efferent fibers. White matter is located in the central and subcortical regions of the cerebral and cerebellar hemispheres, accounting for approximately 60% of total brain volume. During infancy through young childhood, volumetric brain changes occur rapidly. By 5 years of age, total brain volume is approximately

95% of adult volume (Giedd, 1999; Matsuzawa et al., 2001; Reiss et al., 1996). Determination of brain volume in children is important because: "Measurement of cerebral volume is necessary for accurate or objective measurement of brain development and of change in the brain in the normal and in the pathological state" (Iwaskaki et al.,1997, p.841). Further, volumetric analyses of brain development can lend further insight into the connection between brain and behavior.

Magnetic Resonance Imaging (MRI) studies of the brain have enabled researchers to examine how brain volume relates to factors such as cognitive functioning, learning disabilities, developmental disabilities, and behavioral difficulties associated with disorders such as attention deficit/hyperactivity disorder (ADHD). Reiss et al. (1996) reported that in normal children, IQ is positively correlated with total cerebral volume in a sample of children ranging 5-17 years of age, with total cerebral volume accounting for up to 20% of the variance among IQ scores. Pennington et al. (1999) reported findings from an adolescent twin study that examined morphometric analyses of MRI scans examining brain correlates of reading disabled participants. They reported positive correlations for total cerebral volume and full scale IQ in both reading disabled and control participants. Castellanos et al. (2002) conducted a longitudinal MRI study in which brain films of typically developing children and children with a diagnosis of ADHD were analyzed. They reported that in children with ADHD, cerebral volume was 3.2 % smaller than controls and reported a 9.2% decrease in temporal white matter in children with ADHD. Such studies provide insights into how brain volume may be

associated with areas of cognitive and behavioral functioning, as the degree of myelination is likely strongly linked to cognitive ability.

Cerebral Volume and Asymmetry of White Matter. Studies assessing brain volume frequently use the cerebrum as the index for total brain volume due to its large size (Jancke & Steinmetz, 1998). The cerebrum contains large regions of white matter although levels of myelination tend to differ according to hemispheric location, as different structures in the brain have been reported to have non-uniform distributions of asymmetry patterns within certain areas (Herbert et al., 2005). In studies of normal patients, differences in cerebral myelination have been demonstrated between the cerebral hemispheres. The left hemisphere has been reported to have a greater ratio of gray matter to white matter, while the right hemisphere is reported to be slightly larger and to have a greater ratio of white matter to gray matter (Kolb & Wishaw, 1996). The greater proportion of white matter in the right hemisphere appears to be due to its specificity of function. To illustrate, the right hemisphere appears to process more complex information than the left hemisphere, presumably due to greater intraregional connections (Teeter & Semrud-Clikeman, 1997).

Additionally, there are equivocal findings regarding the relationship between cerebral asymmetry with handedness and gender (Collinson et al., 2003; Hynd & Semrud-Clikeman, 1989; Kolb & Wishaw, 1996). Despite equivocal findings regarding such associations, there has been documentation that normal brain asymmetries occur less frequently in left-handed individuals (Luchins et al., 1982), as there may be differences in cerebral dominance for handedness in these

individuals. In regard to gender differences in cerebral asymmetry, some studies have reported a lack of evidence for significant differences in gross hemispheric differences for males and females (Watkins et al., 2001), although others have reported significant gender differences (Amunts et al., 2000).

In normally developing children, age related volumetric changes in white and gray matter have been documented. From birth until the second year of life, the brain undergoes rapid growth. During this time, marked increases in volume are noted, as well as more pronounced left-right cerebral asymmetry, particularly in the temporal lobes. Further, increases in gray matter are noted to be larger than that of white matter during the first two years of life. Subsequently, white matter volume increases at a higher rate from age 2 throughout childhood (Matsuzawa et al., 2001). Overall, the rate of white matter growth has been reported to be slower than total volume of the cerebral hemispheres in neurologically normal cases (Iwaskai et al., 1997).

Abnormalities in Neuroanatomical Asymmetry. There have been numerous studies that have documented abnormalities (reversals) in asymmetry of neuroanatomical structures in various developmental disorders, such as autism, dyslexia, Klinefelter's syndrome, ADHD, and schizophrenia (Crow, 1990; Filipek, 1995; Herbert et al., 2003; Herbert et al., 2005; Semrud-Clikeman et al., 2000; Watkins et al., 2001). Such studies have highlighted the implications of structural, or neuroanatomical, abnormalities on the lateralization of function, as anomalous patterns of asymmetry in the hemispheres may indicate altered regional specialization, in addition to impaired information processing (Herbert et al., 2005; Hynd et al., 1995a). For

example, neuroanatomic abnormalities associated with complex cognitive processing (i.e., as with language) have been reported to involve widely distributed circuit-disrupting abnormalities (Herbert et al., 2005; Just et al., 2004). The pathogenesis of alterations in normal neurodevelopment can vary, however. Herbert et al. (2005) suggest that abnormalities in neuroanatomical asymmetry may emerge as a response or adaptation to an abnormal brain growth trajectory, particularly in regard to white matter development. Indeed, exploration into the cytoarchitectural underpinnings of abnormal neuroanatomical asymmetry have revealed that volume asymmetries in homologous neural regions can be associated with both neuronal loss and decreased axonal (interhemispheric) connectivity (Rosen et al., 1991; Watkins et al., 2001). It is possible that abnormalities in the development of myelination associated with 18q- is also related to abnormal right/left cerebral asymmetry, although this possibility has not yet been determined.

The Corpus Callosum

The corpus callosum is the largest of the commissures and is therefore easily identifiable in brain images (Kandel et al., 2000). The corpus callosum comprises the largest fiber system in the brain, containing 200-300 million axons (Gazzaniga, Ivry, & Mangun, 1998; Teeter & Semrud-Clikeman, 1997) that serve to link the two cerebral hemispheres of the brain. The callosal fibers serve to connect different parts of the brain by projecting either homotopically (connect corresponding sections of the two hemispheres via the corpus callosum), heterotopically (link different areas of both hemispheres), or ipsilaterally (connect the same side). The majority of callosal fibers connect mostly homotopic regions of the two hemispheres and

contain both excitatory and inhibitory connections. Different areas of the brain are connected by specific regions of the corpus callosum: the genu connects rostral portions of the frontal lobes, the body interconnects regions of the frontal and parietal lobes, and the splenium is connected to temporal and occipital areas (Teeter & Semrud-Clikeman, 1997).

Development of the Corpus Callosum. The corpus callosum develops during the early weeks of fetal gestation, resulting from axonal migration across the lamina terminalis of the telencephalon (i.e., cerebral hemispheres). During the 7th and 13th weeks of gestation, broad interhemispheric axonal tracts are developed. The direction of the development of the corpus callosum typically proceeds along an anteroposterior course, with initial development of the genu, followed by the body, splenium, and lastly, the rostrum. Abnormalities in development of the corpus callosum during this time has been shown to also affect the simultaneous development of other CNS structures, as it plays an important role in providing structural integrity to the brain, in regard to acting as a stabilizing "anchor" to the development of surrounding brain structures. Therefore, disruption to callosal genesis can result in neural abnormalities, such as dilation of the lateral ventricles, which are close in proximity to this structure (Barkovich, 1995). For example, disorders such as Dandy-Walker malformation, Arnold-Chiari malformation, holoprosencephaly, intracranial lipoma, and Nijmegen Breakage Syndrome (NBS) have been associated with malformed corpus callosum (Barkovich, 1990; Barkovich & Norman, 1988; Bekiesinska-Figatowska et al., 2004).

Function of the Corpus Callosum: Studies of Callosal Incision. As previously mentioned, a primary function of the corpus callosum is to segregate and integrate brain functions that are lateralized to one hemisphere or the other (DeMyer, 1988; Peterson, et al., 1994). Understanding of the role of the corpus callosum in the integration of information can be gleaned from observation of functioning after incision of the corpus callosum. Individuals who have had callostomy to treat intractable seizure disorders have exhibited deficits in interhemispheric transference of information. For example, callosal sectioning in human patients has revealed that the anterior and posterior halves of the corpus callosum play different roles in integrating stimuli. Severing the anterior region will result in deficits in higher order semantic information, while severing the posterior half of the corpus callosum will the result is severe disruption of visual, tactile, and auditory sensory information (Gazzaniga, 1998). Clinical deficits of complete callostomy (e.g., in which the two cerebral hemispheres have been completely disconnected via severing of the corpus callosum) can be demonstrated by specific tests. For example, a right-handed patient will be unable to execute a command with the left hand because the right hemisphere (disconnected from the left) will not understand language (DeMyer, 1988; Gazzaniga et al., 1998). While such an example represent extreme effects of incising the corpus callosum, it serves to illustrate the crucial role that the corpus callosum plays in integrating and transferring information.

Morphology of the Corpus Callosum. In addition to the corpus callosum having certain areas of specialized functioning, the morphology of the corpus callosum is also implicated in cognitive functioning. Corpus callosum size can be related to a

number of factors, including the number and diameter of axons, the proportion of myelinated axons, thickness of myelin sheaths, size of blood vessels, and volume of extracellular space (Gazzaniga, et al., 1998; Jancke & Steinmetz, 1998). Agenesis of the corpus callosum occurs when all or part of this region fails to develop, and is a common finding associated with many genetic disorders (Teeter & Semrud-Clikeman, 1997). Additionally, the existence of severe cognitive impairment or mental illness (i.e., mental retardation, schizophrenia, and autism) appears to be implicated in variations of callosal size and shape (Herbert et al., 2005). Shape and thickness of the corpus callosum is also related to gender and handedness although there have been equivocal findings regarding the relationship of these factors with corpus callosum morphology (Beaton, 1997; Bogen, 1993; Gazzaniga et al., 1998; Hopper et al., 1994; Jancke et al., 1997; Peterson, et al., 1994; Mitchell et al., 2003; Witelson, 1989). However, meta-analyses of studies examining gender and handedness indicates that, overall, females tend to have larger corpus callosum than males relative to total brain volume and left-handed individuals tend to have larger callosal size than right-handed individuals (Driesen & Raz, 1995; Hoffman & Polich, 1999).

Callosal Size, Attention, and Information Processing Speed. Abnormalities in the size of the corpus callosum are also implicated in attentional deficits and decreased information-processing speed, which are crucial components of cognitive ability (Corballis & Finlay, 2000; Elliott, 1990; Sattler, 1992; Wechsler, 1991). Rao et al. (1989) reported finding corpus callosum atrophy in MS patients, and reported that level of demyelination significantly correlated with degree of cognitive impairment

on a range of neuropsychological measures. Specifically, they hypothesized that white matter abnormalities in the corpus callosum are implicated in impairment in attention and rapid problem solving as, "such performance depends on precisely timed interhemispheric communication that is disrupted by demyelinated callosal fiber tracts" (p.165). Further, MRI studies of children with Attention Deficit Hyperactivity Disorder (ADHD) have reported that the corpus callosum is smaller in children with ADHD than in developmentally normal controls. Regional abnormalities of the corpus callosum were specifically reported (e.g., in the genu and splenium). These areas of the corpus callosum have interhemispheric connections throughout the brain, including the frontal regions (Hynd, et al., 1991; Semrud-Clikeman, et al., 1994). Such abnormalities were concluded to be implicated in sustained and advanced levels of attention, presumably due to impaired self-regulation (i.e., the ability to attend to and process stimuli while adjusting behavior accordingly) (Lezak, 1995). Overall, it appears that the function of the corpus callosum during cognitive activity is to maintain the balance of arousal and attention between the cerebral hemispheres, thus enabling whole integration of information between the two sides of the brain (Gladstone & Best, 1983).

The Corpus Callosum and Learning Disorders. Abnormalities of the corpus callosum have been implicated in learning disorders, presumably due to disruption of the integration and coordination of brain regions implicated in higher order cognitive processes. Smaller corpus callosum are believed to be implicated in suboptimal neural connectivity and coordination of neural circuits, thus resulting in pervasive processing abnormalities (Herbert et al., 2005; Just et al., 2004). For

example, defective callosal transfer has been implicated in oral and written language disorders, and particularly in developmental dyslexia (Castro-Caldas et al., 1999; Fabbro et al., 2001; Fine et al., submitted). Developmental dyslexia is a disorder that can involve impairment in a number of complex neuropsychological mechanisms, including in visual perceptual processing of letters, word recognition, phonological processing, and reading comprehension (Pennington, 1991). Such components of reading involve integration and transfer of information between cerebral hemispheres, as well as requiring focused and sustained attention, which are processes that involve mediation by the corpus callosum. While there has been equivocal findings regarding the relationship of callosal morphology and dyslexia, there have been studies documenting smaller regions of the corpus callosum in these individuals (Castro-Caldas et al., 1999; Fine et al., 2005; Hynd et al., 1995b).

The Corpus Callosum in 18q-. Miller et al. (1990) reported normal myelination patterns in the corpus callosum, although abnormalities in size of the corpus callosum have also been reported in individuals with 18q- (Bekiesinska-Figatowska & Walecki, 2001; Gay et al., 1997; Kochunov et al., 2005). Indeed, Kochunov et al. (2005) found that the children with 18q- have 25% smaller corpus callosum when compared to normal controls, even after correcting for differences in overall brain size. Such a difference in callosal volume is substantial when considering that the missing regions could account for more than 25 million nerve fibers (Witelson, 1989). It is probable that variability in size of the corpus callosum in individuals with 18q- is related to widespread diffuse white matter abnormalities (Loevner, 1996; Mahr et al., 1996; Miller, et al., 1990). However, it is unclear at this time as

to whether such corpus callosum abnormalities are also associated with cognitive and behavioral abnormalities in individuals with 18q-.

Biochemical and Genetic Factors Affecting the Brain in 18q-

The Link Between Growth Hormone and Myelination. Numerous biochemical factors have been associated with 18q-, such as abnormal levels of growth hormone (GH), insulin-like growth factor-I (IGF-I), IGF binding protein (IGFBP-1), and thyroid hormones (Cody et al., 2005; Hale, 2000; Noguchi, 1996; Noguchi, Sugisaki, & Tsukada, 1982; Rosman, et al., 1972). Growth hormone regulates growth of cells and tissue by affecting the metabolism of proteins (Rozenzweig, Leiman, & Breedlove, 1996; Strobl & Thomas, 1994) and is also involved in lipolysis, protein synthesis, carbohydrate metabolism, and fluid-electrolyte imbalance. IGF-I has an important role in the regulation of growth hormone secretion (Strobl & Thomas, 1994) and is implicated in developmental myelination, although it is considered to have primary effects on neuronal growth and survival (Bondy & Lee, 1993; Keyvani & Schallert, 2002; Niblock et al., 2000; Ye et al., 2002). Growth hormone and IGF-I also interact with other hormones (e.g., thyroxine, cortisol, and insulin) and growth factors (e.g., transforming growth factor-β, basic fibroblast growth factor) to modulate overall physical growth. Hale et al. (2000) reported that children with 18q- had significantly lower IGF-I values when compared to normally developing children of the same age.

In general, GH is released from the anterior pituitary, which is regulated by the hypothalamus, with separate but interrelated mechanisms for secretory pattern, receptor sites, and circulation level regulators (Drake et al, 2001). Primary GH

deficiencies are due to primary deficits in GH production in the pituitary, versus hypothalamic dysfunction that impairs the release of GH hormone from the pituitary (Strobl & Thomas, 1994). Individuals who are diagnosed with 18q- are often identified with growth hormone deficiency, most likely due hypothalamic dysfunction, resulting in delayed growth (Cody et al, 2005).

Growth hormone deficiency is of particular interest to this study, as individuals with 18q- who are GH deficient have been identified to be missing 2 Mb of DNA at 18q23 that contains an as of yet unidentified component for GH production (Cody et al 1997; Gay et al., 1997). While this region is estimated to contain 30 genes, there are 2 particular genes in the18q23 region could be associated with GH deficiency: the myelin basic protein (MBP) gene and the galanin receptor-1 (GALNR1) gene. MBP has been identified as the major protein component of CNS and peripheral nervous system myelination and the GALNR1 gene is implicated in GH secretion (Cody et al., 1997a; Ono et al., 1994; Strobl & Thomas, 1994). Individuals with 18q- who are deficient in this region have therefore been noted to have a high incidence (~95%) of dysmyelination (Kochunov et al., 2005).

Implications for Growth Hormone Treatment in 18q-

Growth and the Brain. A child's growth rate is determined through periodic measurement and comparison to standardized growth charts that report normal expected growth patterns based on a child's age. Standard determinants of growth include head circumference, height, and weight, all of which are roughly proportionate to each other in normally developing children (Legler & Rose, 1998), with males generally exhibiting larger head size, weight, and height (Nagy, 2001)

than females. Head circumference has been found to correlate with brain weight and volume (Miles et al., 2000). While head circumference can be used to estimate total brain volume, it cannot account for extracerebral space or CSF in the brain as imaging analyses allows (Abernethy et al., 2004). Microcephaly, or head circumference that is disproportionately small compared with the rest of the child's body (i.e., < 2.0 *SD* below normal), is often an indicator of abnormal development (Legler & Rose, 1998; Miles et al., 2000). Microcephaly in individuals with 18q- is of particular interest to this study, as microcephalic individuals are reported to have lower IQ scores in comparison to those who are macrocephalic or normocephalic (Arends et al., 2004; Miles et al., 2000).

Head Circumference as an Index of Brain Growth. Much of the research devoted to the effects of GH treatment in children has focused on change in linear growth or increases in head circumference (Drake et al., 2001; Laron & Galatzer, 1980; Spadoni et al., 1989). For example, increases in head circumference post GH treatment have been reported in individuals with isolated growth hormone deficiency, which was used as an indirect index of brain growth following GH replacement therapy (Laron & Galatzer, 1980). GH has also been successfully utilized in increasing linear growth in other disorders, such as sporadic primary hydrocephaly (Spadoni et al., 1989) intrauterine growth retardation (Van der Reijden-Lakeman et al., 1997), and in children identified as small for gestational age (SGA) (Arends et al., 2004). According to Strobl and Thomas (1994), optimal growth response to GH therapy occurs during the initial first two years of treatment. They further contend that the largest increases in growth rate are achieved with GH

treatment occurs when it is administered to children younger than 10 years of age. Therefore, they argue for the necessity of early identification and treatment of GH deficiency for optimal results.

Growth Hormone Treatment and Psychological Functioning. Growth hormone treatment has been associated with improvements in fine motor skills in children with Prader-Willi, a genetic disorder that is associated with hypothalamic GH deficiency (Anneren, Tuvemo, & Gusafsson, 2000; Eiholzer, Bachmann, & Allemand, 2000). GH treatment has also been associated with increases in adaptive motor skills in children with 18q- (More et al., 2000). Laron & Galatzer (1980) reported increases in IQ in children with isolated growth hormone insufficiency who received GH replacement therapy. Children who received GH treatment prior to age 2 years were reported to have the greatest increases in IQ. Cody et al. (submitted) examined the effects of GH treatment on intelligence in children with 18q-. Individuals with 18q- who were GH deficient and treated with GH replacement exhibited increases in linear growth and in IQ post treatment. Further, preliminary findings reported by Hardies et al. (2000) indicate that GH treatment does increase levels of brain myelination in children with 18q- as indicated by improved MRI T1 values.

The mechanism by which growth hormone is related to improvement in cognitive functioning is not currently understood. Even less well understood are the effects of GH in improving adaptive or behavioral functioning, particularly with 18q-. Behavioral improvements post-GH-treatment have been reported in individuals with other disorders. For example, Stabler et al. (1998) reported that in

GH deficient children, levels of behavioral problems decreased following 3 years of GH treatment. At post treatment assessment, GH treated children were reported to have improvements on Child Behavior Checklist scores for total behavior problems, internalizing problems, and on 3 components of the ungrouped subscales (e.g., attention, social problems, and thought problems).

Children diagnosed with intrauterine growth retardation and adolescent girls with Turner's syndrome have also demonstrated some improvements in psychosocial functioning post GH treatment (Lagrou et al.,1998; Van der Reijden-Lakeman, 1996). However, caution must be used when trying to link global improvements in behavioral functioning as a result of GH treatment, as such improvements may be due to a variety of intra-individual and disorder specific factors and therefore, not solely attributable to GH treatment. To illustrate, Sartorio et al. (1996) stressed that in individuals with GH deficiency, the specific role of GH on psychological functioning can be masked by a variety of associated hormonal deficiencies (e.g., thyroid dysfunction). However, since cognitive and motor improvements have been reported post GH treatment in 18q- and behavioral improvements have been associated in other disorders following GH treatment, it is possible that there also might be associated behavioral improvements in 18q- post GH treatment.

Statement of the Problem

This study will examine the effects of GH treatment on brain development and cognitive, adaptive, and behavioral functioning in children with 18q-. Specifically, participant MRI scans will be analyzed, specifically in regard to

measurement of left, right, and total cerebral hemisphere volume; left, right, and total lateral ventricle volume, and midsagittal corpus callosum area. It is hypothesized that brain growth will be related to improvements across psychological measures. The rationale for this proposal is based on several factors: 1) an increase in overall brain volume may be related to increases in IQ post GH treatment, as brain volume has been shown to be positively correlated with IQ (Andreasen et al., 1993; Pennington et al., 2000; Reiss et al, 1996), 2) comparisons between the right and left hemispheric volume pre and post GH treatment may provide clues as to changes in myelination, as greater ratios of white matter to gray matter have been reported in the right hemisphere of normally developing children (Teeter & Semrud-Clikeman, 1997). If greater right than left (R>L) cerebral volume asymmetry is found in individuals with 18q deletion post treatment, it is possible that such an increase may be associated with increased myelination, and 3) predicted growth in midsagittal corpus callosum area post GH treatment might also indicate improved interhemispheric transfer of information, and hence, related to increased cognitive functioning.

Preliminary findings of increased myelination in individuals with 18q- following GH treatment has recently been reported using MRI relaxometry (Hardies et al., 2000). However, as previously mentioned, changes in brain volume associated with increases in white matter may be due to a number of factors, including an increase in number of fibers, thickness of axons, or the myelin content of the axons or fibers per unit area (Woiciechowsky et al., 1997). Given the limitations in this study regarding use of indirect indices of white matter growth,

increased cerebral volume and/or corpus callosum area post GH-treament can not be attributable solely to increased levels of myelination.

Although less is understood about the potential benefits of GH in decreasing levels of behavioral difficulties associated with 18q-, such as with adaptive behavior functioning (e.g., the ability to function independently in one's environment) or with behavioral dysfunction such as hyperactivity or aggression, it is possible that improved levels of intellectual functioning in individuals with 18q- who are administered GH treatment may likewise be associated with improvement in behavioral functioning. While such changes post GH treatment have not yet been reported for 18q-, behavioral improvements have been noted post GH treatment in individuals with other disorders, such as Turner's syndrome and isolated growth hormone deficiency (Lagrou et al., 1998; Stabler et al., 1998). Therefore, an area of exploration in this study will involve whether any behavioral improvement following GH treatment is associated with brain growth.

It is hoped that through early detection of chromosome abnormalities and GH deficiency, treatment with GH will improve the quality of life and capacity for independent living in individuals with 18q- and other deletion disorders by improving intellectual, adaptive, and behavioral functioning.

CHAPTER 3: METHODS

The purpose of this study is to investigate possible benefits of short-term GH treatment for individuals diagnosed with 18q-. Of particular interest is whether individuals will display improvements in cognitive, adaptive and behavioral functioning following GH treatment and whether such changes are associated with increases in corpus callosum area, right and left cerebral volume asymmetry, and total cerebral volume.

Participants

Participants for this study were recruited from ongoing research conducted by the Chromosome 18 Clinical Research Center. The majority of the participants included in this study are predominantly Caucasian and from middle class socioeconomic backgrounds. Although there is not current evidence that suggests a preponderance of 18q- in any particular race, there is an ascertainment bias in this sample.

Participants in this study were identified to have a deletion on the long arm of the 18th chromosome (18q) using polymorphic marker analysis. Those individuals included in the study had variable breakpoints, ranging from a proximal breakpoint at 18q21 to a more distal breakpoint at 18q23. Individuals who had more complex chromosome arrangements or mosaicism were excluded. Patients with untreated thyroid dysfunction were also excluded, as thyroid dysfunction can be associated with abnormal brain development and cognitive disability (Noguchi et al., 1982; Rodriguez-Pena, Ibarroloa, Inguez, & Bernal, 1993). Approval for the use of human participants in this study was obtained from the Institutional Review Board of the

University of Texas at Austin, the University of Texas Health Science Center in San Antonio and the Audie L. Murphy Veterans Administration Hospital. The parents or caregivers of the participants were informed of the various procedures that are included in the research protocol. Parents of participants with GH deficiency were informed of the potential risks and benefits of GH treatment.

There were two groups of participants examined, including 13 participants with 18q- (five males, eight females) and 13 normal controls (seven males, six females), for a total of 26 participants. Control participants were typically developing children as determined by developmental history. Control participants were excluded if developmental history revealed notable neurological, medical, or psychiatric difficulties. Control participants were recruited locally or were siblings of patients. Participants ranged in age from 30 months to 167 months of age.

The criteria for participant inclusion for clinical treatment with GH was based on anthropometric, radiographic, and biochemical measures. Inclusion criteria for GH deficiency required identification of abnormal height, growth velocity, insulin-like growth factor (IGF), IGF-binding protein-3, bone maturation, and responses to pituitary stimulants of GH (Hale et al., 2000) by a board-certified pediatric endocrinologist. Specifically, individuals with 18q- were required to have at least four abnormal values fitting the following algorithm: heights <-2 *SD*, growth velocities <-1 *SD*, bone age <75% of chronological age, IGF-1 <-1 *SD*, IGFBP3 <-1 *SD* and peak GH <10ng/ml (Cody et al., 2005). Participant height, length, and head circumference were measured, with *SD* calculated using a computer program designed for this purpose (Growth Base III, Eli Lilly and Company) or based on

normative data (Hall, Froster-Iskenius, & Allanson, 1989). Participant growth velocity was determined by subtracting height or length obtained at least 3 months prior to the visit from the height or length obtained at the time of visit. Bone age (BA) was obtained from X-ray films of the left hand and wrist. Delayed BA was considered to be >2 *SD* below the mean for age. Participants were evaluated to determine measurement of insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), l-thyroxine and thyrotropin. Genetech, Inc. (San Francisco, CA) provided normative data for calculating IGF-1 *SD* and IGFBP-3 *SD*. GH production was evaluated using arginine hydrochloride and/or clonidine as the provocative agent. The Nichols Institute (San Juan Capistrano, CA) performed all hormonal assays. GH was measured by polyclonal radioimmunoassay. Participants with 18q- who were identified to be GH deficient were treated with the standard dose of GH of 0.3 mg/kg/wk.

Design

This study included between and within subject comparisons. Participants were analyzed from 14 months to 60 months post GH treatment, with an average of 24 months post treatment. Although 1-2 years post GH treatment has been found to be the time frame in which children will exhibit optimal linear growth rates in response to GH treatment (Strobl & Thomas, 1994), some participants did not have usable MR scans for that time interval due to factors such as movement artifacts. The doctoral students administering the assessment battery and MR measurements were blind as to whether the participants are receiving GH treatment to prevent assessment biases.

There were two primary areas for exploration in this study. The first question pertained to whether individuals with 18q- who are GH deficient will exhibit improvements in cognitive, adaptive and behavioral functioning following GH treatment. There is a paucity of available literature regarding potential beneficial effects of GH treatment on adaptive and behavioral functioning, although recent findings have demonstrated the role of GH in improving intellectual functioning (Cody, et al, submitted; Semrud-Clikeman et al., 2005). Participants who received GH treatment were administered a battery of cognitive and psychosocial measures prior to and after treatment. Control participants were assessed on only one occasion.

The second area of exploration involved volumetric analysis of total cerebral brain volume, left/right cerebral hemisphere volume symmetry, left/right and total lateral ventricle volume, and area of the midsagittal slice of the corpus callosum. The original intention was to analyze differences in gray and white matter change from pre to post GH treatment in individuals with 18q-, but preliminary review of the MR images indicated poor differentiation of gray and white matter boundaries due to dysmyelination associated with the disorder, thereby preventing distinction and demarcation of brain matter boundaries (J.L. Lancaster, personal communication, August 2003).

Measures

Cognitive Functioning

The the Differential Ability Scales (DAS) (Elliott, 1990) was selected for analysis of participant cognitive functioning in the current study. Participants who

were unable to complete the DAS due to cognitive impairment were administered the Bayley Infant Scales of Infant Development, although performance on this measure was not included in the overall analyses of intellectual functioning in this study.

Differential Ability Scales (DAS) (Elliott, 1990)

The Differential Ability Scales (DAS) is a test for determining psychometric intelligence level in children ages 2 years 6 months to 17 years, 11 months. The DAS was designed to measure reasoning and conceptual abilities in children. It contains 17 cognitive and 3 achievement subtests grouped in 2 overlapping levels: the Preschool and School Age batteries. The School age battery is for children ages 6-0 to 17-11 years of age. The Preschool battery is further divided into the lower (ages 2-6 to 3-5 years) and upper (ages 3-6 to 5-11 years) levels according to the child's age range. The lower preschool level consists of four core subtests, six core subtests for the upper preschool level, and six core subtests for the school age level. There are two to five additional diagnostic subtests that are administered according to the child's age.

While Verbal, Nonverbal, Spatial, and General Cognitive indices can be obtained, a Special Nonverbal Composite can also be obtained, which is recommended for use in assessing hearing impaired children (Kamphaus, 2001). However, for this study the Nonverbal Reasoning Composite (NVC) of the DAS will be used as the index for intellectual ability instead of the General Cognitive Ability (GCA) score or the Special Nonverbal Reasoning Composite, as the NVC has been shown to be positively correlated with the WISC-III PIQ scale (Elliott,

1990) and has also been shown to be appropriate for use with children who are hearing or language impaired (Kamphaus, 2001). The NVC mean internal consistency reliabilities ranged from .70-.92 for individual subtests, .88-.94 for composite scores, and .90-.95 for the GCA. The DAS Nonverbal Reasoning Composite reliability is reported to be .89 for preschool aged children and .83 for school-aged children. Construct validity for the DAS Nonverbal Ability Cluster score is .75 when compared to the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, Wechsler, 1989) for the Performance IQ for preschool aged children (3 years, 6 months to 5 years, 11 months) and .78 for the Nonverbal Ability Cluster score when compared with the Performance IQ WISC III for school-aged children (6 years, 0 months to 16 years, 11 months) (Elliott, 1990). Therefore, use of the WISC-III PIQ and DAS NVC score can be determined as measuring commensurate abilities.

DAS Speed of Information Processing Subtest. The DAS allows for testing of diagnostic abilities in addition to the core subtests. Speed of Information Processing is a diagnostic subtest used for children ages 6 years to 17 years, 11 months that is designed to gauge a child's ability to quickly perform simple mental operations. According to the child's age, he or she is required to scan rows on a page that has either circles with boxes or numbers. The child is required to mark the circle with the most boxes in each row or the highest number in each row. The child is instructed to perform these tasks as quickly as possible. The time until completion and number of errors are recorded for each page in the booklet. The DAS Speed of Information Processing subtest score has been reported to correlate highly with the

WISC-III Processing Speed Index score (r = .67) in male and female children ages 7 to 14 years old (Wechsler, 1991).

Use of the DAS Nonverbal Reasoning Ability Composite. The DAS was used to determine cognitive functioning with study participants, selected for it's appropriateness for use in assessing children with hearing difficulties, as the subtests are not as reliant on oral directions as other IQ measures (i.e., WISC-III) and can instead be conveyed through pointing, drawing, or manipulation of objects (Kamphaus, 2001). Further, as previously mentioned, only the nonverbal composite from was used instead of GCA because the DAS Verbal composite score and the GCA include verbal components of the test, which would put many of the participants with 18q- at a disadvantage, as many are hearing impaired or have difficulties with oral motor control which can affect their ability to form words (i.e., due to cleft palate).

Adaptive Functioning

Vineland Adaptive Behavior Scales Interview Edition Survey Form (Sparrow, Balla,& Cicchetti, 1984)

Adaptive behavior is a construct defined by Sparrow et al (1984) as "the performance of the daily activities required for personal and social sufficiency" (p. 6). Adaptive behavior is further described as being age related, defined by societal expectations, and is related to typical performance and not ability. The Vineland Adaptive Behavior Scales-Interview Edition (VABS) assesses adaptive (social competence) in individuals from birth through age 18 years, 11 months. The VABS is also frequently used to assess individuals with mental retardation for their ability

to function in society and their level of self-sufficiency. The VABS is presented to a participant's caregiver regarding his/her behavior in a question-answer format.

The Vineland Adaptive Behavior Scales will be utilized for all participants in this study to assess adaptive functioning across four domains. The VABS specifically measures four components related to adaptive functioning: Communication, Daily Living Skills, Socialization, and Motor skills, as well as an overall Adaptive Behavior Composite (ABC). The motor skills domain is used solely for individuals up to 5 years, 11 months, 30 days. The Communication domain evaluates receptive, expressive, and written communication skills; the Daily Living Skills domain focuses on personal living habits, domestic task performance, and functional behaviors; the Socialization domain samples social interactions, such as play, hobbies, and responsibility; the Motor Skills domain evaluates gross and fine motor functioning. The ABC is converted to a normalized standard score based on the overall sum of three or four domain standard scores, with a mean of 100 and a standard deviation of 15, although it can vary according to comparative age group (Sattler, 1992). Sattler (1992) warned that caution should be exercised when making longitudinal and cross-age comparisons using the VABS due to the variability in means and standard deviations across age groups. Despite this caveat, the ABC was solely used as an overall determinant of study participant adaptive functioning, as it reflects many of the subdomains of adaptive behavior.

Split-half reliability coefficients for the Adaptive Behavior Composite range from .84 to .98. Test-retest reliability for the Survey form using a 2 to 4 week retest interval ranged from .80 to .90 and interrater reliability range from .62 to .75.

Standard errors of measurement for the ABC range from 2.2 to 4.9. Concurrent validity for the VABS and the WISC-R was .52 for emotionally disturbed children and .47 for hearing impaired children (Sattler, 1992), indicating only a modest correlation between intellectual functioning and adaptive behavior skills.

Behavioral Functioning

Behavior Assessment Scales for Children-Parent Rating Scales (BASC) (Reynolds & Kamphaus, 1998)

The Behavior Assessment System for Children-Parent Rating Scales (BASC-PRS; Reynolds & Kamphaus, 1998) is a behavior rating system for parents that provides domain scores for various emotional and behavioral difficulties, such as anxiety, depression, hyperactivity, and aggression, as well as adaptive behaviors. Respondents rate the child's behaviors using a four-point scale (e.g., never, sometimes, often, and almost always) based on the child's behavior in the last six months. The BASC-PRS has three different forms that are based on the child's age range: preschool (ages 2 years, 6 months-5 years), school age (ages 6-11), and adolescent (ages 12-18).

Completed forms are scored via the BASC Enhanced Assist Program software. Validity scales are provided to ensure that the respondent does not over or under represent behavioral problems, as well as to ensure consistency across responses. The scoring profile provides T scores based on a general national norm group, by gender, or in comparison to clinical populations. Scores are given for items that comprise the Adaptive and Clinical Scales as well as for the following

composite scores: Internalizing, Externalizing, School Problems, Adaptive Skills and Behavioral Symptoms Index (BSI).

The BSI is an index that includes all the clinical scores and their corresponding composite classifications that reflects the level of overall problem behavior the child exhibits. In this study, only the Behavior Symptoms Index will be used, as it provides a quantitative index for measuring the child's level of behavioral dysfunction longitudinally. The higher a child's BSI, the greater reported behavioral difficulties the child is experiencing. On the BSI, males tend to have higher scores than females on the PRS for child and adolescent ratings (Reynolds & Kamphaus, 1998). However, the combined gender norms for the BSI will be used due to its utility in identifying clinical levels of behavioral dysfunction (Reynolds & Kamphaus, 1998).

For the BASC PRS, the Behavioral Symptoms Index (BSI) reliabilities range from .88 to .94 across the three age levels, test-retest correlations for the BSI were reported to range from .73 to .91, and interrater reliability coefficients for the BSI ranged from .61 to .71. The Behavioral Symptoms Index is similar to the Child Behavior Checklist (CBCL; Achenbach, 1991) Total Problems Scale in that they both reflect parental perceptions of a child's overall level of behavioral dysfunction. The BSI was found to highly correlate (e.g., .76 to .86 across the three age levels) with the CBCL's Total Problems scale, although they define behavioral domains differently (Reynolds & Kamphaus, 1998).

Procedure

The project's Research Coordinator provided transportation arrangements for participants and their families and an evaluation itinerary detailing the type of and time schedule for each procedure. Participants generally stayed for 4 days at accommodations located near the research facilities, during which time a standard research protocol was completed that included genetic analysis, Magnetic Resonance Imaging (MRI), endocrine screening to determine GH deficiency, behavioral audiology exam, and psychological testing. Growth hormone levels were measured using provocative agents, clonidine hydrochloride and/or arginine. Control participants were only evaluated on one occasion with psychological testing and MRI scanning. Participant handedness was not included as a variable of interest in this study due to lack of data for all participants. Head circumference of participants with 18q- was measured at both pre and post treatment assessment, although this information was not obtained for control participants.

The psychological assessment for each participant typically took 2-2 ½ hours, including parental interview, cognitive testing and parental completion of screeners for adaptive and emotional/behavioral functioning. The assessment battery and analysis of MRI scans was conducted by this author who was blind as to whether the participant was receiving GH treatment. Parents were informed that a psychological report will be made available to them based on the assessment results.

Magnetic Resonance Image Analyses: Overview

Magnetic Resonance Imaging (MRI) was used to analyze the total cerebral volume, right and left cerebral hemispheres, lateral ventricles, and midsagittal area

of the corpus callosum. MR images were obtained prior to treatment with growth hormone (GH) and after one year or more post GH treatment.

Magnetic Resonance Image Acquisition

Magnetic Resonance Images were obtained using a 1.9 Tesla General Electric Elscint imager using conventional spin-echo techniques. Axial T1-weighted and double-echo axial T2-weighted images with identical slice alignment (e.g., 5 mm slice thickness and a 1 mm gap) were obtained for all participants. Digitized image data were converted to quantitative T1 and T2 image maps using Magnetic Resonance Parametric Analyzer software (Research Imaging Center, University of Texas Health Science Center at San Antonio; Hardies, et al, 2001). Signal intensity for T1 and T2 image maps in a brain region corresponds to the average T1 or T2 for the selected region. The image acquisition time for participants was approximately 20 minutes. Participants who had difficulty remaining immobile during the procedure were sedated by a nurse with chloral hydrate, which was dosed by 50-100 mg/kg of body weight (Gay et al., 1997; Lancaster et al., 2001). Immobility is necessary during MRI acquisition to assure quality and accuracy of brain images.

Volumetric Analyses

MR images were stored on DAT tapes converted into MINC (Medical Image NetCDF) file format by a research technician at the Research Imaging Center in San Antonio, Texas. Volumetric analyses were performed using a PC version of DISPLAY software, developed at the Montreal Neurological Institute (MacDonald, 1996). DISPLAY is a three dimensional application designed to manipulate three-dimensional orthogonal images of a brain, thus allowing the user to correct manual

measurements of the same region through simultaneous observation in the coronal, sagittal, and horizontal planes. DISPLAY is utilized for MRI volume analysis and manipulation through manual tracing and highlighting of brain regions. The brain images were oriented along the posterior and anterior commissures and reformatted into a coronal 1.0 mm positionally normalized scan to account for differences in the participant's head position during the imaging procedure. The MRI scans were also spatially normalized to a standard brain size to allow for comparison of brain region volumes while controlling for developmental size differences. The rationale for this correction is to adjust for brain size discrepancies due to factors such as gender, as males tend to have larger brain volumes when compared to females (Castellanos et al., 2002; Mitchell et al., 2003) and to adjust for age differences (e.g., a three year old child's brain would be smaller than a 13 year old child's brain). This normalization procedure takes into consideration the individual differences in brain structure and volume, thus adjusting the brains to a standardized size for comparison.

Each brain region to be measured was highlighted using DISPLAY and performed in 3-dimensions to most clearly view and correct for structural boundaries (coronal, sagittal, and horizontal [axial] planes) (see Figure 2).

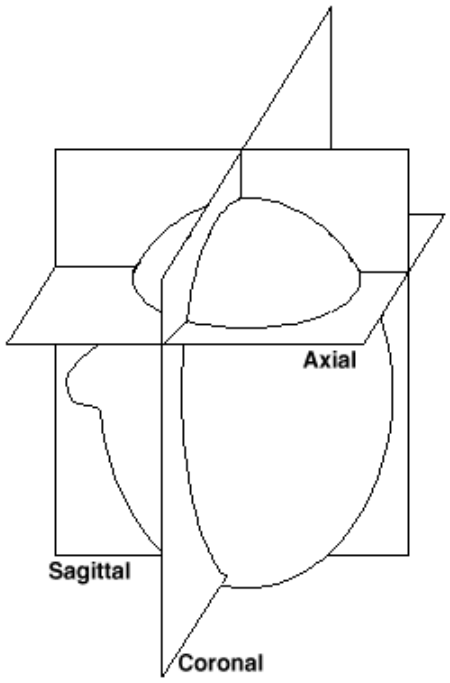

Figure 2. Three dimensional depictions of coronal, sagittal, and horizontal planes.

Each normalized image intensity contour algorithms were kept constant across all images to control for voxel intensity differences. Several brain analyses were conducted: 1) midsagittal area of the corpus callosum, 2) volumetric analysis of the left and right cerebral hemispheres, 3) volumetric analysis of the total cerebrum, 4) volumetric analysis of the left and right lateral ventricles, and 5) analysis of total lateral ventricle volume. In DISPLAY, volumetric estimates in cubic centimeters are generated by multiplying the total number of voxels for each structure by the absolute volume of each voxel (Murphy, 2000). Intrarater reliability analyses were conducted on a selected number of scans per brain region (i.e., 30%) to gauge accuracy of the highlighting in all three dimensions. Volumetric and area

analyses were done blind to the participant's gender, diagnosis, and treatment status through coding of participant MRI scans.

Estimates of total cerebral hemisphere volume were obtained through summation of separate measurements of the left and right cerebral hemispheres. Cerebral hemisphere boundaries were separated from the brain stem at the superior limit of the pons and did not include the cerebellum, based on techniques described by Mackay et al. (1998), Sparks et al. (2002), and Collinson et al. (2003). Additionally, the lateral ventricles were measured separately for each hemisphere and subtracted from the cerebral volume totals. The lateral ventricles were measured separately to assist in the determination that any increase in volume post treatment could be attributed to brain tissue growth rather than ventricular enlargement. (see Figure 3, below).

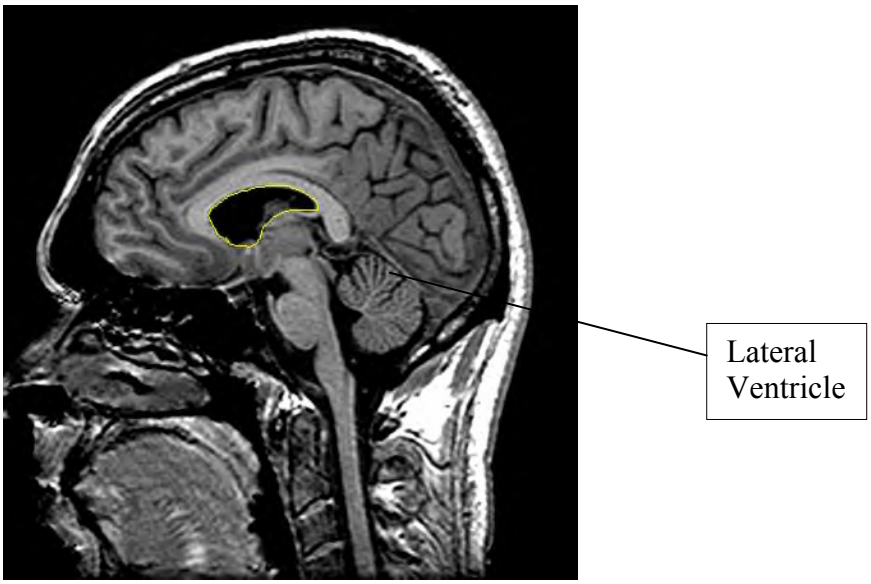

Figure 3. Midsagittal view of highlighted lateral ventricle.

From the Digital Anatomist Project website: http://www.digitalanatomist.com

The third and fourth ventricles, additional points lying within CSF and non-brain tissue were excluded from measurement. The interhemispheric fissure was used as the coronal boundary between the left and right hemispheres (DeMyer, 1988). Guidelines for determining accuracy of anatomic boundaries for these structures were obtained from a brain atlas (Mai et al., 1997) and from cadaver and MR images provided by the Digital Anatomist Project (http://www.digitalanatomist.com). It should be noted that the volume measurements in this study are estimated, as there can be a significant margin of measurement error (0.3%-9.6%) when determining cerebral volume due to various issues, such as image artifact (e.g., distortion due to movement) (Iwasaki et al., 1997). However, use of volumetric estimates provide a valuable approach to determining left-right asymmetry of brain structures (Lim et al., 1995).

Area of the corpus callosum was calculated by highlighting the entire corpus callosum region on the midsagittal slice (in sq cm). The midsagittal view is often used when measuring area of the corpus callosum, as it is the largest of the commissures and can readily be identified due to its size, shape, and location when viewed midsagittally. Further, area of the corpus callosum that is computed from the midsagittal slice has been shown to correlate highly (r =.88, p = .01) with total corpus callosum volume (Fine et al., submitted). Anatomical boundaries of the midsagittal view of the corpus callosum were taken from Mai et al., (1997) and methods employed by Hynd et al., (1991) and the John Hopkins School of Medicine that involves using the anterior end of the genus (g), the center of the anterior commissure (AC), the center of the posterior commissure (PC), and the posterior

end of the splenium as landmarks to determine the medial and ventral boundaries of the corpus callosum (Refer to Figure 4).

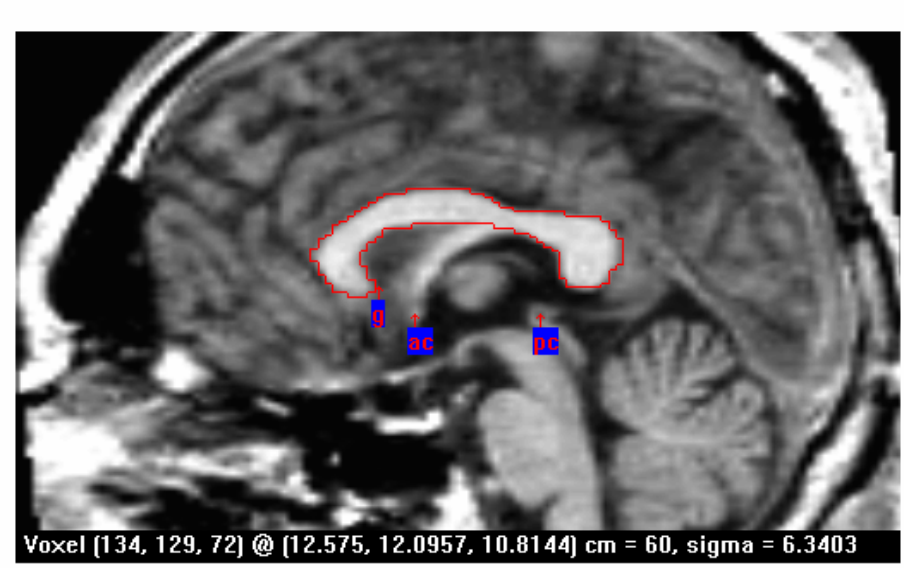

Figure 4. Midsagittal view of highlighted corpus callosum.

From John Hopkins School of Medicine: Department of Psychiatry and Behavioral Sciences

Reliability of Analyses

The rater was blind to participants' identity and performance on neuropsychological tests. Participant psychological test scores and MRI scans were assigned codes to assure anonymity. The rater measured right and left lateral ventricle and cerebral hemispheres separately, by visualizing the structures in three orientations simultaneously. Corpus callosum was measured only in the midsagittal slice. A percentage (30%) of the participant scans were re-measured to determine intrarater reliability estimates. Intraclass correlations are reported for the following brain regions: midsagittal corpus callosum area (r=.93), right lateral ventricle

volume (r=.94), left lateral ventricle volume (r=.99), right cerebral volume (r=.96), and left cerebral volume (r=.98).

Hypotheses and Rationales

The Statistical Package for Social Sciences SPSS, version 12 software, was used to conduct the statistical analyses. The independent variable in this study is treatment group (i.e., GH treated, control). The dependent variables (DV) include psychological testing measures, such as the DAS Nonverbal Composite (NVC), DAS Speed of Information Processing (SIP), Vineland Adaptive Behavior Composite (ABC), and BASC Behavioral Symptoms Index (BSI) scores. Additional DV's include left/right cerebral hemisphere volume, total cerebral volume, left/right lateral ventricle volume, total lateral ventricle volume, and midsagittal corpus callosum area. The data was analyzed to test the following hypotheses:

Hypotheses 1A-1C

Ho1A: Participants with 18q- (pretreatment) will perform lower on the NVC and ABC and higher on the BSI when compared to normal controls.

Ho1B: Scores for participants with 18q- on psychological measures will be significantly improve after GH treatment than before treatment.

Ho1C: Post-treatment, there will be no differences across psychological domains for participants with 18q- when compared to normal controls.

Rationale for Ho1A-Ho1C

The rationale for predicting improvements post GH treatment in GH deficient participants with 18q- is based on previous research that has reported improvements in IQ (Cody et al., 2005; Semrud-Clikeman et al, 1999; Semrud-

Clikeman et al., 2005). While improvements in behavioral functioning after GH treatment have not been reported in individuals with 18q-, GH treatment has been indicated to improve behavioral functioning in other disorders, such as Turner's syndrome (Lagrou, et al., 1998), intrauterine growth retardation (Van der Reijden-Lakeman, et al., 1997), and isolated growth hormone insufficiency (Laron & Galatzer, 1980). Possible adaptive and behavioral benefits from GH treatment in 18q- will therefore be explored.

Hypotheses 2A-3

Ho2A: Participants with 18q- (pre-treatment) will have less cerebral volume and smaller midsagittal corpus callosum area when compared to normal controls.

Ho2B: Participants with 18q- (pre-treatment) will not show significant differences in cerebral hemispheric asymmetry, while normal controls are predicted to have greater right to left asymmetry.

Ho2C: Participants with 18q- (post GH treatment) will show significant increases in total cerebral volume when compared with pretreatment measurements.

Ho2D: Participants with 18q- (post GH treatment) will show asymmetry in cerebral hemispheric volume, with greater right hemispheric volume when compared to left hemispheric volume.

Ho2E: Participants with 18q- (post GH treatment) will show significant increases in midsagittal corpus callosum area when compared with pretreatment measurements.

Ho2F: Pre and post treatment measurements of head circumference (cm) and total cerebral volume will show commensurate growth patterns for participants with 18q-

.

Ho2G: Exploratory hypothesis: There will be no significant differences in post treated participants with 18q- in regard to cerebral volume, right/left cerebral asymmetry and corpus callosum area when compared to controls.

Ho3: In post treated participants with 18q-, brain region measurements (total cerebral brain volume, cerebral asymmetry, and midsagittal corpus callosum area) will be predictive of an increase in mean scores for the DAS-NVC, VABS–ABC, and decreases in the BASC-BSI.

Rationale for Ho2A-Ho3

The original intent of this study was to measure white and gray matter change post GH treatment to infer increase in myelination. However, preliminary review of the MRI images revealed that due to the marked levels of dysmyelination revealed in the scans, there was poor gray-white matter differentiation. Therefore, a more indirect approach of examining total cerebral volume change and midsagittal corpus callosum area is more feasible, as the corpus callosum is generally easily identifiable due to its location and shape. Estimates of total brain volume change post GH treatment would indicate some general degree of neuronal or axonal growth, while change in size of corpus callosum may be an indirect structural correlate for increased interhemispheric transfer of information that may be related to an increase in callossal myelination. However, it should be noted that change white matter can be due to length, or thickness may be due to total number of fibers, thickness of axons, or the myelin content of the axons or fibers per unit area (Woiciechowsky, Vogel, Myer, & Lehmann, 1997) and, therefore, distinct cerebral changes (i.e., increased myelination) associated with any volume or area change

would be unknown. Further, it is important to rule out whether increased brain volume is affected by ventricular enlargement rather than an increase in brain tissue, as increased ventricular size has been associated with cognitive difficulties due to increased intracranial pressure and associated damage to brain tissue, as well as due to possible atrophy and shrinkage of brain tissue (Kolb & Wishaw, 1996).

Given the aforementioned caveats regarding inference of white matter change in 18q-, additional areas of research deserve further consideration. For example, increases in head circumference, white matter and IQ have been reported for individuals with 18q- who have been treated with GH (Cody et al., 2005; Hardies et al., 2001). It follows that there may be an associated increase in total cerebral brain volume post GH treatment for these individuals as well. In normal children, greater levels of white matter have been reported in the right cerebral hemisphere when compared to the left cerebral hemisphere. Further, the right hemisphere is reported to be slightly larger overall when compared to the left hemisphere (Kolb & Wishaw, 1996). It is unknown whether children with 18q- exhibit this asymmetry. It is predicted that such asymmetry does not exist in children with 18q- who are not receiving GH treatment, as global deficits in white matter have been reported in such individuals and would presumably affect the differential white matter distribution in the brain. If GH treatment is associated with an increase in white matter (myelination), then it is predicted that greater asymmetry in the right hemisphere will be noted as in normally developing children. Comparisons of left-right cerebral volume hemispheric symmetry will be based on a formula that measures direction of asymmetry: (L - R)/(0.5[L + R]) (Collinson et al,

2003; Galaburda et al., 1987; Preis et al., 1999; Semrud-Clikeman et al., 2000). In this formula, the variance in total brain volume is removed from the asymmetry measure. Hemispheric asymmetry is then expressed as a proportion of the total brain volume. Therefore, a resulting positive value would indicate a larger left hemisphere and a negative value a larger right hemisphere. Additionally, individuals with 18q- syndrome are reported to have abnormally small corpus callosum. Since white matter increases are predicted post GH treatment, it is possible that the corpus callosum size will increase, as this area is associated with high levels of myelination.

Hypotheses 4A-4B

Ho4A: Participants with 18q- (pre-treated) will have lower DAS Speed of Information Processing (SIP) scores than normal controls.

Ho4B: In post treated participants with 18q-, increases in SIP scores are predicted to significantly positively correlate with increases in midsagittal area of the corpus callosum.

Rationale for Ho4A-Ho4B:

The corpus callosum has been implicated in speed of information interhemispheric transference, as lesions in this area have been associated with slowed processing speed (Rao et al., 1989). Therefore, predicted increase in corpus callosum size post GH treatment may be linked to increased processing speed performance.

Power Analysis

Based on previous findings regarding the effects of GH treatment in 18q- (Cody et al., 2005), a large effect size is expected for this study. A power analysis was calculated using a t-test for means, using a total sample size of 26 participants (13 participants with 18q-, 13 controls). Using a reported large effect size (Cohen's d = .8) (Maxwell & Delaney, 1990) as a predictor, with alpha of .05, the calculated statistical power was estimated at .5. Therefore, there is a 50% chance of rejecting a false null hypothesis. Although the level of power for this study is affected by the relatively low number of participants in this study, it is nonetheless limited by the rare occurrence of 18q- (i.e., 1/40,000 births, Cody et al 1997).

CHAPTER FOUR: RESULTS

Overview

There were 26 participants in the study, including 13 18q- treatment participants and 13 controls. Pre-GH treatment and post-GH treatment scores were obtained for treatment participants on several psychological measures, including the Nonverbal Reasoning Composite (NVC) and Speed of Information Processing Index of the Differential Ability Scales, the Adaptive Behavior Composite (ABC) of the Vineland Adaptive Behavior Scales, and the Behavior Symptoms Index (BSI) of the Behavior Assessment System for Children. Additionally, comparisons of controls and pre and post-GH treated participants with 18q- were made of cerebral volume, lateral ventricle volume, head circumference, and midsagittal corpus callosum area.

The time period between pre and post scores varied for the treatment participants due to difficulty in obtaining viable pre and post treatment MRI scans for the same time intervals. Control participants were measured only once for psychological test performance and for MRI acquisition due to cost constraints. The mean age of the control participants was 9.1 years while that of participants with 18q- at their pre and post points were 6.1 and 8.0 years, respectively. Six (46%) of the control participants and eight (62%) of the treatment participants were female. Table 2 displays the participant age range at pre and post treatment.

Table 2

Age Data for Overall Sample

	18-q Participants (N=13 [8 fem., 5 male])		Controls (N=13 [6 fem., 7 male])	
	Mean (SD)	Range	Mean (SD)	Range.
*Age				
Pre	6.1 (3.8)	2.5 - 12.8	9.14 (3.9)	2.4 - 14.9
Post	8.0 (3.7)	3.8 - 13.9	---	---

* Age given in years and months

It should be noted that for the analysis of performance on the NVC of the DAS, there were only seven participants with 18q- that had both pre and post treated data on this measure. Given the difficulties in administering cognitive testing to children with 18q-, some participants were unable to complete the DAS at either pre or post treatment due to a combination of issues that hindered reliable test acquisition, such as profound cognitive delay, inattention, and hearing impairment. Therefore, analyses of performance on the ABC and BSI were run separately given that there were data for all participants with 18q- on these two measures. The number of participants with 18q- included in the brain measurement analyses ranged from (N = 11) to (N= 13), depending upon the analysis, and were comparable to the number of controls for which there were data available, which varied between (N=12) and (N=13), depending upon the analysis. The differences in the number of participant MRI scans used for the various analyses was attributable to variability in scan quality, as some were discarded due to poor image resolution (i.e., due to movement artifacts).

Performance on Psychological Measures

Comparison of Pre-Treated Participants with 18q- and Controls

Intellectual functioning of participants was assessed using the NVC of the DAS. However, several participants with 18q- were missing NVC data due to difficulties in obtaining valid scores on this measure (i.e., due to inattention, etc.). All 13 participants with 18q- had complete data for the ABC and BSI, however, as these measures were completed based on parental information and were not subject to the same difficulties in obtaining assessment data for the DAS. Since the NVC data reflected scores for only seven participants, the decision was made to analyze pre-treated, control and post-treated NVC data separately from ABC and BSI data by conducting a separate MANOVA to: (1) analyze ABC and BSI data together and (2) conduct an ANOVA to analyze the NVC data. This strategy was used in order to maximize the participant data available for each analysis.

The first MANOVA examined differences in mean scores between pre GH-treated participants with 18q- and controls on the ABC and BSI measures. Results of the MANOVA were significant ($F_{2,22} = 37.30$, $p = .001$), indicating that performance of participants with 18q- significantly differed from controls. As predicted by the research hypothesis, pre-GH treated 18q-participants had significantly lower adaptive behavior composite scores (ABC) ($F_{1,23} = 78.05$, $p = .001$) and higher BSI scores than controls ($F_{1,23} = 4.93$, $p = .04$) on follow-up univariate analyses.

On the Vineland Adaptive Behavior Composite (ABC), participants with 18q- had a mean ABC score of 60.69 ($SD = 14.7$), which is well below average, and

control participants had a mean ABC score of 107.83 (*SD* = 11.5), which is in the average range. On the Behavior Symptoms Index (BSI) of the (BASC), participants with 18q- had a mean score of 52.31 (*SD* = 9.86) and controls had a mean score of 44.67 (*SD* = 6.9), although BSI scores for both participants with 18q-and controls were not clinically meaningful. These results support the research hypothesis that pre-treated participants with 18q- have overall lower adaptive functioning. Although participants with 18q- scored significantly higher on the BSI than the controls, their scores were not clinically meaningful in suggesting any significant behavioral difficulties.

Results from the ANOVA for the DAS NVC showed that pre GH-treated participants with 18q- scored statistically significantly lower on the Nonverbal Reasoning Composite score (NVC) than did controls ($F_{1,17} = 20.44$, $p = .001$) as was predicted. The mean score for participants with 18q- was 81.71 (*SD* = 15.4), which is in the below average range of intellectual functioning, and control participants had a mean NVC score of 113.16 (*SD* = 14.3), which is in the high average range. These results support the research hypothesis that pre-treated participants with 18q- have lower non-verbal reasoning skills when compared to controls. Table 3 displays the descriptive information for all three measures (ABC, BSI and NVC).

Table 3

Mean Differences of Pre-Treated Participants with 18q- and Controls on Psychological

Measures

Psychological Measure	18-q Participants (N=13)		Controls (N=13)			
	Mean	S.D.	Mean	S.D.	*F*	*p*
*Nonverbal Reasoning Composite (NVC)	81.71	15.21	113.17	14.29	20.44	.001
Adaptive Behavior Composite (ABC)	60.69	14.79	108.15	11.09	78.05	.001
Behavior Symptoms Index (BSI)	52.31	9.86	44.67	6.96	4.93	.037

** N=7 for NVC analysis*

Comparison of Participant Performance on Psychological Measures at Pre- and Post-GH Treatment

Repeated-measures MANOVA and ANOVA were conducted to determine whether participants with 18q- treated with GH showed significant improvement on psychological measures post-treatment. Results of the MANOVA (examining the ABC and BSI data) showed that, contrary to the predicted results (i.e., improved adaptive behavior skills and a decrease in behavioral symptoms), ABC and BSI scores for participants with 18q- were not significantly different at post-GH treatment ($F_{2,11}$ = .19, p=.83). Results of the ANOVA (examining NVC data) also found that NVC scores for participants with 18q- did not improve post-GH treatment ($F_{1,12}$ = *.04, p=.83*) at a statistically significant level. Overall, performance across psychological measures did not change from pre to post treatment assessment to a statistically significant degree.

Comparison of Post-Treated Participants on Psychological Measures with Controls

A MANOVA was conducted to determine whether the performance of post-GH treated participants with 18q-was commensurate with controls' performance on the ABC and BSI measures. The research hypothesis in this case was that there would be *no* significant differences on these two measures between post-GH participants and controls. Results showed that the research hypothesis was partially supported, as the overall multivariate test was statistically significant ($F_{2,22} = 11.98$, $p = .001$). Univariate follow-up analyses revealed a statistically significant difference on the ABC measure between post GH-treated participants and controls: ($F_{1,23} = 24.88$, $p = .001$). Post-GH treated participants with 18q- achieved a mean score of 63.85 ($SD = 14.79$) on the ABC, still below average, whereas controls scored a mean of 107.83 ($SD = 11.51$), which is in the average range. For the BSI, participants with 18q- scored lower than controls, but that difference was not statistically significant ($F_{1,23} = 3.12$, $p = .09$; $M_{post} = 51.5$ [$SD = 11.7$]; $M_{control} = 44.6$ [$SD = 6.96$]). These results--showing a difference across groups--are not surprising in light of the results of the previous tests, which indicated that post-GH treated participants with 18q- did not show improvement across psychological domains.

An ANOVA, comparing post-GH treated participants with 18q-with controls on the NVC scale, which revealed a statistically significant difference between the two groups on the overall test: ($F_{1,18} = 22.44$, $p = .001$). On this measure, post-GH treated participants with 18q- had a mean score of 81.25 ($SD = 15.46$), with a mean

score for controls of 113.17 (*SD* = 14.29). Table 4 displays the descriptive information for all three measures (ABC, BSI and NVC).

Table 4

Mean Differences of Post-Treated Participants with 18q- and Controls on Psychological Measures

	Psychological Measure					
	18-q Participants (N=13)		Controls (N=13)			
	Mean	S.D.	Mean	S.D.	*F*	*p*
*Nonverbal Reasoning Composite (NVC)	81.25	15.46	113.17	14.29	4.73	.001
Adaptive Behavior Composite (ABC)	63.85	14.79	107.83	11.51	5.23	.001
Behavior Symptoms Index (BSI)	51.54	11.70	44.67	6.96	3.12	ns

* N=7 for NVC analysis

Volumetric Analyses and Comparisons of Brain Regions

Correlational Analyses

Prior to conducting statistical analyses comparing the brain regions/volumes of pre-treated participants with 18q-and controls, correlational analyses (Pearson Product Moment correlations) were performed on pre-GH treated participant data to explore the relations between all measured brain regions prior to GH treatment. It should be noted that due to numerous tests of hypotheses based on the same sample of data, there is the likelihood of inflated type I error in the correlational analyses, and thus, these are presented as descriptive information. Despite this caveat, the first correlation matrix shows that, for the pre-GH treatment group, head circumference was significantly negatively correlated with measures such as right

and left lateral ventricles (r = -.64, r = -.67) and total lateral ventricle volume (r = -.67), and was weakly correlated *(*r = .29*,* r = .26) with measures such as right and left hemisphere cerebral volume. The same pattern of results was found for the midsagittal corpus callosum area: This area was significantly negatively correlated with the same measures of right, left, and total ventricle volume (r = -.70, r = -.66, and r = -.69, respectively) and moderately correlated with hemispheric and total cerebral volumes. Both pre-treatment left and right ventricles were moderately, and negatively, correlated with right, left and total cerebral volumes. These correlations are shown in Table 5.

Table 5

Correlations Among All Brain Structures for Pre-Treated Participants with 18q-

	1	2	3	4	5	6	7	8
1. Pre-treatment head circumference	1.00	.60	-.64	-.67	-.67	.29	.26	.27
2. Pre treatment corpus callosum		1.00	-.70	-.66	-.69	.43	.48	.46
3. Pre-treatment right lateral ventricle			1.00	.94	.98	-.58	-.43	-.52
4. Pre-treatment left lateral ventricle				1.00	.99	-.60	-.46	-.54
5. Pre-treatment total lateral ventricle					1.00	-.60	-.45	-.54
6. Pre-treatment right hemisphere cerebral volume						1.00	.92	.98
7. Pre-treatment left hemisphere cerebral volume							1.00	.97
8. Pre-treatment total cerebral volume								1.00

Additionally, correlational analyses (Pearson Product Moment correlations) were conducted to explore the relationship between brain regions of control participants. A somewhat different pattern was evident in this correlation matrix

when compared to that of pre-GH treated participants. For the controls, there were no significant correlations, either positive or negative, between midsagittal corpus callosum area and any of the other brain measures. The only significant correlations evident were those between the right lateral ventricle, left ventricle and total ventricle volume, as expected. The remaining correlations were not significant, except for those among the hemispheric cerebral volumes and the total cerebral volumes**.** Correlations for controls are shown in Table 6.

Table 6

Correlations Among All Brain Structures for Control Participants

	1	2	3	4	5	6	7	8
1. head circumference	1 .00*							
2. corpus callosum		1.00	.22	-.05	.13	-.13	-.13	-.13
3. right lateral ventricle			1.00	.74	.96	.22	.35	.29
4. left lateral ventricle				1.00	.89	.19	.47	.34
5. total lateral ventricle					1.00	.22	.42	.34
6. right hemisphere cerebral volume						1.00	.89	.97
7. left hemisphere cerebral volume							1.00	.97
8. total cerebral volume								1.00

**Note.* The data for this variable was unavailable for controls, and thus, PPM coefficients were not calculated.

Volumetric Analyses

Results of volumetric analyses of brain regions comparing: (1) pre-treated participants with 18q- and controls; (2) pre- and post-treated participants with 18q-; and (3) post-treated participants with 18q- and controls are presented in separate subsections by brain region. “Pre-treatment” analyses are discussed first, followed

by pre- / post- treatment analyses for the participants with 18q- and the "post-treatment" analyses of treated participants with 18q- and controls are presented last in each of the respective subsections. Volumetric or size measurements of the brain regions analyzed are found in the descriptive statistics for pre- and post-GH treated participants and controls. These are displayed below in Table 7.

Table 7

Mean Measurements of Brain Regions for Pre- and Post- Treated Participants and Controls*

Measurement	Pre GH Treated 18q-			Post GH Treated 18q-			Controls		
	M	SD	n	M	SD	n	M	SD	n
Corpus Call. Area	.462	125	13	.501	.099	13	.592	.064	13
Rt Lateral Ventricle Volume	12.47	7.34	12	12.84	7.23	11	7.81	4.18	12
Lt Lateral Ventricle Volume	13.03	10.27	12	12.90	9.64	11	7.42	2.41	12
Total Lat. Ventricle Volume	25.50	17.37	12	25.74	16.44	11	15.23	6.19	12
Right Cerebral Volume	605.67	33.73	12	607.75	29.25	11	614.81	31.23	12
Left Cerebral Volume	614.27	29.53	12	611.67	24.70	11	618.17	31.81	12
Total Cerebral Volume	1219.93	61.94	12	1219.39	51.85	11	1232.97	61.29	12

**Note*. Corpus callosum area = cm^2 and all volume measurements = cm^3

Lateral Ventricle Volume

Comparisons of Lateral Ventricle Volume of Pre GH-Treated Participants with 18q- and Controls

A MANOVA was conducted to determine if the right and lateral ventricle volumes were significantly different in pre GH treated participants with 18q- and

controls. The results of this test were not statistically significant, overall ($F_{2,21}$ =-1.80, p =. 20), although the mean volume measurements of the left and right lateral ventricles were larger in participants with 18q- (see Table 7). Results of follow-up MANOVAS revealed no significant gender differences were found on *either* right *or* left lateral ventricle volume measurements between the pre-treated group of 18-q participants and controls ($F_{2,21}$ =1.94, p=.17) for right lateral ventricle volume and ($F_{2,21}$ = 1.30, p=.26) for left lateral ventricle volume. In addition, no significant age differences were found on *either* right *or* left lateral ventricle volume measurements between the pre-treated group of 18-q participants and controls ($F_{2,21}$ =1.13, p=.30) for right lateral ventricle volume and ($F_{2,21}$ = 1.16, p=.29) for left lateral ventricle volume. Finally, neither significant age nor gender differences were found between pre-GH treated 18-q participants and controls on *total* ventricle volume ($F_{2,21}$ =1.22, p=.28) for age and ($F_{2,21}$ = 1.67, p=.20) for gender.

Comparisons of Lateral Ventricle Volume of Pre- and Post-GH-Treated Participants with 18q-

A repeated measures MANOVA was conducted to compare both right and left lateral ventricle volume in pre- and post-GH treated participants with 18q-. The results of the MANOVA did not reveal significant differences in the right and left lateral ventricles from pre to post GH treatment ($F_{2,9}$ = .763, p =. 49). Additional MANOVAS were conducted to determine the presence of gender or age effects on the volumes of these brain regions. No significant gender effects were found for the left lateral ventricle in pre- and post-GH treated participants with 18q-. However, a main effect for gender was found for males but not for females with respect to right

lateral ventricle volume ($F_{1,8}$ = 6.23, p =. 037). Post-GH-treated males registered a mean volume of 10.15 cm^3 compared with pre-treated males, whose mean volume was 6.47 cm^3. There were no significant age effects on either the right or left lateral ventricle volumes for the pre- to post- GH treated participants with 18q-.

Lateral Ventricle Volume of Post-GH Treated Participants and Controls

A MANOVA was conducted to compare the right and left lateral ventricles in post GH treated participants with 18q- and controls. Overall, results of the MANOVA did not result in significant differences between GH treated participants with 18q- and controls ($F_{2,20}$ =2 .08, p =.15). However, univariate analyses revealed significance in the right lateral ventricle volume: ($F_{1,\ 21}$ =4.26, p =.05), in the expected direction, as the mean for the post-GH treated participants was 12.84 cm^3 (SD = 7.23) while the mean for the controls was 7.81 cm^3 (SD = 4.18), indicating a larger *right* lateral ventricle volume for the GH treated group over that of e controls.

There was not a significant difference between the left-lateral ventricle volume in post-GH treated participants and controls*:* ($F_{1,21}$ =3.65, p =.07). However, the mean for the control group was smaller at 7.42 cm^3 (SD = 2.41) than for the post-GH treated group at 12.90 cm^3 (SD = 9.64). Results of additional MANOVAS revealed no significant gender differences were found on *either* right *or* left lateral ventricle volume measurements between the post-GH treated 18-q participants and controls ($F_{2,20}$ =1.50, p=.23) for right lateral ventricle volume and ($F_{2,20}$ =1.45, p=.24) for left lateral ventricle volume. In addition, no significant age differences were found on *either* right *or* left lateral ventricle volume measurements between the post-GH treated participants with 18q- and controls ($F_{2,20}$ =.47, p=.50) for right

lateral ventricle volume and ($F_{2,20}$ = .52, p=.47) for left lateral ventricle volume. Finally, neither significant age nor gender differences were found between post-GH treated 18-q participants and controls on *total* ventricle volume($F_{2,20}$ =.54, p=.47) for age and ($F_{2,20}$ = 1.63, p=.21) for gender.

Left and Right Cerebral Hemisphere Volume

Comparisons of Left and Right Cerebral Hemisphere Volume of Pre and Post GH-Treated Participants with 18q- and Controls

Subtracting right and left lateral ventricle volume from corresponding right/left cerebral hemispheric volume measurements derived participant cerebral volume measurements. This procedure was done for each hemisphere prior to obtaining the total cerebral volume. A MANOVA was conducted to determine whether right and left cerebral hemisphere volumes differed significantly in pre GH treated participants with 18q- when compared to controls. Contrary to predicted differences, there was not a statistically significant difference in pre GH treated participants with 18q- and controls in regard to either right and left cerebral hemisphere volume ($F_{2,21}$=.471, p=.631). A repeated measures MANOVA was conducted to determine if individual right and left cerebral hemisphere volumes were significantly different from pre to post GH treatment. Overall, there was not a statistically significant difference found in comparisons of pre-to post-GH treatment measurements of both the right and left cerebral hemispheres ($F_{2,9}$ = 2.36, p=.15). There were no statistically significant age or gender effects on differences in right or left cerebral hemisphere volumes from pre- to post-GH treatment. Additionally, there was not a statistically significant difference in post GH-treated participants

with 18q- and controls for either right or left cerebral volume ($F_{2,20}$=.156, p=.857). Finally, neither significant age nor gender differences were found between post-GH treated 18-q participants and controls on right and left cerebral volume($F_{2,20}$ =1.77, p=.201) for age or ($F_{2,20}$ = .127, p=.882) for gender.

Further analyses revealed that, in pre GH treated participants with 18q-, the right and left cerebral hemisphere volumes were statistically different, with significantly larger left than right hemispheres (t_{11} =- 2.21, p = .05). These results are contrary to what was predicted in these individuals, as no hemispheric volume differences were expected due to global dysmyelination. Additionally, this result is inconsistent with findings in prior studies of normally developing individuals, who typically exhibit larger right than left cerebral hemisphere volume. At post GH treatment, although the left cerebral hemisphere remained slightly larger than the right hemisphere, the hemispheres did not statistically differ (t_{10} =-.828, p = .427). Control participants were also found to not statistically differ on measures for the right or left hemisphere volume (t_{11} =- .789, p = .447).

Analysis of Cerebral Asymmetry

Participants were evaluated to determine whether GH treatment would be associated with greater right to left cerebral asymmetry. Comparisons of left-right cerebral volume hemispheric symmetry were determined by a formula that measures direction of asymmetry: (L - R)/(0.05[L + R]) (Collinson et al, 2003; Galaburda et al., 1987; Preis et al., 1999; Semrud-Clikeman et al., 2000). Hemispheric asymmetry is then expressed as a proportion of the total brain volume, with a resulting positive value indicating a larger left hemisphere and a negative value a larger right

hemisphere. It was hypothesized that there would *not* be cerebral asymmetry in pre-GH treated participants due to associated global dysmyelination. (i.e., the mean asymmetry would equal to zero)

First, a one-sample t-test was conducted to determine whether mean asymmetry differed from zero in either direction for pre-GH treated participants and whether the null (research) hypothesis of asymmetry equal to zero in pre-GH treated participants should be accepted or rejected. Since the results of the t-test were significant (t_{11} = 2.21, p = .05) the null (research) hypothesis was rejected. This finding suggests that participants with 18q- do exhibit overall cerebral asymmetry, with the trend of asymmetry being toward greater left than right cerebral hemispheres (M = .15, a positive value indicating a larger left hemisphere). Figure 5 graphically depicts the distribution of pre-treatment asymmetry values.

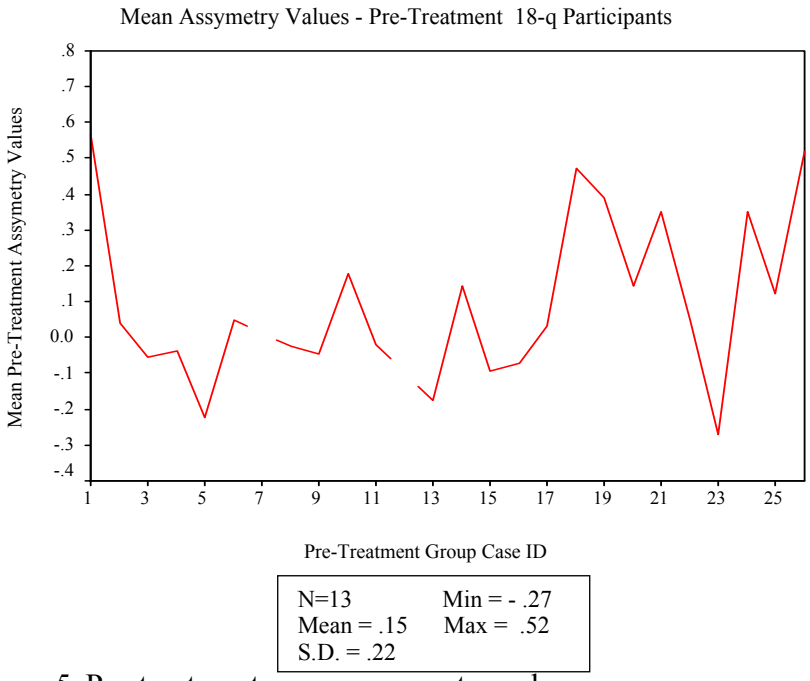

Figure 5. Pre-treatment group asymmetry values.

Secondly, to test the hypothesis that controls have greater *right to left* asymmetry (as is expected in the typically developing population), another one-sample t-test was conducted. The research hypothesis was that mean asymmetry was less than zero (i.e., a negative value which would indicate a larger right hemisphere) for controls. Results of the t-test were not statistically significant: (t_{11} = .781, p=.45; M = .05), indicating a lack of evidence that controls have greater right asymmetry.

To further explore differences in cerebral asymmetry, a MANOVA was conducted to determine whether the right and left cerebral hemispheres differed significantly in pre GH treated participants with 18q- when compared to controls. Contrary to predicted differences, there was not a statistically significant difference in pre GH treated participants with 18q- and controls in regard to both right and left cerebral hemisphere volume ($F_{2,21 =}$ .471, p=.631).

Analysis of Cerebral Asymmetry Post GH Treatment

Contrary to the hypothesis that pre-GH treated participants with 18q- would have no cerebral asymmetry, their cerebral hemispheres were found to exhibit reversed asymmetry (L > R). Post GH treatment, it was predicted that participants with 18q- would show greater *right* than *left* hemisphere volumes, presumably due to expected increases in myelination. A one sample t-test was done to determine if the mean value for the cerebral asymmetry coefficient was less than zero (a negative value would indicate a larger right hemisphere). Contrary to predicted R > L asymmetry, post-GH treated participants were found to have greater *left* hemispheric asymmetry (mean asymmetry coefficient was positive, (M=.07; t_{10}=.86,

p = .41), indicating greater *left* hemisphere volume. Further, a paired t-test did not indicate a statistically significant difference in participants with pre to post GH treatment in overall mean asymmetry coefficients (t_{10} =1.41, p =.189). Mean cerebral asymmetry coefficients are shown below in Table 8.

Table 8

Mean Asymmetry Coefficients for Pre and Post Treated Participants with 18q- and Controls

	Total Cerebral Asymmetry		
	M	SD	n
Pre GH treated 18q-	.15	.23	12
Post GH treated 18q-	.07	.26	11
Controls	.05	.24	12

Finally, there were no statistically significant age effects on differences in cerebral asymmetry for the pre- and post-treated participants with 18q-. However, a significant main effect for asymmetry was found for pre- and post-treated females, but not for males ($F_{,1,11}$ =6.43, p = .028). The asymmetry coefficient mean value for the pre-treated female participants with 18q- was .14, while for the post-treated female participants it was .05. This result indicates a trend for a decrease in the strength of the L > R cerebral asymmetry in female participants with 18q-.

Comparison of Total Cerebral Volume Pre- and Post-GH Treatment

It was predicted that post-GH treated participants with 18q- would exhibit a significant increase in total cerebral volume when compared to their pre-treatment measurements. A paired-samples, repeated measures t-test was conducted, the results of which were statistically insignificant (t_{10} = .236, p=.81). Overall, this

finding indicates that participants with 18q- did not show statistically significant increases in cerebral volume post-GH treatment. Further, there were no significant age or gender effects on differences in total cerebral volume from pre- to post-GH treatment.

Comparison of Total Cerebral Volume and Midsagittal Corpus Callosum Area of Pre-GH-Treated Participants with 18q- and Controls

A MANOVA was conducted to determine whether pre-GH treated participants with 18q-have less total cerebral volume and smaller midsagittal corpus callosum area when compared to normal controls. Results showed that the research hypothesis was partially supported, with the overall multivariate test significant ($F_{2,,21}$ = 5.39, p = .01). Univariate follow-up analyses revealed a statistically significant difference for corpus callosum area (F= 11.16, p = .003), but not for total cerebral volume (F = .269, p = .61). These results indicate that pre GH-treated participants had a significantly smaller midsagittal corpus callosum area when compared to controls, although there was not such a statistically significant difference in total cerebral volume measurements.

In order to determine whether the mean difference in corpus callosum area between pre-treated participants and controls was statistically significant, an independent samples t-test was performed. Results of this analysis was statistically significant: (t_{24} = -3.36, p = .003). The mean difference of -.13 between the two groups was significant at p = .003 in the expected direction, with pre-treated participants with 18q- evidencing a smaller corpus callosum (M = .46 cm^2) compared to controls (M = .59 cm^2).

Analysis of Midsagittal Corpus Callosum Area Post-Treatment

A repeated measures ANOVA was computed to determine if participants with 18q- had a significant increase in midsagittal corpus callosum area post GH treatment, presumably due to a predicted increase in myelination. Results of the test showed that, overall, post-GH treated participants did experience a statistically significant increase in midsagittal corpus callosum area ($F_{1,12} = 4.27$; p=.03) from pre- to post GH treatment measurements (M_{pre} =.46 cm^2 , M_{post}=.50 cm^2).

Although post-GH treated participants with 18q- did show a significant increase in midsagittal corpus callosum area, it was unclear as to whether their post-treated corpus callosum area were smaller overall than controls. Results of an independent t-test showed that they continued to be significantly smaller than controls after GH treatment ($t_{24} = 2.79$, p = .01; M =.59 cm^2 for controls, M=.50 cm^2 for post-GH treated group).

Results of additional MANOVAS to determine whether there were age or gender effects on differences in corpus callosum area revealed no significant age effects for participants with 18q-. Additionally, no significant gender differences were found on corpus callosum measurements between the pre-treated group of participants with 18q- and controls ($F_{23} = 2.16$, p=.15). Further, pre- to post-treatment measures of corpus callosum area did not differ significantly between males and females in the 18-q treatment group ($F_{23} = 2.48$, p=.13). However, a main effect for treatment was found for *males,* but not for females ($F_{23} = 6.79$,

p=.026, M =.62 for controls, M =.51 for post-treatment group) between the post-GH treated group and controls.

Relationship of Head Circumference and Cerebral Volume at Pre-and Post-Treatment

It was predicted that participant head circumference and brain volume would be positively correlated (Miles et al., 2000), at both pre- and post- GH treatment. Two separate correlational analyses (PPM) were performed to determine whether head circumference and total cerebral volume were related: the first used pre-GH treatment measures of head circumference and total cerebral volume and the second used post- GH treatment measures of head circumference and total cerebral volume. Results of both analyses failed to find a significant correlation between either pre-treatment head circumference and total volume (r_{pre} =.28, p=.37) or post-GH treatment head circumference and total volume (r_{post}=.25, p=.47).

Finally, both age and gender effects were found between pre- and post-GH treatment measures of head circumference. Results of a repeated-measures MANOVA revealed a statistically significant main effect for gender in both pre- and post-treated females ($F_{1,11}$ =81.63, p = .001) and males ($F_{1,11}$ = 13.93, p = .02) , with mean differences for both males and females in the expected direction. Additionally, a repeated measures MANOVA was conducted to test the effects of age in regard to head circumference. A statistically significant main effect for age was found in pre- and post-treated participants with 18q- ($F_{1,11}$ = 11.42, p = .006), indicating that an increase in head circumference was associated with increasing

age. Table 9 displays the mean differences in head circumference between pre- and post-treated participants with 18q-.

Table 9

Mean Differences for Pre and Post-Treated 18q-Participants on Head Circumference

	Pre-Treatment(N=13)		Post-Treatment(N=13)			
	Mean	S.D.	Mean	S.D.	F	p
Factor						
Gender						
Male	48.76	2.02	50.80	1.68	13.93	.02
Female	48.08	2.89	49.67	3.09	81.63	.001
Age	48.34	2.52	50.10	2.62	11.42	.006

**Note*. Univariate significance tests showed that the size of the mean differences for both males (2.04) and females (1.58) was significant at p = .02 for males and p = .001 for females.

Figure 6 graphically depicts the distribution of pre- and post-treatment head circumference measurements based on gender.

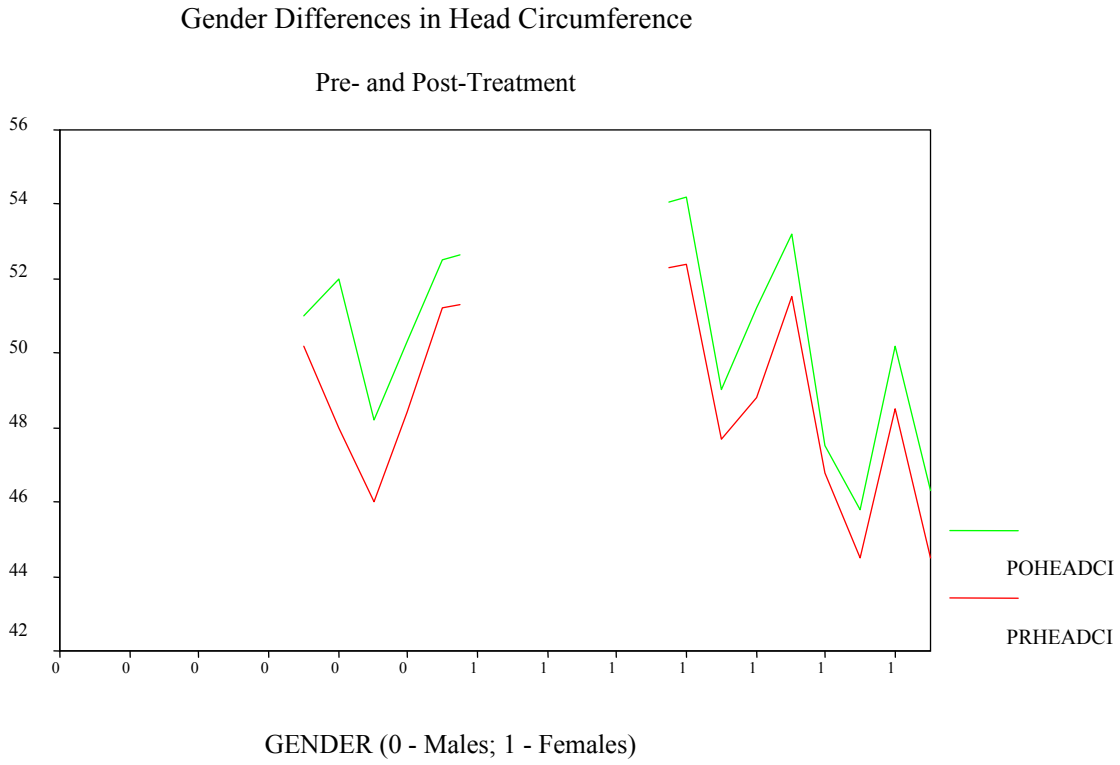

Figure 6. Pre- and post-treatment group head circumference (cm) by gender.

Relationship Between GH Treatment and Brain Growth

It was hypothesized that GH treatment would be associated with brain growth approaching that of normal control participants, meaning that there would be no significant differences in total cerebral volume, cerebral asymmetry, and midsagittal corpus callosum area between post GH-treated 18q-participants and controls. Results of an overall MANOVA were not statistically significant ($F_{,3,19}$ = 1.88, p = .17). However, follow-up univariate analyses revealed a statistically significant difference, but only with the midsagittal corpus callosum area ($F_{,2,,21}$ = 5.39, p = .02), with participants with 18q- exhibiting smaller corpus callosum than controls. Therefore, the hypothesis that there would be no differences between post

GH-treated participants with 18q- and controls was supported in regard to total cerebral and cerebral asymmetry, but not in regard to midsagittal corpus callosum area.

To further explore the relationship between all measured brain regions in post GH treated participants, PPM correlations were computed. As discussed previously, due to the risk of inflated type I error, the results are provided for descriptive purposes. For the post GH-treatment group, the pattern of correlations among head circumference, corpus callosum and all of the ventricle volume measures remained relatively commensurate with pre GH treated results, and were in the same direction: positively correlated with corpus callosum, negatively correlated with the ventricle measures and weakly correlated with the hemispheric and total cerebral volume measures (r =.19, r = .29 and r = .25, respectively). Post GH treatment, the negative correlation between the left, right, and total ventricle volumes were smaller than at pre-treatment, indicating some degree of change: For example, the correlation between pre-treatment right lateral ventricle and left cerebral volume was -.43, while the correlation between post-treatment right lateral ventricle and post-treatment left cerebral volume was .26 with measures such as right and left hemisphere cerebral volume. The same pattern of results was found for the corpus callosum area: This was significantly negatively correlated with the same measures of left, right and total ventricle volume and moderately correlated with hemispheric and total cerebral volumes. Both pre GH-treatment left and right ventricles were moderately, and negatively, correlated with right, left and total cerebral volumes (see Table 10).

Table 10

Correlations Among all Brain Structures for the Post-Treated Participants with 18q-

	1	2	3	4	5	6	7	8
1. Post-treatment head circumference	1.00	.63	-.46	-.60	-.56	.19	.29	.25
2. Post treatment corpus callosum		1.00	-51	-.65	-.60	.22	.22	.23
3. Post-treatment right lateral ventricle			1.00	.89	.96	-.28	.01	-.15
4. Post-treatment left lateral ventricle				1.00	.98	-.49	-.24	-.39
5. Post-treatment total lateral ventricle					1.00	-.41	-.13	-.30
6. Post treatment right hemisphere cerebral volume						1.00	.85	.96
7. Post-treatment left hemisphere cerebral volume							1.00	.95
8. Post-treatment total cerebral volume								1.00

Analysis of Speed of Information Processing Performance: Pre-GH Treated Participants with 18q- and Controls

It was predicted that pre-treated participants with 18q-would have significantly lower scores for the Speed of Information Processing (SIP) subtest when compared to controls, presumably due in part to smaller corpus callosum and global dysmyelination. Results of the independent-samples t-test supported this hypothesis, as pre GH-treated participants with 18q-scored significantly lower (M = 30.67) than did controls (M = 55.80; t_{11}= 5.48, p = .001).

Relationship Between Brain Size and Performance on Psychological Measures

It was predicted that increased midsagittal corpus callosum area would be positively related to improved SIP performance post-GH treatment. However, this

analysis was affected by the extremely low number of participants with 18q-who had both SIP scores for both pre and post GH treatment (*N*=3), and thus was not interpretable.

Analysis of the Relationship Between Performance on Psychological Measures and Brain Measurements

Covariate regression models were performed to determine whether performance on psychological measures (NVC, ABC, and BSI) at post-treatment could be predicted from pre and post brain measures (total cerebral volume, cerebral asymmetry, and corpus callosum area), after controlling for influences due to psychological scores obtained at pre-treatment. Given the limitations imposed by the small sample size, it was not possible to simultaneously test the impact of all brain measures on the psychological measures. So, instead, for each psychological instrument, three separate models (one for each of the brain measurements) were conducted. Contrary, to predictions, none of the regression models tested successfully predicted variability on any of the brain measurements in regard to improvement on psychological measures.

Follow Up Analyses

Exploratory Analysis of relationship of Corpus Callosum Area and Total Lateral Ventricle Volume

Given that midsagittal corpus callosum area was found to be smaller in participants with 18q-, Pearson product moment correlations were computed to determine if total lateral ventricle volume and corpus callosum area were correlated. There was not a significant correlation between midsagittal corpus callosum area

and total lateral ventricle volume in control participants (r = 0.13, p=.69) although there was a significant negative correlation between corpus callosum area and ventricle volume at both pre GH treatment (r=-0.69, p=.013) and at post GH treatment (r=-0.60, p=.014).

Exploratory Analysis of Relationship of Brain Volume to Head Circumference

The relationship between head circumference, cerebral volume, and lateral ventricle volume in participants with 18q- was further expored using covariate regression models. The first model assessed the impact of participant pre-treated and post-treated total cerebral volume, with lateral ventricle volume included, on post treated head circumference, while controlling for pre-treated head circumference measurements. The data supports that participant cerebral volume (with lateral ventricles included) is related to head circumference, ($\hat{a}$ =.014, t = 4.45, p = .003), with a potential cross-lagged causal influence of pre-treatment cerebral volume that explains variance in post-treatment head circumference above and beyond what can be predicted with pre-treatment head circumference alone. The influence is positive, implying that higher pre-treatment cerebral volume is related to significant increases in post-treatment head circumference.

To assess the degree to which pre-treated participant cerebral volume is attributable to lateral ventricle volume, an additional regression analysis was conducted that allowed for measurements of cerebral volume (without inclusion of lateral ventricle volume) and lateral ventricle volume to predict head circumference. Again, pre-treatment cerebral volume was found to be statistically significantly related to post-treatment head circumference, even after accounting for pre-

treatment head circumference ($\hat{a}$ =.016, t = 4.43, p = .007). This time, however, cerebral volume excluded any influence of the lateral ventricle volume. Instead, this latter influence was tested independently with the inclusion of pre and post-treatment ventricle volume. Neither lateral ventricle measurement appears to have an effect on head circumference change.

CHAPTER FIVE: DISCUSSION

Chapter Five is divided into several sections. The first section pertains to the goals of this study and the findings in reference to the hypotheses. The results and implications of the analyses will be discussed in the context of existing research. The final sections will focus on the limitations of this study as well as how the current findings may inform future research pertaining to individuals with 18q- and related disorders.

Summary and Integration of Findings

Overview

The current study investigated the effects of short-term growth hormone (GH) treatment on individuals with 18q- who are GH deficient, specifically examining its effect on psychological functioning and brain development. This study was informed by previous studies that examined the positive effects of GH treatment on GH deficient individuals in regard to linear growth (Spadoni et al., 1989), improvement in cognitive ability (Cody et al., 1999b; Laron & Galatzer, 1980), adaptive behavior (More et al., 2001) and behavioral functioning (Lagrou et al., 1998; Stabler, 1998). Research on the neurological implications of 18q-, specifically, global dysmyelination, and preliminary evidence of the positive effects of GH treatment on brain development (Hardies et al., 2000), also provided the additional initial theoretical bases for this study.

Due to the rare occurrence of individuals with deletions of the 18th chromosome and relatively recent advances in genetics and neuroimaging, the full

understanding of this disorder is still in its preliminary stages. However, studies of individuals with 18q- have often focused on associated cognitive functioning, with corroboration among studies documenting high incidences of impaired intellectual ability in such individuals. There has been less examination of adaptive and behavioral functioning in individuals with 18q-although there is reported increased incidence of autism, attention deficit hyperactivity disorder (ADHD), adaptive behavior impairment, and emotional difficulties in this population (Semrud-Clikeman et al., 1999; Semrud-Clikeman et al., 2005). Although there have been studies that examine the neurophysiological underpinnings associated with 18q-, it is an area that deserves further examination, especially given the paucity of information regarding the effects of growth hormone treatment on neurophysiology and neuropsychological functioning in this population.

In regard to neurological correlates of 18q-, prior studies have shown that there are differences in regions of the corpus callosum in individuals with 18q- when compared to controls (Kochunov et al, 2005), as well as global abnormalities in white matter (Gay et al., 1997). Although there has been prior documentation that post GH treatment, global increases in myelination have occurred in individuals with 18q- (Cody et al., 2005; Hardies et al., 2000), examination of morphological structures in brain regions after treatment with GH have not yet fully been explored. This study examined both the psychological functioning and specific brain regions in children with 18q- before and after treatment with GH, specifically in regard to corpus callosum area, cerebral hemisphere volume and asymmetry, and lateral ventricle volume. Analysis of midsagittal corpus callosum area and cerebral

hemisphere asymmetry were subjects of focus for this study due to the association of abnormalities in corpus callosum size and in structural asymmetries with other neurodevelopmental disorders, such as dyslexia, autism, and schizophrenia (Crow, 1990; Filipek, 1995; Herbert et al., 2003; Herbert et al., 2005; Watkins et al., 2001). Further, given the existence of abnormal neuroanatomical asymmetries, the underlying assumption in such studies is that abnormal brain development is related to abnormal functional organization, and thus, related to impairment in cognitive and behavioral functioning.

Focus of Current Study

Based on previous findings regarding the positive influence of GH treatment on GH deficient individuals, it was hypothesized that GH treatment of children with 18q- would be associated with improvements across various psychological domains, specifically in regard to cognitive, adaptive, and behavioral functioning. It was predicted that improvements in psychological functioning would be associated with related significant increases in brain development, specifically in regard to the corpus callosum, total cerebral volume and in asymmetry of the cerebral hemispheres. The lateral ventricles were also measured, to account for the possible impact that abnormalities in this region may have on other cerebral structures, such as the cerebral hemispheric volume.

Analysis of Performance on Psychological Measures

In the first part of the study, scores on the Nonverbal Reasoning Composite (NVC) and of the Speed of Information Processing Index (SIP) of the Differential Ability Scales (DAS), the Adaptive Behavior Composite (ABC) of the Vineland

Adaptive Behavior Scales, and Behavior Symptoms Index (BSI) of the Behavior Assessment System for Children (BASC) were analyzed for pre and post GH treated participants with 18q-, as well as normally developing control participants. As predicted, control participants generally scored within the average range for both IQ and adaptive behavior functioning, and were rated to have a low incidence of behavioral symptoms. The overall analysis of 18q- participant performance across these domains failed to support the predicted improvements that GH would have on psychological functioning. Results from this portion of the analysis in regard to cognitive and adaptive functioning are surprising given that nonverbal intellectual functioning and, to a lesser extent, motor components of adaptive behavior functioning have been reported to improve after GH treatment in previous studies (Cody et al., 2005; Cody et al., 1999b; More et al., 2001).

In this study, the mean intellectual performance (NVC) for both pre and post GH treated participants with 18q- fell in the low average range of functioning. While the NVC scores did not improve after GH treatment, it is notable that scores also did not decrease upon post-test examination. Further, the overall IQ of individuals in this study is higher than reported in previous studies examining intellectual ability in this population, as 68% to 93% are reported to have some degree of mental retardation (Cody et al., 1999a; Strathdee et al., 1996). However, the relatively higher level of intellectual functioning represented in this study may be misleading, as only participants who were able to complete the nonverbal reasoning subtests of the DAS were included in this sample. This selection process may have produced a truncated sample that in turn resulted in conflicting findings

from those of other studies which utilized the full range of abilities in this population.

Analysis of the ABC scores of the Vineland revealed that, overall, the mean of parent rating scores of this measure for control participants fell in the average range of functioning. However, participants with 18q- in this study were found to have significantly impaired adaptive behavior functioning, with scores falling well below average at both pre and post treatment. Further, there was not evidence of improvement in overall adaptive behavior functioning at post treatment. It is unclear as to which of the four domains of the Vineland may have differentially contributed to the overall comparatively lower adaptive behavior composite scores, although further analyses is possible in the future. According to More et al. (2001), post GH treatment, participants with 18q- exhibited slightly improved motor skills but did not improve in the domains of communication, socialization and daily living skills. Despite the previous findings reported by More et al. (2001), this study nonetheless predicted overall improvement in adaptive behavior in individuals with 18q- due to inclusion of a slightly larger number of GH treated participants. However, the current findings are generally consistent with those reported in the More et al. (2001) study in that, overall, adaptive behavior does not significantly improve post GH treatment. Additionally, it is notable that overall adaptive behavior functioning in participants with 18q- was not commensurate with nonverbal intellectual ability, the latter of which fell in the low average range of functioning. The discrepancy in intellectual ability and adaptive behavior functioning is significant, as adaptive behavior may be a greater indicator of ability to function independently than

cognitive ability alone (Liss et al, 2001). Therefore, adaptive life skills in children with 18q- deserves further consideration, particularly in regard to seeking additional services that would enhance adaptive functioning.

As predicted, based on mean BSI scores, control participants exhibited overall low incidences of behavioral symptoms. Additionally, pre GH treated participants with 18q- differed significantly from controls in regard to overall BSI scores on the BASC, with significantly higher behavioral symptoms reported for participants with 18q-. It is important to note that all groups scored within the average range, and although a significant difference was present, it was not clinically meaningful. Contrary to predictions, the BSI of post GH treated participants with 18q- did not differ significantly from those at pre GH treatment. The BSI of post GH treated participants with 18q- and controls also did not differ significantly, although the BSI of participants with 18q- remained higher than that of controls, thus indicating a slightly higher parental report of behavioral symptoms for children with 18q- than control participants. Therefore, it does not appear that GH improves behavioral functioning in individuals with 18q-. However, the overall mean for the BSI did not significantly increase at post treatment assessment. The stability of BSI scores at post treatment is an important finding, as non-GH treated children with 18q- have been reported to exhibit increased behavioral difficulties with age, particularly when entering adolescence (Semrud-Clikeman et al., 1999). However, it is unclear as to whether non GH treated children with 18q- exhibit a greater degree of behavioral symptoms when compared to GH treated children, and,

ultimately, whether GH treatment helps prevent regression of behavior in this population.

MRI Analyses

Overview

In the second part of the study, participant MRI scans were evaluated through analysis of midsagittal corpus callosum area and cerebral hemisphere volume. The lateral ventricles were also measured separately to determine if lateral ventricle size affected total cerebral volume in participants with 18q- and controls. Given that individuals with 18q- have been identified with neurological abnormalities, particularly in regard to global dysmyelination (Gay et al., 1997), this study attempted to 1) establish that overall cerebral volume and midsagittal corpus callosum area differed significantly in pre GH treated participants with 18q- from normal control participants, 2) following GH treatment, participants with 18q- would exhibit significant growth in the aforementioned brain regions, to the extent that there would not be significant differences in brain regions when compared to normally developing children, and 3) predicted growth in measured brain regions would be related to predicted improvements in performance on psychological measures.

Analysis of Corpus Callosum

In the first part of the MRI analysis, the midsagittal corpus callosum area of pre GH treated 18q- and control participants were measured and compared. As predicted, participants with 18q- were found to have significantly smaller midsagittal corpus callosum area. This finding was consistent with the Kochunov et

al. (2005) study that reported significantly smaller overall corpus callosum volume in participants with 18q- when compared to controls. Additionally, given that the corpus callosum is comprised of myelinated fibers, smaller corpus callosum area found in participants with 18q- further support previous documentation that global dysmyelination is pervasive in individuals with 18q-. At post treatment, participants with 18q- exhibited an overall modest, albeit significant, increase in midsagittal corpus callosum area, although the overall corpus callosum area remained smaller in post GH treated participants when compared to controls. There were also significant gender effects in regard to post GH treated participants and controls, as male participants with 18q- were found to have significantly smaller corpus callosum area than male control participants. Overall, results suggest that there were modest increases in myelination following GH treatment, which is consistent with previously reported findings by Hardies et al. (2000). However, without retest MRI data for controls, as well as the absence of a non-GH treated group of participants with 18q-, it is unclear if GH treatment resulted in increased corpus callosum growth in children with 18q- that follows a normal course of development.

Analysis of Cerebral Volume

It was predicted that pre GH treated participants with 18q- would have significantly smaller cerebral volume measurements when compared to control participants. Contrary to predicted differences, participants with 18q- and controls were found to not significantly differ in regard to total cerebral volume, regardless of age or gender. This finding was also consistent for comparisons of mean measurements of individual right and left cerebral hemisphere volumes for both pre

and post GH treated participants with 18q- and controls. The failure to detect significant differences in total cerebral volume was surprising given that there is a high incidence of microcephaly occurring in children with 18q- (Cody et al., 1999a), a condition that is typically associated with reduced brain volume (Miles et al., 2000). However, it is likely that the sample obtained for this study did not include the full range of ability as was included in other studies. The relationship between microcephaly and mental retardation is well established and by not including children with more severe cognitive impairment in this study, the findings may reflect this omission rather than being in conflict with previous findings.

Additionally, in post GH treated participants, there was also not a significant increase in cerebral volume. This finding is in contrast to evidence in this study that participants with 18q- had a significant increase in head circumference growth from pre to post treatment, which would be expected given age-related growth patterns (i.e., increased head growth with age). Also, males were found to have larger head circumference than females, which is consistent with prior research (Nagy, 2001). It is unclear as to the reason head circumference and total cerebral volume were not strongly correlated in this study, as this finding is contrary to other studies examining this relationship (Miles et al., 2000). Nevertheless, participants with larger cerebral volume at pre-treatment were found to have significantly larger head circumference at post-treatment, regardless of lateral ventricle size. These findings suggest that children with larger cerebral volume demonstrate greater head growth at post treatment that those with smaller cerebral volume at pre-treatment, perhaps due to having a more "normal" developmental trajectory than those who had

comparatively smaller cerebral volumes at pre-treatment. As the presentation and severity of symptoms vary considerably in children with 18q-, differences in cerebral volume at pre-treatment may be related to size and site of missing genetic material from the 18th chromosome, although this issue remains to be explored.

Analysis of Cerebral Asymmetry

Analysis of pre GH treated 18q- participant and control cerebral asymmetry also resulted in findings contrary to predictions. Control participants were predicted to have greater right than left (R > L) cerebral hemisphere volume, as such patterns have been reported in normally developing individuals (Kolb & Wishaw, 1996). Contrary to predicted R > L asymmetry, controls were found to have symmetric cerebral hemispheres. It is unclear as to why controls were not found to have predicted R > L cerebral asymmetry, although the low sample size may have contributed to the lack of the predicted results.

Additionally, pre-GH treated participants with 18q- were predicted to have symmetrical cerebral hemispheres (i.e., predicted not to have R > L asymmetry). The rationale for this hypothesis was predicated on the assumption, that since individuals with 18q- exhibit global dysmyelination (Gay 1997; Kochunov et al., 2005), normal developmental patterns of greater right hemispheric volume and distribution of white matter would not be found. However, contrary to predictions, participants with 18q- exhibited greater left than right hemispheric asymmetry (L > R) and additionally, pre-GH treated participants with 18q- were found to have significantly larger left hemisphere volume when compared to right hemisphere volume. At pre-GH treatment, females were found to have more pronounced L > R

cerebral asymmetry than at post treatment, although this pattern was not observed in male participants. Overall, participants with 18q- continued to exhibit L > R cerebral asymmetry at post treatment, although the right and left cerebral hemispheres were found to not differ significantly post GH treatment. This finding indicates a trend towards lateralized growth in the right hemisphere after treatment. Such an increase in right hemisphere volume may be attributable to increased white matter growth in this region, although further study is needed to definitively determine gray/white matter differences before and after GH treatment. The current study was unable to provide these measures due to limits of the software utilized by the Research Imaging Center at the University of Texas Health Sciences at San Antonio.

Implications of Reversed Asymmetry

The development of neurophysiological pathways related to the reversal in "normal" cerebral asymmetry is subject to speculation. However, it is possible that larger left than right hemisphere volume exhibited in individuals with 18q- may be related to disruption of the normal neurodevelopmental trajectory for the hemispheres associated with global dysmyelination. Further, the development of abnormal hemispheric asymmetry may be associated with disproportionately smaller corpus callosum, presumably due to axonal disconnection (Herbert et al., 2005; Suh et al., 1997). It is unclear at this time to what degree anomalous anatomic lateralization impacts functional lateralization (i.e., language development) in children with 18q-. However, it is likely that pervasive delays in speech and language development, in addition to general cognitive impairment in children with

18q-, is related to abnormal distribution of myelination throughout the cerebral hemispheres, although this relationship remains to be explored.

While reversed cerebral asymmetry has been reported in individuals with genetic disorders such as Klinefelter's syndrome (Warwick et al., 2003), autism, language disorders, (Herbert et al., 2005), and schizophrenia (Crow et al., 1990), it is unclear whether such disorders are primarily associated with disruption of white matter growth. However, Herbert et al. (2005) provided an explanation regarding the genesis of abnormalities in white matter specific to autism and developmental language disorders that may also serve as a theoretical basis for a similar pathogenesis of neurological abnormalities found in individuals with 18q-. Specifically, they suggest that altered cortical asymmetries emerge as a response or adaptation to an underlying abnormal brain and white matter growth trajectory. Further, the authors propose that abnormal white matter development and resulting reversals in asymmetry result in suboptimal connectivity, and hence, aberrant lateralization and degradation of functioning in cortical networks. For example, abnormal anatomical asymmetry has been associated with impaired cognitive functioning, such as been found in language-based disorders, motor difficulties, and difficulties in processing of faces (Herbert et al., 2005). Therefore, there may be a similar relationship between neuroanatomic anomalies and specific areas of cognitive and behavioral dysfunction in individuals with 18q-.

Analysis of Lateral Ventricle Volume

An interesting and unpredicted finding from this study pertained to enlarged lateral ventricle volume found in participants with 18q-, as this is an area that has

previously been unexplored in this population. At pre-GH treatment, participants with 18q- exhibited larger right and left lateral ventricles when compared to controls, although these differences were not statistically significant. Comparison of lateral ventricle volume in pre and post-treated participants with 18q- revealed that the right lateral ventricles were larger than the left lateral ventricles in male participants with 18q-. Overall, at post treatment, participants with 18q- had larger right lateral ventricle volume when compared to controls, although there were not significant gender differences found in this comparison.

Notably, the lateral ventricles were found to be negatively correlated with right and left cerebral volume and corpus callosum area in both pre and post treated participants with 18q-, but not in controls. The causal mechanisms behind these relationships is subject to speculation. Although cerebral volume did not significantly differ in participants with 18q- than controls, overall cerebral volume was nonetheless smaller in participants with 18q- at both pre and post treatment. Given the existence of enlarged lateral ventricles in participants with 18q-, it is possible that ventricular volume may be impacting cerebral volume. Specifically, it appears that significantly larger right lateral ventricles may be impacting the volume of the right cerebral hemisphere volume in participants with 18q-, and related to the reversed L > R cerebral asymmetry found in these individuals. Further, it is unclear whether the corpus callosum is being impinged upon by increased CSF volume in lateral ventricle space. However, it is likely that in the absence of increased intracranial pressure in individuals with 18q-, widening of the lateral ventricles may be attributed to abnormal genesis of the corpus callosum, as has been in this

population (Kochunov et al., 2005; Ono et al., 1994). Similar relationships between small corpus callosum and enlarged lateral ventricles have been reported in other disorders that involve abnormalities of the corpus callosum, such as Nijmegen breakage syndrome (NBS) (Bekiesinska-Figatowska et al., 2004). Thus, in individuals with 18q-, decreased size of the corpus callosum may account for widening of the lateral ventricles.

Notably, at post GH treatment, while lateral ventricle volume continued to be negatively correlated with corpus callosum area and cerebral volume, such correlations were smaller than at pre GH treatment measurements. Such a reduction in correlation strength may be indicative of slight, albeit notable, brain growth in GH treated participants with 18q- in regard to the impact of ventricular volume on corpus callosum area and cerebral volume.

Summary

Overall, results of this study generally support the hypotheses that children with 18q- score lower across composite measures of cognitive, adaptive behavior, and behavioral functioning when compared to normally developing children. Although the results of this study failed to support predictions that GH treatment would improve psychological functioning in children with 18q-, it is notable that performance across cognitive, adaptive behavior, and behavioral measures did not *decrease* at post treatment assessment. Additionally, there are several important neuroanatomical findings from this study that may help to contribute towards an understanding of the neuropsychological underpinnings associated with 18q-. First, given that individuals with 18q- are reported to have global dysmyelination, it

appears that such widespread abnormalities in white matter is related to reversed cerebral asymmetry, and hence, probable deficits in interhemispheric connectivity. Further, in individuals with 18q-, it appears that lateral ventricle volume is negatively correlated with corpus callosum size, as well as cerebral volume, at both pre and post GH treatment. Such a relationship in brain regions was not found for control participants. Therefore, it is likely that such neuroanatomical dynamics impact psychological functioning in these individuals, resulting in decreased cognitive and behavioral functioning. Although indicators of brain growth were generally modest, it appears that GH treatment does significantly impact head circumference and midsagittal corpus callosum area. Additionally, although predicted normal patterns of cerebral asymmetry were not observed in post GH treated participants, it appears that there is a trend towards greater right hemispheric growth, particularly in female participants.

Limitations

There were several methodological issues that arose that warrant discussion regarding their impact on this study. First, due to the rare occurrence of 18q- in the general population, one of the primary limitations to this study is the relatively small number of participants available for analyses. A further limitation to the study is the lack of random assignment of participants to treatment versus control groups. This study also lacked a placebo control group as it was deemed unethical to withhold the treatment that could significantly improve the quality of life for the participants and their families. Additionally, the original intent of this study was to compare GH treated participants with 18q- with non GH treated participants to determine whether

performance on psychological measures and brain measurements in treated participants with 18q- differed significantly from each other. However, there was not a sufficient number of non- GH treated participants with 18q- who had viable MRI scans available for comparison to GH treated participants (i.e., N = 3). Another limitation was the lack of pre/post testing of control participants, which would have yielded information regarding normally developing children for comparison to the participants with 18q-. Also, the time between pre and post GH treatment was not consistent throughout the study due to difficulty in obtaining viable MRI scans, as this may have affected the outcome of the results due to developmental differences. Finally, although it was not addressed in the analyses, many of the participants with 18q- were reported to participate in extracurricular activities (i.e., sports, clubs, etc.) and were receiving rehabilitative services (i.e., occupational therapy, physical therapy, speech therapy), which could have impacted the cognitive, adaptive, and behavioral functioning of participants.

While the results from this study did not reveal significant improvement in performance on measures of nonverbal intelligence, adaptive behavior ability, and behavioral functioning following GH treatment, there are several factors to consider that possibly contributed to these results. Prior analyses of participants with 18q- that have demonstrated significant improvements in intellectual functioning (Cody et al., 1999b) had a greater age range than utilized for the current study. Inclusion of a broader age range allowed for larger sample sizes, and thus, sufficient power for detecting significant change across psychological domains. Additionally, the current study's sample size was greatly reduced due to the small number of participants

with 18q- who had data available for both psychological domain scores and MRI scans. Several participants were excluded from this study as they did not have viable MRI scans (e.g., due to factors such as pronounced movement artifacts).

Since this study is longitudinal in nature, the failure to detect improvements in cognitive, adaptive, and behavior scores may not have fully reflected participant cognitive and behavioral functioning at post treatment. Specifically, their scores at post treatment may have reflected a plateauing of abilities or a slower rate of skill acquisition, especially given that their scores were compared to performance levels attained by normally developing, same aged peers. It is also important to note that despite a failure to detect improvement across the psychological domains in this study, overall mean scores for pre and post GH treated participants were generally commensurate. Therefore, although this study did not demonstrate predicted improvements in psychological functioning post GH treatment, it is possible that GH treatment may prevent regression of cognitive and adaptive behavior skills, as well as behavioral functioning, that can be associated with other genetic disorders, such as Down's syndrome (Wishart, 1993) and Fragile X (Fisch et al, 2002).

Future Directions

Given that this study revealed multiple neuroanatomical anomalies associated with individuals with 18q-, there are several areas that should be further explored. First, since this study revealed an increase in corpus callosum area in post GH treated participants with 18q-, additional analyses examining regional differences in the corpus callosum in individuals with 18q- (as described in Kochunov et al., 2005), comparing the corpus callosum at pre and post GH

treatment would lend insight into whether GH treatment is increasing size in specific callosal regions that have been reported to be smaller in individuals with 18q-, such as the splenium. Although it was not a primary area of exploration for this study, the existence of lateral ventricle enlargement in individuals with 18q- was unexpected. This finding would be an area of interest for further exploration to determine whether site and size of deletions on the 18th chromosome are associated specifically with ventricular enlargement. Additionally, given the equivocal findings from this study regarding cerebral volume measurements, future studies that provide automated calculation of gray and white matter may yield more accurate determination of myelination at pre and post GH treatment in individuals with 18q-.

It is possible that there might have been differences in response to the growth hormone treatment depending on the child's age. The average age at pre GH treatment in this study was 6.1 years of age. While children under the age of 10 years have been reported to respond optimally to growth hormone treatment (Strobl & Thomas, 1994), it is possible that, for individuals with 18q-, earlier intervention may result in greater impact both brain development and cognitive and behavioral functioning. The age at first administration of GH may indeed prove to be a crucial factor in the prognosis in children with 18q-, particularly in light of the rapid process of myelination that occurs from birth until two years of age. It may well be that for optimal development of myelination, infants who are identified with 18q- may demonstrate greater improvement in regard to linear growth and cognitive functioning.

Finally, despite the lack of evidence for significant differences in total cerebral volume between 18q- and control participants, the presence of reversed cerebral asymmetry, enlarged lateral ventricles, and smaller corpus callosum area in participants with 18q- suggest that there is significant and pervasive neural system disruption in these individuals that is likely associated with global dysmyelination. Overall, in light of the neuroanatomical abnormalities found in this study, it likely that such neurophysiological correlates have various functional implications, in addition to those found in the comparatively lower scores for children with 18q- on psychological measures. Therefore, future research that expands knowledge regarding the relationship of neurological underpinnings with psychological functioning in individuals with 18q- will hopefully help inform medical professionals, parents, and educators regarding the unique needs for children with this disorder.

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VITA

Andrea Lynn Hester was born in Ft. Riley, Kansas on March 26, 1971. Being born into a military family, she later moved to Okinawa and Ft. Campbell, Kentucky. In 1979, her parents returned to their hometown of Austin, Texas, where Andrea was raised. She received her Bachelor of Arts degree in Psychology at the University of Texas in August of 1995. Andrea later returned to the University of Texas to attend graduate school, where she received her Master of Arts degree in Educational Psychology in August of 2002 while pursuing her doctoral degree in School Psychology. Following completion of her doctorate, Andrea will begin a postdoctoral residency in neuropsychology at the University of Texas Southwestern Medical Center in Dallas, Texas.

Permanent address: 4709 Clawson Rd., Austin, TX 78745

This dissertation was typed by the author.