EXECUTIVE AND BEHAVIOURAL FUNCTIONING IN GIRLS WITH TURNER'S SYNDROME

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ABSTRACT

Turner's syndrome (TS) is a genetic disorder that arises from the complete or partial absence of the second sex chromosome. The TS behavioural phenotype has been characterised by a specific neuropsychological profile of normal verbal skills, impaired visuo-spatial and/or visuo-perceptual abilities and difficulty with motor function. Recently there have been reports of deficits in executive functions. The current study investigated the role of executive and behavioural functioning in TS females aged 6-16 years. The performance of 41 individuals with TS was compared with normative data on IQ, visuo-spatial, executive and behavioural measures. Further, a subsample of 15 TS individuals was compared on a selection of neuropsychological measures with 15 female sibling controls. As anticipated, TS females had significantly lower non-verbal than verbal intellectual abilities, with poorer performances on the measures of Full Scale IQ, Performance IQ and Perceptual Organisation. Verbal IQ did not differ from normal in the larger TS sample, however it was significantly lower than sibling controls. Arithmetic ability was significantly reduced. Performances on visuo-spatial and executive measures (Block Span, Rey-Osterrieth Complex Figure and Tower of London) were significantly below those measured by Australian normative data. TS individuals performed more poorly on the Animal Size, but not the Animal Automatic or Animal Alphabet conditions of the Controlled Animal Fluency Test, a newer test of executive functioning. No effect was found on the Controlled Oral Word Association Test or the Behavioural Dyscontrol Scale-2. Performances on the Wisconsin Card Sorting Test were within the normal range compared to normative data alone, but significantly poorer than controls. Results on the Behavioural Assessment System for Children (BASC) revealed areas of vulnerability for TS females on scales of adaptive skills, attention, atypicality, behaviour problems, hyperactivity, interpersonal relations, leadership skills and self-esteem. Analyses conducted on the basis of the parental origin of the X chromosome (maternal: X^m, paternal X^p) revealed no significant relationship between chromosomal origin and cognitive performance. No differences were found between X^m and X^p on measures of socio-emotional or behavioural functioning. No karyotypic differences were found between X-monosomy and non-

45,X monosomy individuals on all measures. These results suggest that the specific cognitive difficulties experienced by TS females are due to deficits in visuo-spatial working memory and executive functioning arguably mediated by the prefrontal cortex.

STATEMENT OF AUTHORSHIP

Except where reference is made in the text of this thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis presented by me for another degree or diploma. No other person's work has been used without due acknowledgement in the main text of this thesis. This thesis has not been submitted for the award of any other degree or diploma in any other tertiary institution.

Wendy Marian Kelso

Date: 28/02/2005

ETHICS APPROVAL

I, Wendy Kelso, declare that the research reported in this thesis was conducted in accordance with the principles of ethical treatment of human participants, as approved for this research by the School of Psychology, Victoria University, the Royal Children's Hospital (Melbourne) and Monash Medical Centre's Human Research Ethics Committees.

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TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

TABLE OF CONTENTS (CONTINUED)

TABLE OF TABLES

TABLE OF FIGURES

LIST OF APPENDICES

1.1 TURNER'S SYNDROME

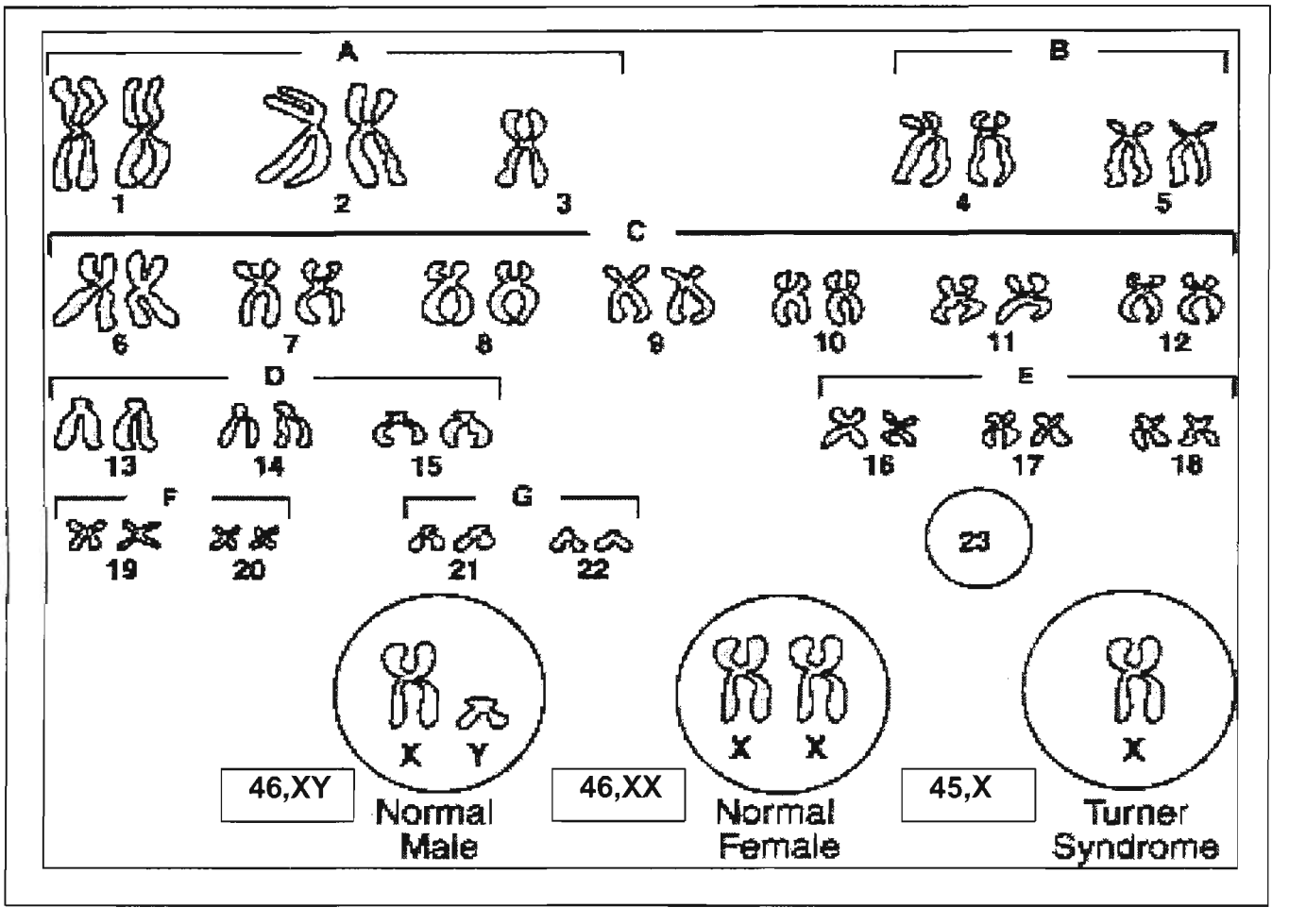
Turner's syndrome (TS) is a genetic disorder occurring in approximately 1 in every 2000-5000 live female births (Maeda, Ohno & Matsunobu, 1991; Nielsen & Wohlert, 1991). TS results from the absence or inactivity of all or part of an X chromosome (See Figure 1). The second X chromosome expected in a female is either missing or structurally abnormal, and as a result, the affected female may have a number of physical and psychological characteristics not typical of females. The karyotype of X-monosomy is termed, '45,X' meaning that an individual has 44 autosomes and a single X-chromosome. Monosomy X may be present in as many as 2% of all conceptions, but fewer than 1% of all 45,X embryos survive to term. (Hassold, 1986; Hook & Warburton, 1983). TS can result from the meiotic nondisjunction during either spermatogenesis or oogenesis, or from an error in mitosis after conception (Ross, 1990). In approximately three quarters of the TS population the single X chromosome is maternal in origin, therefore the meiotic error is usually paternal (Jacobs et al., 1997; Thompson, McInnes & Willard, 1991). TS is not associated with increased maternal or paternal age or birth order (Mathur et al. 1991).

Physical characteristics in TS include short stature, ovarian dysgenesis, lack of pubertal maturation, infertility, webbing of the neck, low posterior hairline, increased carrying angle of the arms, shieldlike chest, triangular facies, renal tract malformations, hypertension, a predisposition to deafness, and cardiac abnormalities (Bender, Linden & Robinson, 1994; Hall & Gilchrist, 1990; Rosenfeld et al., 1994; White, 1994). (See Table 1 for a comprehensive list of clinical characteristics.)

There is a wide variation between individuals in the number and severity of these features. More than 99% of girls with 45,X TS and 95% of girls with non-45,X TS have short stature (Park, Bailey & Cowell, 1983). Global studies have reported the mean adult height to range from 142-148.3cm. The average difference between adult height of women with TS and that of unaffected women is 20cm (Dean, 1991; Plotnick, Attie, Blethen & Sy, 1998; Ranke & Grauer, 1994; Ranke, Pfluger & Rosendahl, 1983). The most important variable affecting adult height is the mid-parental height (Dean, 1991). TS females are increasingly being offered growth hormone therapy aimed at increasing stature.

FIGURE 1.

CHROMOSOMES IN TS



Note: From Human Genetics Webpage, Estrella Mountain Community College, Avondale, Phoenix, USA
*Website:*http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBookhumgen.html

TABLE 1.

CLINICAL CHARACTERISTICS IN TS

Type	Characteristics
Classical	Short stature Short webbed neck Broad chest Cubitus Valgus Gonadal dysgenesis
Growth	Decreased mean birth weight Lack of pubertal growth spurt
Skeletal	Scoliosis Madelung wrist deformity Genu valgum Exostosis medial tibial condyle Short metacarpals, metatarsals
Craniofacial	Craniosynostosis Narrow palate Micrognathia Strabismus Malrotation of ears Inner ear defects
Cardiovascular	Aortic coarctation Bicuspid aortic valve Mitral valve prolapse Septal defect Partial anomalous venous return
Renal	Horseshoe or pelvic kidney Unilateral aplasia or hypoplasia Unilateral double ureter
Lymphatic	Intestinal lymphangiectases Congenital lymphedema of hands, feet
Hair and skin	Low posterior hairline Increased pigmented naevi Hypoplastic nails Dermatoglyphic variations

Note: From *Paediatric Neuropsychology. Research, Theory, and Practice* (p.253) by K.O. Yeates, M.D. Ris, and H.G. Taylor (eds.), 2000, New York, The Guilford Press.

Gonadal failure occurs in more than 90% of the TS population, and greater than 99% are infertile (Plotnick et al., 1998). The ovaries in girls with TS are thought to form normally initially, but involute prematurely at 4-5 months gestation (Held et al., 1992). As a result of this gonadal dysgenesis, the children lack ovarian oestrogen production and therefore do not usually undergo spontaneous pubertal maturation (Hassold, 1986). Androgen production is also reduced (Gravholt, Svenstrup, Bennett & Christiansen, 1999). Approximately 10% - 20% of girls with TS develop breasts spontaneously, and a small minority (2%-5%) will have spontaneous menses (Lippe, Westra & Boechat, 1993; Pasquino, Passeri, Pucarelli, Segni & Municchi, 1997; Ranke et al., 1983). Secondary sex characteristics are sometimes achieved and maintained through supplemental oestrogen therapy.

Females with TS commonly have craniofacial and oral abnormalities that can interfere with speech production (Midtbo, Wisth & Halse, 1996). These include a short mandible, retrognathic jaws and an increased prevalence of malocclusions. More than one third of TS females have a high arched palate and/or a narrow palate. In addition, pre-speech oral motor skills such as sucking, munching, and swallowing have been reported to be poorly developed in infants with TS (Mathisen, Reilly & Skuse, 1992). Speech and language disorders are common, with a significant proportion of TS females receiving treatment for stuttering, articulation difficulties and/or delayed language development (Van Borsel, Dhooge, Verhoye, Derde & Curfs, 1999).

There is also a predisposition to middle ear infections in children with TS due to an abnormality of the Eustachian tube (Sculerati, Ledesma-Medina, Finegold & Stool, 1990). Mild to moderate hearing loss is very common in both children and adults with TS and is usually sensorineural in type (Gungor, Boke, Belgin & Tuncbilek, 2000; Hultcrantz, 2003; Roush, Davenport & Carlson-Smith, 2000).

1.2 CHROMOSOMAL ABNORMALITIES

Approximately 50% of all affected females have a classic monosomic TS karyotype in which there is only a single X chromosome (45,X or 45,XO) (Hall, Sybert, Williamson, Fisher & Reed, 1982; Hook & Warburton, 1983; Jacobs et al. 1997). The 45,X karyotype occurs when a single X chromosome is lost during meiosis. As the 45,X karyotype has been detected in as many as 1 in 15 spontaneous abortions (Hall & Gilchrist, 1990), this genotype is thought to be potentially lethal, with only a minority of foetuses surviving to birth (El Abd, Turk & Hill, 1995).

Thirty percent of TS females have a mosaic condition that reflects the presence of two or more cell lines (Held et al., 1992). These individuals have a mixture of cell lines, some which are 45,X (45 chromosomes per cell, with only 1 sex chromosome) and others that are either 46,XX, 46,XY or aberrant sex chromosomes complements (Fernandez, Mendez & Pasaro, 1996; Hook & Warburton, 1983). The most common mosaic condition is a 45,X/46,XX karyotype where the female has a combination of both 45,X cells and normal cells with the full chromosomal complement. Held et al. (1992) hypothesised that mosaicism in TS, which can arise post-zygotically is a prerequisite for foetal survival in early pregnancy.

The remaining TS individuals have a variety of chromosomal abnormalities that differ as to the portion of the second chromosome (typically an X but occasionally a Y) that is missing. These karyotypes include: a deletion of the short arm (Xp) or long arm (Xq); a rearrangement or translocation of part of a chromosome to or from the X; a ring chromosome; and an isochromosome, in which the chromosome consists of two long arms and is missing the short arm. (See Table 2 for karyotype descriptions and frequencies and Figure 2 for X-chromosome types).

TABLE 2.

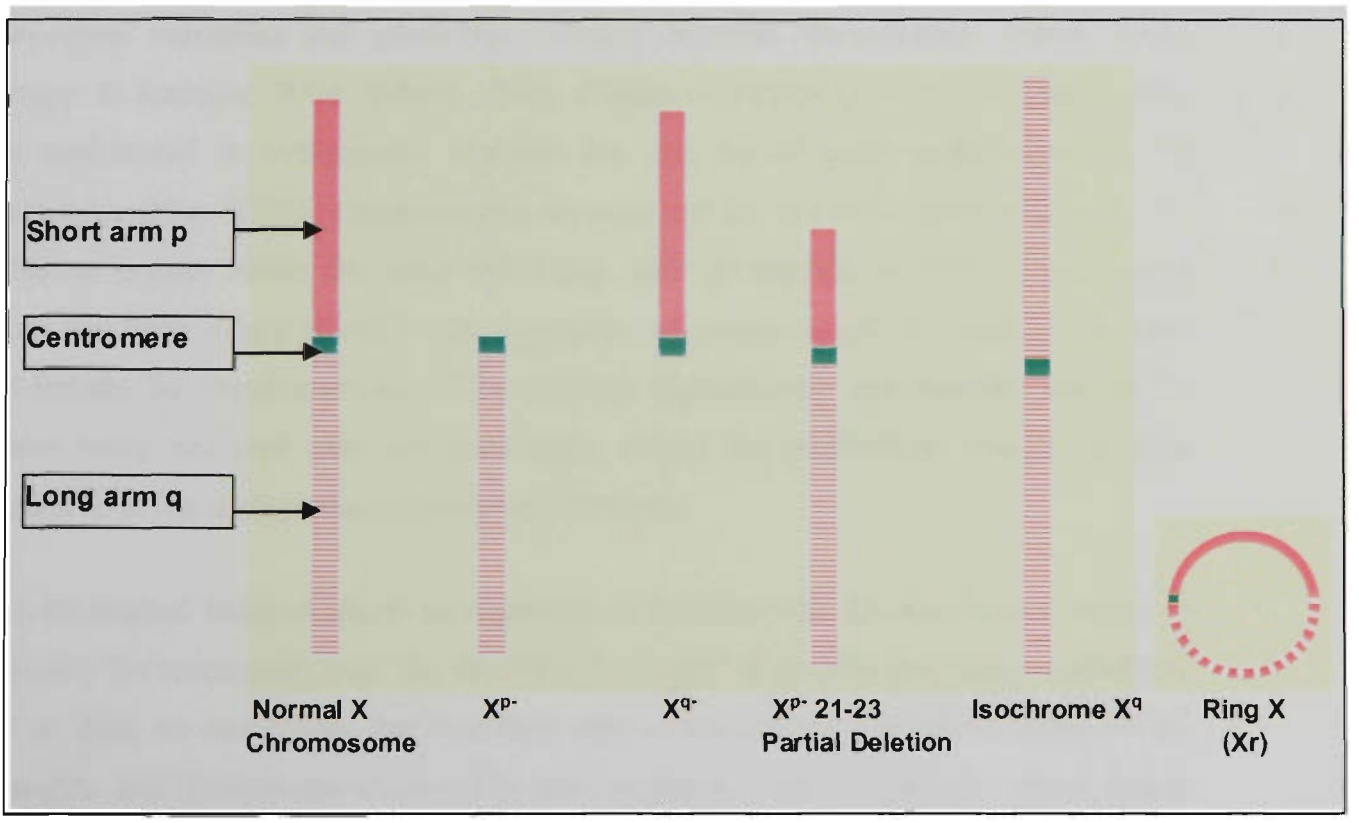
CHARACTERISATION OF TURNER'S SYNDROME ETIOLOGIES

	Karyotype	*Frequency*	*Description*
Monosomy X	45,X	45-50%	Two-thirds maternally derived; occurs during meiosis
Mosaicism	45,X/46,XX or 45,X/46,XY	30%	Occurs early in mitotic cell division; almost all are female
Isochromosome	46,isoX^{p} or 46,isoX^{q}	10%	Occurs during anaphase when chromosome strand divides in transverse direction, not axially
Deletions, rearrangements, and translocations		10%	Abnormality during meiotic division
Ring X		2-5%	Loss of centromere causing ring to form

Note: From "Turner syndrome: Genetic and hormonal factors contributing to a specific learning disability profile," by J. Rovet, 2004, *Learning Disabilities Research and Practice, 19*, p. 134.

FIGURE 2.

X-CHROMOSOME TYPES



Note: From Diagram C: X-Chromosomes, Turner Unit, National Institute of Child Health and Human Development, National Institutes of Health. Website: http://turners.nichd.nih.gov/GenFrDiagC.html

1.3 GENETIC FACTORS IN PHYSICAL AND COGNITIVE DEVELOPMENT IN TS

Research has correlated specific genotypes (genetic profiles) with specific phenotypes (physical manifestations) amongst individuals with TS (El Abd, Turk & Hill, 1995; Rosenfeld & Grumbach, 1990). Both a ring X chromosome and an X-autosomal translocation are associated with the most severe consequences of TS, including developmental delay, increased risk of learning difficulties and social, behavioural and communicational deficits (El Abd, Patton, Turk, Hoey & Howlin, 1999; Kuntsi, Skuse, Elgar, Morris & Turner, 2000). The next most severe condition is monosomy X. Mosaicism involving a normal 46,XX cell line has often been reported to have the least severe phenotype, with many of these females performing within normal limits on neuropsychological tests (O'Neill, Ghelani, Rovet and Chitayat, 2000).

Although some studies have suggested that TS females with mosaicism may not be as severely affected as non-mosaic 45,X individuals, others have argued that for a variety of reasons, it is particularly difficult to assess relationships between specific karyotypic variations and phenotypic clinical features (Haverkamp, Zerres, Rietz, Noeker & Ruenger, 2004; Sybert, 1990). Clones of variant cells in TS females often are undetected in cytogenetic analysis but can be of great significance to the phenotype (Hsu, 1994). Chromosomal mosaics can be unevenly distributed between different organs within the same individual, and the analysis of blood lymphocytes alone has been shown to fail to detect mosaicism present in other tissues of the same TS female. So, the proportions of the different chromosome complements seen in the tissue being analysed may not necessarily reflect the proportions present in other tissues or in the embryo during early development.

The etiological basis of impaired cognition in females with TS has been a source of curiosity for researchers over the decades. A number of theories have been postulated, but to date, no one theory that has been able to explain the variety of characteristic strengths and weaknesses observed in this condition. Altered cognitive development could be due to genetic, endocrine or environmental factors, either alone or in combination (Ross & Zinn, 1999). The possible genetic bases for the neurocognitive deficits in TS will now be discussed.

1.3.1 Haploinsufficiency Hypothesis

In normal females, the second X chromosome is inactivated very early in embryonic development. This inactivation is random: in some cells the X inherited from the mother is inactivated, in others, the X inherited from the father. The Y chromosome has fewer functions other than primary sex determination, so if X inactivation did not occur, then normal males would have only half as much gene product as females. X inactivation ensures equal dosage of gene product for both sexes. Thus normal females, normal males, and females with TS all have only one activated X-chromosome (Zinn & Ross, 1998). It is therefore intriguing why TS females differ from those with two sex chromosomes. The common explanation is the haploinsufficiency hypothesis, which attributes the phenotype of TS to insufficient dosage of gene product. This explanation implicates genes on the X chromosome which are exceptions to the general rule of X-inactivation (Zinn & Ross).

Molecular studies have confirmed that there is a region of the X chromosome (the pseudoautosomal region) that escapes activation, so genes from both X chromosomes are active in normal females. In this region, there is evidence that males have functionally equivalent genes on the Y chromosome, so both males and females have a double dose of gene product. More recently, other areas of the X chromosome which escape inactivation have been discovered (Brown, Carrel & Willard, 1997).

According to the haploinsufficiency hypothesis, the phenotypic abnormalities in TS, including the cognitive profile, can be explained in terms of a deficiency in gene products from a region of the X-chromosome which escapes inactivation (Bishop et al. 2000). In females who have only one gene copy, there would be a reduced gene dosage leading to reduced production of certain critical proteins required for growth and/or neural development. Adverse effects could be direct effects of genes on brain development, or more indirect consequences of the hormonal deficiencies which result from the genetic deficit (Zinn & Ross, 1998).

Evidence of pseudoautosomes have been found in several loci on the short arm of the X chromosome (Xp) in the region Xp11.2 to Xp22.1. Zinn and Ross (1998) found that individuals missing this region had high arched palates and ovarian dysgenesis,

whereas those who were not missing this region did not show these characteristics. Short stature was localised to a more discrete region midway between Xp11.2 to Xp22.1. Ross, Roeltgen, Kushner, Wei and Zinn (2000) compared visuo-spatial abilities in children and adults with partial Xp monosomy. All individuals with poor visuo-spatial ability were missing the part of the chromosome within the pseudoautosomal dominant region (Xp22.3) known to escape X inactivation. They concluded that both copies of genes in this region must be present to express the trait properly.

Skuse, Good, Elgar, Thomas and Morris (2001) reported that a region at Xp11.3 was associated with social adjustment difficulties in TS. Individuals who did not have this area of the X chromosome had difficulties processing fear emotions in faces, demonstrated poor social adjustment and had limbic system abnormalities on neuroimaging (Good et al., 2001).

The SHOX or short homeobox gene was one of the first genes to be identified in TS (Rao et al., 1997). This gene is located at Xp22 or Yp11.3 and is important for growth. If it is abnormal or missing, growth failure results causing idiopathic short stature. Within the TS population, SHOX genes are also associated with skeletal abnormalities (Clement-Jones et al., 2000). As yet, SHOX genes have not been linked to neuropsychological deficits in TS.

In summary, a number of areas on the X chromosome have been linked with a variety of physical, cognitive and psychosocial phenotypes witnessed in TS. Genetic research in TS is flourishing, however researchers are yet to determine which exact gene/s cause the cognitive deficits in TS, and how exactly this occurs (Rovet, 2004).

1.3.2 Genomic Imprinting

Recently, it has been suggested that a phenomenon known as 'genomic imprinting' might be responsible in determining the phenotype associated with TS (Bishop et al., 2000). Genomic imprinting is another mechanism whereby one member of a pair of alleles is inactivated, but in this case, the inactivation is not random, but is determined by the parental origin of the chromosome (Bishop et al.). The phenomenon of imprinting is a relatively new discovery, which has been investigated, both experimentally and clinically, with a focus mainly on autosomal rather than sex chromosomes (Keverne, 1997). Imprinted X-linked genes have recently been identified in humans (Naumova, Leppert, Barker, Morgan & Sapienza, 1998) as well as autosomal imprinted genes that are expressed in the brain (Keverne). Bishop et al. argue that if humans had imprinted genes affecting neurodevelopment on the X chromosome, then one would expect neurocognitive differences between females with a single X-chromosome (monosomy X) depending on the parental origin of the X chromosome. For example, if there were an X-linked gene that was expressed only when inherited from the father, then females with a single maternal X chromosome would lack the relevant gene product, whereas those with a single paternal X chromosome would show normal gene expression. Thus the imprinted locus would predict differences within TS depending on the parental origin of the X chromosome.

This theory of genomic imprinting was supported by Skuse et al. (1997) when studying social adjustment in TS females. The study consisted of 80 TS females (45,X monosomy) with 55 having a maternally derived X chromosome ($45,X^m$) and the other 25 having a paternally derived X chromosome ($45,X^p$). Members of the X^p group were reported to be significantly better adjusted, with superior verbal and higher order executive function skills. Although TS females generally had a slightly elevated risk of social adjustment, the risk of serious difficulties was substantially greater in those with a maternal X chromosome than in those with a paternal X chromosome.

This finding was controversial and encouraged further studies to test the postulate of imprinted loci on the X chromosome. In response to Skuse's 1997 paper, Henn and Zang (1997) provided an alternative explanation for the findings. As sex chromosome

mosaicism is frequent in TS, they argued that the presence of the residual Y chromosomal sequences in the brain, which is exclusively possible in X^m TS females, might be a realistic alternative to the hypothesis of an imprinted X-linked locus as a reason for the behavioural differences between X^m and X^p TS females. Skuse and Jacobs refuted this suggestion and stated that as it was not yet possible to observe the chromosomal constitution of brain cells, Henn and Zang's hypothesis was untestable.

Ross and Zinn (1999) studied 30 monosomic 45,X individuals to determine whether imprinting affected cognitive abilities. They found no apparent imprinting effects on Verbal or Performance IQ and concluded that the TS neurocognitive phenotype was not the result of a total absence of imprinted gene products. Similarly, Tsezou et al. (1999) found no significant relationship between parental origin of the retained X chromosome and a variety of physical stigmata, including response to growth hormone therapy.

In support of the imprinting hypothesis, Donnelly et al. (2000) reported a case study where an individual had both autistic disorder and monosomy TS with maternal X chromosome origin. Three similar cases were reported by Skuse et al. in 1997. Donnelly concluded that this case provided further support for the hypothesis that the parental X origin influences social cognition. In a similar vein, Lawrence, Kuntsi, Coleman, Campbell and Skuse (2003) investigated facial and emotional recognition skills in 45,X^m TS and normal females. Facial and emotional recognition skills were impaired, but normal configural face processing abilities were apparent. They postulated that these results suggested anomalies in amygdala function in maternal origin X monosomy and speculated whether there might be a role for X-linked genes in amygdala development. However, while the above study did identify facial and emotional recognition deficits in 45,X^m TS, they did not compare these abilities with 45,X^p females. Therefore it is difficult to conclude that the deficits reported were due to imprinting.

Bishop et al. (2000) provided further support for genomic imprinting after contrasting verbal and visuo-spatial memory functioning in females with 45,X^m versus 45,X^p. Immediate story recall was normal in both groups. Interestingly, after adjusting for the level of immediate recall, delayed verbal recall was poorer in 45,X^m when compared with controls. Copy score performances on the Rey-Osterrieth Complex Figure were reduced in both groups, but after adjusting scores for initial copy score and strategy, only 45,X^p females demonstrated disproportionate forgetting on the delayed recall task relative to controls. Their results suggested that 45,X^m had poorer recall for verbal information, while 45,X^p had poorer recall for visuo-spatial information (when compared with a normal control group). Bishop et al. proposed that there may be imprinted genes on the X chromosome that affect the development of lateralised brain regions important for memory function.

Kesler et al. (2003) investigated the effects of TS on superior temporal gyrus (STG) volumes by use of MRI. The STG is involved in language processing and was hypothesised to be a biological marker of preserved verbal function in girls with TS. They found that the right STG was significantly larger in a group of 30 TS individuals when compared with age-matched controls. This involved both white and grey matter and was irrespective of IQ. The TS subgroup with a maternally derived X chromosome demonstrated more aberrant STG volumes when compared with those with paternally derived X and controls. The difference in STG volumes between X^m and control subjects involved both white and grey matter, while the X^m individuals differed from X^p individuals only in grey matter. The authors interpreted these findings as preliminary evidence for an X-linked imprinting effect on STG morphology.

In summary, genomic imprinting research in TS is at an early stage, and further investigations are necessary to assess the relationships and relative contributions of maternal versus paternal X chromosome inheritance on the physical and cognitive phenotypes. Thus far, results have been inconclusive, with mixed support for the imprinting hypothesis.

1.4 COGNITIVE FUNCTIONING

1.4.1 The Cognitive Profile of TS

It has been recognised for over 30 years that TS is often associated with neuropsychological impairment (Polani, 1961; Waber, 1979). The neuropsychological profile of TS has been reported with reasonable consistency, however there is wide variation in the level of functional severity witnessed in individuals (Bender, Linden & Robinson, 1994; Berch & Bender, 2000). Past literature has reported particular deficits in the areas of visual, spatial and perceptual processing in the context of intact verbal processing. A Verbal/Performance IQ discrepancy has frequently been reported in this population, with stronger verbal than non-verbal intellectual functioning (Bender, Linden & Robinson, 1993; Lewandowski, Costenbader & Richman, 1985; Reiss et al., 1993; Romans, Stefanatos, Roeltgen, Kushner & Ross, 1998; Ross, Roeltgen & Cutler, 1995; Rovet, 1990; 1993; Rovet, Szekely & Hockenberry, 1994; Shaffer, 1962; Waber, 1979).

While early studies reported that intellectual disability was a clinical feature of TS (Bishop, Lessof & Polani 1960; Haddad & Wilkins 1959; Goldberg, Scully, Soloman & Steinbach 1968; Grumbach, Van Wyck & Wilkins, 1955; Leao, Voorhess, Schlegel & Gardner 1966; Lindsten 1963; Polani 1960; Van Gemund & Van Geldern 1961), it is now thought that this conclusion may have been based on biased sampling. More recent studies have concluded that TS is *not* usually associated with general intellectual disability, with the majority of individuals having Full Scale IQ's in the average to low average range (Garron, 1977; Money and Granoff, 1965; Pennington et al., 1985; Pidcock, 1984). A reduction in Full Scale IQ in TS individuals is often the reflection of a lowered Performance IQ, with normally distributed Verbal IQ (Rovet, 1990). Subtests with scores significantly below those of population norms or controls include Arithmetic, Digit Span, Picture Completion, Coding and Object Assembly (Ross et al., 1995; Silbert, Wolff and Lilienthal, 1977). Block Design is not as consistently affected (Waber, 1979).

Undue focus has been placed on the Verbal-Performance IQ discrepancy with the assumption that Performance IQ best captures the cognitive impairment of TS patients. While IQ scores have traditionally been used as a measure of cognitive

ability, the summated IQ score can mask specific features of an individual's neuropsychological profile, or misrepresent it generally (Lezak, 1988). Reports of reduced Performance IQ in TS do little to further our understanding of the specific neuropsychological deficit responsible for weaker non-verbal processing in the TS population.

Verbal abilities and language skills in TS are generally age appropriate with normal performances on confrontation naming, sentence repetition and oral reading (Murphy et al., 1994; Rovet and Netley, 1982; Temple, 2002). However, children who have a high arched palate or hearing loss may have early speech and language difficulties (Bender, Puck, Salbenblatt and Robinson, 1984). Temple (2002) investigated oral fluency and narrative production in children with TS, and found that while their receptive vocabularies were better than controls, there was a reduction in verbal generativity on tests of oral fluency. As naming skills and vocabularies were age appropriate, Temple attributed the difficulties with oral fluency to abnormal action of executive language retrieval processes. On tests of narrative production, the TS individuals performed normally on picture description, however performed more poorly on executive narrative tasks in terms of narrative length. This impairment on narrative generation tasks was thought to represent a selective impairment within executive retrieval skills and/or episodic memory.

Other cognitive deficits reported in the TS population include impaired left-right orientation (Waber, 1979), visuo-motor construction (Murphy et al., 1994), design copying (Waber), mental rotation (Berch and Kirkendall, 1986), visual perceptual and visual conceptual skills (Alexander and Money, 1966; Temple and Carney, 1995), visual discrimination (Silbert et al., 1977), visual sequencing (Robinson et al, 1986), visual memory (Murphy et al.), drawing, (Silbert et al.), attention, (Ross et al., 1995) spatial reasoning (Money and Alexander, 1966), non-verbal memory (Ross et al.), spatial working memory (Romans et al. 1997) and short-term memory (Berch, 1996). Specific difficulties with arithmetic have also been consistently reported (Alexander & Money, 1966; Bender, Linden & Robinson, 1993; Garron, 1977; Mazzocco, 1998; 2001; Rovet, 1993; Rovet, Szekely & Hockenberry, 1994). Women with TS have also been found to have difficulties in judging mental state and in interpreting 'fear' from displays of the eye region of the face (Lawrence et al., 2003).

Visuo-spatial abilities appear to be lower in TS individuals, regardless of karyotype (Murphy et al., 1994; Ross, Roeltgen & Cutler, 1995). These visuo-spatial difficulties continue from childhood to adolescence and are stable throughout the lifespan (Downey et al., 1991; Murphy et al., 1994; Romans, Stefanatos, Roeltgen, Kushner & Ross, 1998; Ross et al., 1995; Ross et al. 2002). Poor motor skills in TS females have also been thought to affect the results on tests of visuo-spatial and visuo-constructional ability (Ross et al., 1995). Ross et al. compared 56 TS girls with 100 normal age and VIQ matched controls on measures of cognitive ability. In this study, only a few differences were found between TS and controls on perceptual or spatial tasks in which there was *no* motor component (judgement of line orientation and tests of facial recognition). In contrast, for most of the non-verbal tasks requiring motor output, the TS groups performed significantly more poorly than did the normal control groups (Coding sub-test from the WISC-R, Rey-Osterrieth Complex Figure, Money Street Map, and Tests of Visual-Motor Integration).

Further, they confirmed the findings of previous studies in demonstrating that visual and/or spatial memory in TS females was also deficient (Clopper, 1990; Pennington et al., 1985) as measured by the immediate recall of the Rey-Osterrieth Complex Figure. Interestingly, the pattern of performance suggested that the encoding of spatial information was impaired in TS females, but the long-term retrieval ability did not differ from that of control subjects. So, while TS individuals performed more poorly on the immediate recall of the figure, there was little decline from the immediate to the delayed recall conditions. Ross et al. (1995) hypothesised that this impairment in spatial memory encoding in TS may also have a significant motor component.

In examining visuo-spatial deficits from several domains, Ross (1996) reported that TS females had the most difficulty on tasks examining 'how things go together' and spatial location and orientation rather than on tasks of object identity. TS females were reported to be more impaired on the 'where' aspects of visual processing than the 'what'.

Following on from Ross (1996), Buchanan, Pavlovic and Rovet (1998) examined the separate contributions of both visual and verbal working memory to visuo-spatial processing, in order to investigate the exact nature of the processing deficit in TS. They analysed the specific cognitive processes that dissociate the 'what' from 'where'

in the visual system. They conceived that each of the three subsystems of visuo-spatial processing could be a potential site for a specific deficit in TS. These subsystems were characterised as the parvocellular and magnocellular pathways from the retina to the thalamus, followed by the dorsal/ventral (or 'what/where') streams, and the higher cognitive function, working memory. For example, the 'where' pathway is utilised when locating an object in space, while the 'what' pathway is used when determining the identity of an object. Buchanan et al. hypothesised that TS individuals would display deficits in the 'where' (magnocellular) rather than the 'what' (parvocellular) pathway, and they would also be impaired in tasks of visual working memory. The findings of Buchanan et al. indicated global impairment in visuo-spatial processing in TS individuals. However, contrary to expectations, their results indicated that females with TS *did not* show a specific deficit in one of the two pathways that characterise the visuo-spatial system.

Cornoldi, Marconi and Vecchi (2001) further examined the visuo-spatial deficit in TS by administering a comprehensive battery of visuo-spatial working memory tests to four adult TS women. Albeit based on a very small sample, Cornoldi et al. concluded that TS was associated with pervasive visuo-spatial processing deficits, however the pattern of performance did not find clear evidence for a dissociation between visual and spatial processes. The authors stressed the individuality of cognitive performances across tasks.

In summary, the findings of Ross et al. (1995), Ross (1996) and Buchanan et al. (1998) raise the possibility that the core deficiency in the visuo-spatial processing system in TS may in fact be due to deficits in working memory, reflective of higher order cognitive impairment.

1.4.2 Executive Functioning

Although visuo-spatial deficits have been consistently reported in females with TS, little systematic research has been carried out on the exact role of executive functioning in the TS cognitive profile.

The concept of executive function is generally agreed to be an umbrella term, encompassing the skills necessary for purposeful, goal directed activity (Luria, 1966; Shallice, 1982; Spreen, Risser & Edgell, 1995; Stuss & Benson, 1986). Executive functions form a group of mechanisms by which performance is optimised in situations requiring the simultaneous operation of a number of different cognitive processes (Baddeley, 1986). It requires the ability to plan and sequence complex behaviours, attend simultaneously to multiple sources of information, understand complex situations, resist distraction and interference, inhibit inappropriate responses, establish goals, plan, monitor results and utilise feedback and to sustain behaviour for prolonged periods (Denckla, 1996; Stuss, 1992; Stuss & Benson, 1986). Executive functions are conceptualized as a collection of processes that guide, direct, regulate and manage cognitive, emotional and behavioural functions (Gioia, Isquith, Retzlaff & Espy, 2002; Nigg, 2000). These 'higher order' cognitive functions integrate the more basic cognitive processes such as perception, attention and memory.

Baron (2004) defines executive function as:

'The metacognitive capacities that allow an individual to perceive stimuli from his or her environment, respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated or commonsense way, utilising all these capacities to serve a common purposive goal' (p. 135).

Such definitions are commonly operationalised, for the purpose of neuropsychological assessment, to include planning, problem solving, abstract thinking, concept formation, self-monitoring and mental flexibility (Duncan, 1986; Luria, 1973; Neisser, 1967; Pennington & Ozonoff, 1996). Thus 'executive dysfunction' may be reflected in test performances by poor planning and organisation, experiencing difficulties with generating and implementing strategies for problem solving, perseveration, inability to detect and correct errors or utilise feedback, and by rigid or concrete thought processes (Stuss & Benson, 1987; Walsh & Darby, 1999).

Qualitative features of executive dysfunction may include poor self-control, impulsivity, erratic careless responses, poor initiation and inflexibility (Lezak, 1993). It is important to highlight that while the aforementioned behaviours are commonly seen as aberrant in adults, this is not so in the paediatric population. Before deciding

whether such behaviours are reflective of executive dysfunction in children, developmental expectations need to be considered (Anderson, 1998).

Accumulated neuropsychological evidence suggests that these skills may be largely mediated by the prefrontal cortex of the brain and related interacting neural systems (Luria, 1973; Stuss & Alexander, 2000; Stuss & Benson, 1986, 1987). Neuroanatomical evidence supports these links, describing intimate connections between prefrontal and all other cerebral areas (Fuster, 1993; 1999; Mega & Cummings, 2001).

It is thought that the frontal lobes are hierarchically organised, with all areas receiving input from posterior and subcortical regions. The prefrontal cortex, which is thought to be the mediator of executive functions, receives input from all areas of the frontal and posterior neocortex (Barbas, 1992; Fuster, 1993). Thus, sensory and perceptual data are processed by the frontal lobes, where actions are organised and executed. This pattern of connectivity suggests that while prefrontal regions may co-ordinate behaviour, they are also dependent on all other cerebral regions for input.

Disruptions in executive function do not necessarily indicate that solely anterior brain damage has occurred. Prior investigations have questioned the validity of localizing executive function specifically to the frontal lobes, with similar patterns of impairment reported where cerebral pathology was not confined to frontal regions (Albert & Kaplan, 1980; Glosser & Goodlass, 1990). Cases of posterior brain damage have also been reported to affect executive ability; however, this is uncommon (Anderson, Damasio, Jones and Tranel, 1991; Grafman, Jonas and Salazar, 1990). It is now thought that although frontal regions play a vital role in the mediation of executive functioning, the integrity of the entire brain is necessary for efficient executive function (Anderson, 1998; Stuss, 1992; Welsh & Pennington, 1988).

The frontal lobes are relatively immature during childhood, with development thought to be a protracted process which continues into early adulthood (Rabinowicz, 1976; Yakovlev & Lecours, 1967). Parallels between ongoing maturation of the frontal lobes and the emergence of executive capacities have been reported in a number of studies (Bell & Fox, 1992; Levin et al., 1991; Thatcher, 1991, 1992; Welsh & Pennington, 1988). These results suggest that, where developmentally appropriate

assessment tools are employed, evidence of executive skills can be elicited in children as young as the age of 6 years (Anderson, Anderson & Lajoie, 1996; Bruner, 1973; DeLoache & Brown, 1984; Dennis, 1991; Diamond & Goldman-Rakic, 1989; Welsh, Pennington & Groisser, 1991). Clinical research has demonstrated that children have the capacity to perform tasks requiring executive skills successfully (Bruner, 1973). Levin et al. (1991) found that by the age of 10 to 12 years, most children perform at adult levels on tasks requiring executive functioning, including the Wisconsin Card Sorting Test, supporting earlier findings by Chelune and Baer (1986).

It is well documented that assessment of executive functions can be difficult (Anderson, 1998; Stuss & Alexander, 2000). In addition to being accessible only through tests which include lower-order functions, deficits in these skills are often difficult to detect within the clinical context, using standardised assessment tools. Deficits in executive functions can occur despite normal functioning in other domains of cognitive processing, such as those aspects measured by IQ tests. Neuropsychological assessment is often conducted in a controlled and structured clinic setting, where the examiner is responsible for planning and initiating the evaluation. Deficits in executive function are less commonly reflected in test scores, as the majority of assessment tools are also highly structured (Lezak, 1993). This leaves the clinician to rely on qualitative observations and informed judgments, as well as reports from family and social contexts (Parker & Crawford, 1992).

Deficits in executive function tasks have now been documented in a number of different disorders of childhood, including both disorders with and without a known etiology (Pennington & Ozonoff, 1996). Such problems may interfere with the child's capacity to develop normally and interact effectively with the environment, thus leading to ongoing cognitive, academic and social disturbances (Anderson & Moore, 1995; Dennis, 1989). A handful of recent studies has focused on the role of higher order cognitive functioning in the TS profile. These studies will be discussed in detail below.

Temple, Carney and Mullarkey (1996) investigated the role of executive functioning in a group of 16 TS girls between the ages of 8 and 12 years and 18 matched controls. The tests administered included the Stroop, Verbal Fluency, the Self-Ordered Pointing Task, the WCST and the Tower of London. They reported that children with TS were

significantly impaired in comparison to controls, but the effects were task specific. The TS participants were impaired on the Stroop, Verbal Fluency and the abstract Self-Ordered Pointing Task but not on the Tower of London, the WCST or the concrete version of the Self-Ordered Pointing Task. The authors concluded that their results supported the fractionising of executive control processes in development.

Romans, Roeltgen, Kushner and Ross (1997) reported a study of attentional and executive functioning in TS girls between the ages of 7 and 16 years. Measures of attention and executive function were collected from 105 girls with TS and compared with 153 age-matched controls. All ages of TS girls performed significantly less well than did controls on measures of attention (Freedom from Distractibility factor from Wechsler Intelligence Scale Revised and Test of Variables of Attention). However, they only showed task-specific impairment on measurements of executive function. TS females performed at comparable levels on the WCST and semantic clustering, but they exhibited significant deficits on the Rey-Osterrieth organisational component and the Tower of Hanoi. Individuals with TS also displayed increased impulsivity at all ages studied. Their performance on tests of executive function with complex spatial demands showed similar impairment across the age range. Romans et al. concluded that the aspects of executive function that TS girls found most difficult were ones that required integration of visual information, working memory and attention.

Romans et al. (1998) investigated the neurodevelopmental changes that occur in TS women during the transition from adolescence to young adulthood. A comprehensive neuropsychological battery was administered to 99 females with TS and 89 matched controls between the ages of 13 and 21 years. Romans et al. measured executive skills by use of the Controlled Oral Word Fluency Association Test (COWAT), Semantic Fluency, Tower of Hanoi and the WCST. TS participants performed more poorly on the COWAT, Semantic Fluency and the Tower of Hanoi, but they did not display significant differences in performance on the WCST. The Rey-Osterrieth Complex Figure was also administered to examine visuo-spatial and organisation ability and visual memory. TS patients performed more poorly than their peers on both immediate and delayed recall of the figure; however, they demonstrated adequate retention over time of information originally learned. Romans et al. acknowledged that as the TS patients demonstrated reduced executive function, this higher order impairment had the capacity to affect performance on a broad range of tasks. Romans

et al. concluded that the pattern of results described a neurocognitive phenotype comprising impairment in visuo-spatial and attentional abilities and impaired executive function, which was stable from the teenage years into young adulthood.

It can be concluded from the studies outlined above that TS girls demonstrate varying degrees of impairment on tests of executive functioning. Deficits have been found on tests of Verbal Fluency (phonemic and semantic), the Tower of Hanoi, the Tower of London, the Stroop, the Rey-Osterrieth Complex Figure and the Self Ordered Pointing Task. TS females perform at a level comparable to controls on the Wisconsin Card Sorting Test (WCST). While executive deficits have been demonstrated, there is still no consensus as to what is the core deficit for many of the cognitive problems experienced by TS girls. It has been suggested that the role of working memory may be a crucial element in attempts to understand the TS cognitive profile (Berch, 1995; Buchanan et al. 1998; Romans et al., 1997).

1.4.3 Working Memory

Recent studies investigating the role of executive functioning in the TS neurocognitive profile have suggested that the role of working memory deserves further examination (Berch, 1995; Buchanan et al. 1998; Romans et al., 1997). It has been suggested that further investigation using the conceptual frameworks employed in cognitive neuropsychology may assist in understanding the neurocognitive profile in TS (Berch & Bender, 2000; Buchanan et al, 1998; Nijhuis-van der Sanden, 2003; Eling & Otten, 2003). Models of working memory, such as that of Baddeley and Hitch (1974) are thought to be helpful in providing a theoretical approach to the study of neuropsychological deficits in TS.

Working memory refers to memory for, or information processing of, material or events in a temporary mental workspace (Baddeley, 1986). It can be thought of as an online information processing and manipulation system (Mesulam, 2000). Working memory is viewed as a set of cognitive functions that are separate from past experience and accumulated knowledge in long term memory. However, it is a system that can retrieve and manipulate the activated contents of long term memory, allowing those contents to be reinterpreted (Della Sala & Logie, 2002). Working memory is

central to all information processing (Moscovitch, 1992). It keeps active a limited amount of information within a brief timespan and is associated with rapid access and frequent updating. Capacity is limited compared with long-term memory, but dependent on organisation and type of material.

Working memory provides the basis for more complex cognitive functions. Its involvement has been implicated in everyday tasks including mental arithmetic (Hitch, 1980), logical reasoning (Baddeley & Hitch, 1974), vocabulary acquisition (Gathercole & Baddeley, 1989) and sentence processing (Baddeley, Eldridge & Lewis, 1981). Working memory can be put under pressure by adding layers of complexity to a task, such as requiring a longer span. It is also associated with rapid forgetting over short intervals when there is interference, and therefore relies on continuous attention (Morris & Baddeley, 1988).

The traditional view of working memory has been that it depends in part on an older concept, 'short term storage' (Baddeley, 1986). The concept of short-term storage states that there is a part of the mind that is capable of holding a small amount of information for a limited time period. An example of verbal short-term memory would be the ability to hold a new telephone number in mind until the person answers, when the number is then no longer retained. In the case of visual short-term memory, this might involve returning to the correct position on the page after reading has been interrupted (Della Sala & Logie, 2002).

However the concept of working memory differs from short term memory in an important way. Working memory refers to both passive, temporary storage of visual and verbal information and the active mental manipulation of that information (Della Sala & Logie, 2002). Therefore, working memory incorporates short-term memory among its functions.

Even though there have been many reliable findings in the working memory literature, different theoretical views still remain viable. Baddeley's model of working memory has been utilised in the current study as it has been actively tested and modified over a number of decades (Baddeley, 1996; Baddeley & Hitch, 1974, 1994; Gathercole, 1994).

Baddeley's Model of Working Memory

According to Baddeley's original three-component model, working memory is comprised of a phonological loop for manipulating and storing speech-based information and a visuo-spatial sketchpad that performs a similar function for visual and spatial information. Both are supervised by a central executive, which functions as an attentional control system (Baddeley 1986; Baddeley & Hitch, 1994). Each of these three components will be outlined below.

Phonological Loop

The phonological loop is probably the simplest and most investigated aspect of working memory (Baddeley & Hitch, 1994). The phonological loop comprises of two components, a phonological store and an articulatory rehearsal system. Traces within this store fade after about two seconds, unless they are revived by an articulatory control process that is capable of refreshing the memory trace by subvocal rehearsal. The same process is also capable of using subvocalisation to name a visual stimulus and hence register it in the phonological store.

Visuo-spatial Sketchpad

The visuo-spatial sketchpad is specialized for the processing and storage of visual and/or spatial material. It is thought to be capable of temporarily maintaining and manipulating visuo-spatial information, therefore playing a significant role in spatial orientation and visuo-spatial problem solving (Baddeley, 2002). It is also involved in processing and storing other types of input, including linguistic information, which can be recorded into imagined forms that specify visual and spatial co-ordinates (Gathercole, 1994).

Neuropsychological and behavioural studies have demonstrated an association between the Corsi block-tapping task and spatial short term memory. The Corsi block-tapping task (a test of memory span for movements to different spatial locations) is thought to be a reasonably pure measure of the spatial components of the visuo-spatial sketchpad. The visual component is reflected more strongly in pattern span (Baddeley, 2002).

There is now convincing neuropsychological and experimental evidence suggesting that visuo-spatial and verbal working memory involve separate resources (Baddeley & Lieberman, 1980; Brandimonte, Hitch & Bishop, 1992; Logie, 1986). Neuropsychological evidence has shown dissociations between verbal and visuo-spatial working memory (Baddeley et al. 1991). For example, patients with right posterior lesions can be markedly impaired on Corsi blocks, despite having normal auditory-verbal memory spans (De Renzi & Nichelli, 1975). Although the precise processes and mechanisms involved in sketchpad subsystem are not as well understood as the phonological loop components, different methods of investigation are beginning to converge on a common interpretation.

If one assumes that the sketchpad is a workspace for holding and manipulating visuo-spatial information, then it is possible it may serve a wide range of functions. There is some support for the idea that the sketchpad is involved in planning and executing spatial tasks. Updatable visuo-spatial models may be involved in keeping track of changes in the visual perceptual world over time (Kahneman, Treisman & Gibbs, 1992) and in maintaining orientation in space and directing spatial movement (Thompson, 1983). Visuo-spatial mental models may even be involved in the comprehension of certain types of verbal information (Mani & Johnson-Laird, 1982). Neuropsychological and functional imaging evidence support the view of the sketchpad as a multicomponent system, with occipital lobe activation reflecting the visual pattern component, the parietal regions representing spatial aspects, and the frontal circuitry responsible for co-ordination and control (Smith & Jonides, 1996). Whether it is possible for a single mechanism to serve such disparate roles is unknown.

Central Executive

The central executive is the most complex and least well-understood component of working memory (Baddeley & Hitch, 1994). Originally the idea of the central executive was based on the supervisory attentional system (SAS) devised by Norman and Shallice (1980). Baddeley followed the suggestion that patients exhibiting behavioural disruption after bilateral frontal lobe damage may have a deficit in the attentional system or central executive. They proposed that the term 'frontal lobe

syndrome' be replaced by the term 'dysexecutive syndrome' on the grounds that this allowed for the analysis of executive processes to be pursued independently of the question of their anatomical localisation (Baddeley & Wilson, 1988).

The range of cognitive capacities that has been ascribed to the central executive can be classified into two main categories. The first category is control activities. The central executive has been suggested to house the control of attention and action, to regulate information flow through the working memory system, and to operate the retrieval of information from more permanent knowledge systems. The second category is storage and processing capabilities (Gathercole, 1994). The central executive is considered to be run by limited-capacity processing resources that can be flexibly deployed to respond to many different information-processing requirements. Activities suggested to be supported by these resources include retrieval from long-term memory (Baddeley & Hitch, 1974), maintenance rehearsal (Vallar & Baddeley, 1982) and the storage and processing of linguistic material (Daneman & Carpenter, 1980).

Currently, no single model can account for the full range of functions ascribed to the central executive, and indeed Baddeley and Hitch (1994) suggested that the central executive may consist of separate subcomponents. The following describes two relevant models of the central executive.

The Control of Action

As previously outlined, Baddeley adopted the SAS model of control of action developed by Shallice as a framework for characterising the regulatory functions of the central executive. The model distinguished between two levels of control of action. At the lower level, a system of 'contention scheduling' operates. Contention scheduling involves the routine activation of specialized and hierarchical organised schemes that govern behaviour in specific ways. A higher-level control mechanism is used for actions that require conscious control, the SAS. The SAS is a limited capacity system that can activate or inhibit schemes directly and so can override the direct process of contention scheduling. Human action is therefore controlled by a combination of the powerful but resource demanding SAS and the autonomous contention scheduling system (Gathercole, 1994).

The development of the SAS as a model of the control of action has been devised by analysing the neuropsychological syndrome of individuals who have suffered frontal lobe damage (dysexecutive syndrome). Damage to these cortical areas leads to disturbances of the conscious control of behaviour that corresponds closely to the functions of the SAS (Gathercole, 1994). Individuals with such damage have both excessive distractibility and perseveration, both of which could be caused by the control of behaviour only by the contentional scheduling system (Shallice, 1988). Shallice and Burgess (1991) identified four components of planning behaviour that are controlled by the SAS and that are deficient in patients with frontal lobe insults: the articulation of goals for future actions, the formulation of provisional plans, the creation of marker cues that trigger planned actions, and the actual triggering of the cues.

The second attentional process attributed to the central executive is that of divided attention (Baddeley, 1996). Research in the Alzheimer's population has argued for a separable executive capacity to divide attention (Perry & Hodges, 1999). A third potential executive capacity is that of switching attention (Shallice, 1988). The ability to switch attention is often severely compromised after sustaining frontal lobe damage. However, there has been recent evidence to suggest that the capacity to switch attention is not necessarily strongly dependent on executive capacity but may in fact load heavily on the phonological loop (Allport, Styles & Hsieh, 1994). The potential importance of the phonological loop in controlling action is yet to be determined (Baddeley, 2002).

The fourth role for the central executive is that of forming an interface between the subsystems and long term memory (Baddeley, 1996). Baddeley proposed that one of the main problems for the working memory model was the need to integrate information from the subsidiary systems and from long term memory in a way that allows active maintenance and manipulation. This aspect of the model is in the process of being investigated and developed.

Storage and Processing Model

Daneman and Carpenter (1980, 1983) developed an independent theoretical approach to working memory from that of Baddeley and Hitch (1974). Research led them to the

view that working memory consisted of a limited pool of resources that could be used to serve both processing operations and storage of information if necessary (King & Just, 1991; Macdonald, Just & Carpenter, 1992). According to this model, a trade off between processing and storage was necessary whenever a particular task placed demands that exceeded the limited resources of the system.

This model provides a framework for characterising the flexible but limited capacity resources ascribed to the central executive component of Baddeley and Hitch (1974) working memory model.

The central executive is more complex than either of its slave systems (phonological loop and visuo-spatial sketchpad); however, there have been promising advances in the understanding of the central executive component. The major problem faced by theorists concerned with the central executive is the integration of the different executive functions in a single system (Gathercole, 1994). It is likely that neuropsychological perspectives will continue to be a source of useful and relevant evidence for the theoretical basis of the working memory model.

1.5 SOCIO-EMOTIONAL AND BEHAVIOURAL FUNCTIONING

Early behavioural research in TS focused on three main areas: gender-related behaviour, psychiatric disorders, and personality/social behaviour. Findings across the studies are generally consistent and report overall sound psychosocial adjustment, but while suggesting that TS females may be more vulnerable to social and/or adjustment problems when compared to the unaffected population (Downey, Ehrhardt, Morishima, Bell & Gruen, 1987; Ross, Zinn & McCauley, 2000).

Females with TS have been shown to follow a typical female developmental pattern with unambiguous female gender identification (Nielsen and Sillesen, 1981). Heterosexual romantic fantasies are common, but actual dating and initiation of sexual activities may be somewhat delayed (Pavlidis, McCauley & Sybert, 1995). TS women, as a group, do not appear to be at increased risk of psychiatric disturbance. There have been individual case studies which reported significant mental health problems (most commonly depression) in TS females; however, when the studies are

combined, the prevalence rate for psychiatric diagnoses in this population (2%-6%) is similar to those reported in epidemiological studies (3.7%-7.6%) in US adults (Ross et al., 2000).

Research in psychosocial development has documented problems in the areas of immaturity, poor concentration, increased activity level and peer relationships in younger girls with TS (McCauley, Ito & Kay, 1986; McCauley, Ross, Kushner & Cutler, 1995; Rovet & Ireland, 1994). In childhood, a significant proportion of females with TS appear to be hyperactive (Mazzocco, Baumgardner, Freund, & Reiss, 1998; McCauley, Ito, & Kay, 1986; Rovet & Ireland, 1994). By adolescence, up to 10 percent have been reported to exhibit ADHD (McCauley et al., 2001).

During adolescence, self-esteem, social immaturity and anxiety appear to be the most common problems. Girls and women with TS have poorer self-concepts when compared with controls. Control groups have consisted of those with short stature as well as normative sample of women. However, it remains unclear how common or persistent these social and behavioural difficulties are in TS females. Early studies were compromised by small samples sizes and biased sample selection. More recent studies have compared TS females across a wide age range. Thus, it has been difficult to determine whether the deficits found represent persistent individual differences or delays in social and emotional maturation which resolve over time (McCauley, Feuillan, Kushner& Ross, 2001).

Adolescence is thought to be a particularly high-risk period for girls with TS (McCauley et al., 2001). It appears that this is because of delays in pubertal and linear growth. Risk factors associated with poor adolescent psychosocial adjustment include negative body image, cognitive difficulties, poor family acceptance of the diagnosis, low self-esteem and limited access to resources and support (Kagan-Krieger, 1998; Mambelli et al., 1995). Body image and self-esteem problems may be linked to the variety of physical differences found in TS females when compared with those in their peers, rather than short stature alone. Difficulties with weight control could also negatively impact on body confidence. The knowledge of being infertile is thought to affect older adolescents, and especially younger adults.

McCauley et al. (2001) examined the psychosocial adjustment of 122 adolescent girls aged 13-18 years with TS, and 108 normal controls. Tools administered were the Child Behaviour Checklist (CBC), Children's Depression Inventory (CDI), Revised Children's Manifest Anxiety Scale (RCMAS), Self-Perception Profile for Adolescents (SPP-A) and the WISC-R. Mothers completed the parent version of the CDI and CMAS and the Diagnostic Interview for Children and Adolescents (DICA).

Significant differences between the groups were noted on measures of Performance IQ, with TS girls performing below that of controls. On measures of self-perception, TS girls had significantly lower levels (less perceived competence) on social acceptance and athletic competence. Mothers and TS females both reported fewer problems with behavioural conduct such as cheating and inattendance at school. Perception of job competence was similar in both groups. Analysis of behavioural measures (CBC) revealed that TS girls were reported to be less socially competent (fewer friends, less time spent with friends) and to experience more social problems than controls. Social problems in both study groups were more significant at a younger age.

On the CDI and the RCMAS, controls had higher levels of anxiety and depression than the TS females. However, 54% of the TS females scored highly on the Lie scale, suggesting inaccurate self-reporting. This was interpreted as an attempt to respond in a socially acceptable way, thus minimising symptoms, or as an inaccurate view of self. It was reported that the Lie score was as useful as the overall Anxiety score in predicting emotional, peer, academic and family stress related problems. No differences emerged on parent ratings. Levels of psychopathology, measured by the DICA, revealed that TS girls met the criteria for Attention-Deficit Hyperactivity Disorder significantly more often than did female controls. This rate of ADHD was higher than that typically reported in adolescent girls. Examination of the effects of karyotype, breast development, and duration of oestrogen replacement therapy on the behavioural variables (CBC) showed no significant effects. In conclusion, McCauley's findings support prior work in that individuals with TS present with an overall profile of stable behavioural functioning, but remain at increased risk for social and emotional difficulties.

It is possible that the social problems found in some girls with TS are a reflection of the core cognitive or learning disability found in TS girls (Rovet & Ireland, 1994). These problems follow a profile that is similar to that of children with non-verbal learning disabilities as described by Rourke (1995). Individuals with non-verbal learning disabilities frequently have problems with social relationships that are seen as secondary to neuropsychological deficits. These deficits interfere with the child's ability to accurately perceive the impact of behaviours in social situations, to generate problem-solving strategies, and to generalise learning from one situation to another. Difficulties with social cognition have been commonly reported in the TS population (Elgar et al., 2002; Lawrence et al., 2003; McCauley et al., 1987; Skuse et al., 1997). Individuals with TS are more likely to have difficulties interpreting mental states from faces and understanding non-verbal cues than normal controls. TS females have also been reported to intrude on the physical space of others, and fail to understand and/or respect interpersonal boundaries (McCauley et al., 1987). These difficulties in non-verbal functioning, in combination with the cognitive and social limitations often witnessed in TS girls, are thought to have a negative impact on interpersonal relationships with parents, siblings and peers.

1.6 EDUCATIONAL ACHIEVEMENT

It is widely recognized that individuals with TS encounter greater than normal difficulty with mathematics at school (Rovet, 1993; Rovet & Ireland, 1994; Temple & Marriott, 1998). Many individuals with TS perform poorly on tests of arithmetic achievement, but perform at age expectation in reading and spelling. However, few studies have examined the effects of inattention and hyperactivity on school achievement (Rovet, 1993). The area of academic achievement is one of particular importance for both TS individuals and their parents, and can impact on peer acceptance and self-esteem. USA survey reports have revealed that although TS females may achieve levels of education comparable to those of siblings and parents, they do not reach the same occupational status (Downey, Ehrhardt, Gruen, Bell & Morishima, 1991).

Rovet (1993) compared 67 TS children with 27 controls on measures of cognitive ability, achievement, behaviour and self-esteem. Results indicated selective

impairments in visuo-spatial and memory areas and significant underachievement in arithmetic, particularly numerical ability, mental calculation, geometry, and reasoning. A detailed analysis of specific components of mathematical ability revealed that conceptual/factual areas of mathematics seemed to be compromised to a greater degree than computational areas. Multiplication was the least affected of the computational abilities, possibly because of its greater reliance on rote memory skills, which appear to be intact in TS individuals. Older girls were found to be more likely to have an arithmetic disability than younger girls as measured by the WRAT-R. Reading and spelling were within normal limits but written language skills were an area of concern for parents. Behavioural functioning as reported by parents revealed that children with TS were seen as having less adequate social development and greater inattentiveness and hyperactivity. However, these findings were not correlated with indices of educational achievement. Learning problems were of great concern to parents and were not being addressed in the school system.

Rovet suggested that girls with TS were similar to those children who had non-verbal learning disabilities (Rourke, 1989). Similar to children with NVLD, TS girls demonstrate particular difficulty with mathematics, written expression, social awareness and attention.

Individuals with TS are also more likely to have repeated a school grade than normal controls (McCauley et al., 1995; Rovet & Ireland, 1994; Van Borsel et al. 1999). Van Borsel et al. found that almost one third of the 122 TS females investigated had repeated one or more classes, with the first year of primary school being the most common. One fifth of the participants had required special education classes. Of the 70 participants that reported having difficulties at school, 54 of them had specific difficulties with mathematics, compared with 12 and 10 for spelling and reading respectively.

Research investigating the exact nature of the mathematical difficulties witnessed in TS individuals have revealed deficits in addition and subtraction (Rovet, 1993), multiplication, calculation and problem solving (Temple & Marriott, 1998), fact and procedural knowledge (Rovet & Ireland., 1994), difficulties with number alignment (Temple & Marriott, 1998) and confusion of component steps (Rovet & Ireland,

1994). Mathematical errors have been associated with poor visuo-spatial ability (Mazzocco, 1998).

1.7 GROWTH HORMONE, COGNITION AND PSYCHOSOCIAL FUNCTIONING

Short stature occurs in over 95% of girls with TS and is one of the hallmark characteristics of the condition. The important features of the growth pattern in girls with TS include (1) normal growth rate from age 0-3 years, (2) progressive decline in growth rate from ages 3 to 14 years, and (3) prolonged adolescent growth period.

Over the past decade, girls with TS have been treated earlier in life with human Growth Hormone (hGH) and the number of injections (dosage) given each week has increased (Betts et al., 1999). Weight gain is a problem, particularly in older girls with TS, and this will affect the dosage prescribed. The benefits of hGH treatment on final height have been reported as variable (Donaldson, 1997); however, all these studies have used different treatment regimes at varying commencement ages. Reports outline that the earlier hGH is commenced, the greater the chance of increased height gain. Even with sub optimal therapeutic dosage, mean height gain is approximately 5cm, and this height increases the earlier the therapy is commenced (Betts et al.).

The association between short stature and psychosocial problems is well documented in the research literature (Siegel, Clopper & Stabler, 1991). It is evident in Western society that short stature is linked with social disadvantage and it can negatively influence the perception of affected individuals by others (Huisman et al. 1993). Children may be treated as younger than their age, both by adults and other children. Increased anxiety and overprotection at home and at school are not uncommon is these children, as is teasing by their peers. These interactions may contribute to the development of an immature and negative body image and self-concept. Children of short stature can be considered as vulnerable to developing cognitive, social and behavioural problems (Siegel et al.).

The literature to date is inconclusive about whether there are differential effects of short stature on psychosocial functioning in TS. There has been a number of studies comparing psychosocial functioning in TS females and normal short statured controls

(McCauley, 1990) with the robust conclusion that problems in social and emotional functioning in females with TS cannot be primarily attributed to short stature, but may be explained by delayed neurological maturation. The link between specific cognitive deficits and social problems has also been postulated (Mambelli et al, 1995).

Huisman et al. (1993) studied the psychosocial effects of results of human Growth Hormone (hGH) therapy in girls with TS. No significant changes in self-concept and social anxiety scores of individuals with TS were found after two years of hGH treatment. Rates of overall behavioural problems did not change, though the proportion of immature and hyperactive behaviour was reduced. Social functioning was judged by parents and TS girls to have improved after the treatment period. Generally, hGH was well tolerated and favourably looked upon by both parents and TS individuals, with the exception of girls under 6 years of age (Lagrou et al., 1998). Parents and TS girls had increased optimism for growth and functioning; however, the expectation of the degree of attained height was unrealistic (Lagrou et al.).

Siegel et al. (1998) presented longitudinal data about the effects of growth hormone on cognition and behavioural measures. They followed girls with TS, girls with isolated growth hormone deficiency and girls with idiopathic short stature for 3 years of hGH therapy. At baseline, the clinical groups had more internalising behavioural problems, had fewer friends and participated in fewer activities than did control subjects. At baseline, the groups did not differ in mean IQ or academic achievement, but TS girls did have greater difficulties in mathematical achievement. Height and growth rate significantly increased in the clinical groups over the 3 years of hGH therapy. IQ and educational achievement scores did not. These results suggest that although hGH therapy is effective in increasing height, it does not affect cognitive abilities or educational achievement.

1.8 OESTROGEN, COGNITION AND PSYCHOSOCIAL FUNCTIONING

It has been postulated that the cognitive and behavioural deficits seen in TS individuals could result from the deficiency of prepubertal sex steroids owing to severe premature ovarian failure (Ross, Zinn & McCauley, 2000). The sex hormones (oestrogen and androgen) appear to influence brain development in foetal life and

through puberty. However the exact mechanism/s of action are yet to be determined. Sex steroids may function (1) transiently as neuromodulators by potential mechanisms such as occupying receptors and initiating enzyme cascade, modifying uptake of neurotransmitters, or altering neuronal electrical activity; (2) permanently by altering synapse formation and remodelling; or (3) by both of these mechanisms (McEwen, Jones & Pfaff, 1987; Matsumoto, Arai, Urano & Hyodo, 1991).

Postmortem studies of normal ovarian development in infants indicate that female infants appear to have increased ovarian oestrogen production during the first year of life, analogous to the testosterone surge during the first 6 months of life in male infants (Bidlingmaier, Strom, Dorr, Eisenmenger & Knorr, 1987). Therefore, girls with TS would presumably lack this surge of oestrogen due to dysgenesis of the ovaries. The ovaries in normal girls produce minimal amounts of oestrogen and possibly androgen before puberty (Ross & Zinn, 1999). The production of oestrogen in the ovaries increases significantly throughout puberty, until adult levels are reached. It is speculated that this very early oestrogen deficiency may affect later cognitive and behavioural development (Ross & Zinn).

The period from adolescence to young adulthood may be a particularly important period from a neurobiological standpoint since oestrogen replacement therapy (ERT) may have an impact on psychological function (Ross et al., 2000; Ross & Zinn, 1999). Adult TS women who have generally received oestrogen therapy starting in adolescence have a persistent VIQ-PIQ discrepancy as well as impaired visual-spatial processing, visual memory and arithmetic skills (Swillen et al., 1993). Thus, some of the cognitive deficits, such as impaired visual-spatial abilities, manifest themselves in childhood and generally persist into adulthood, while other deficits such as motor function and verbal memory appear to improve (Romans et al., 1998; Ross et al., 2000). The visuo-spatial deficits are relatively consistent across wide age ranges and are not thought to be reversible with oestrogen therapy. In contrast, chronic oestrogen deficiency secondary to ovarian failure may contribute to certain aspects of TS cognitive function. Positive oestrogen treatment effects on memory and motor function have been demonstrated in TS girls aged 8-12 years and young adults receiving low dose ERT (Romans et al., 1998; Ross, Roeltgen, Feuillan, Kushner & Cutler, 1998). However, a cause and effect relationship has not yet been proven and the mechanism of these oestrogen effects is not known.

Johnson, Rohrburgh and Ross (1993) investigated the possible effects of a lack of oestrogen on cognitive processes. Twenty girls without oestrogen replacement therapy were compared with healthy controls on measures of event-related brain potentials and a reaction time test. The TS group was divided into two subgroups: pre and post puberty. Individuals in the older TS group who had not received oestrogen supplements failed to show the normal maturational process whereby the amplitude and duration of frontal negative slow waves decrease. Indeed, their results resembled the younger TS group and the younger control group. Conversely, the younger TS group appeared to process stimuli at the same speed as their control peers. These findings are consistent with a maturational brain abnormality amongst TS girls that appears to result from the absence of oestrogen at a critical stage of puberty.

Studies investigating the role of androgens on cognition in TS individuals suggest that performances on certain memory tasks, particularly those that are sensitive to hippocampal function, improve following androgen therapy (Murphy et al., 1994). Ross et al. (2003) reported a positive effect of oxandrolone on verbal working memory but not verbal abilities, spatial cognition, or executive function.

In conclusion, previous oestrogen research suggest that (1) oestrogen has significant effects on brain and behaviour in animal studies, (2) absence or decrease in oestrogen levels is related to some differences in cognitive function and psychological well-being, and (3) the neurophysiological mechanisms for the effects of oestrogen on brain development are yet to be determined. A lack of oestrogen in TS females appears to lead to weaker visual-perceptual and motor-planning abilities, but does not affect visuo-spatial abilities (Romans et al., 1998; Ross et al., 2000). Reduced androgen is associated with weak memory skills. The deficits in TS visuo-spatial ability appear to be caused by loss of genetic material on the X chromosome.

1.9 NEUROANATOMICAL, NEUROPHYSIOLOGICAL AND NEUROPSYCHOLOGICAL STUDIES

Numerous studies have attempted to identify the neuroanatomic basis of the cognitive deficit in TS. The findings of impaired visual, perceptual and spatial processing in TS were initially interpreted as evidence of right parietal and/or right hemisphere

dysfunction (Netley & Rovet, 1983) with an atypical pattern of hemispheric lateralisation. Early studies of anomalous hemisphere maturation suggested that the right hemisphere was underdeveloped relative to the usual asymmetry seen in age-matched controls (Money, 1973; Netley & Rovet, 1983).

While several studies have found atypical cortical organisation in TS compared to controls, the neuroanatomical localisation of cognitive impairments to either the left or the right hemisphere has been inconsistent (Reiss, Eliez, Schmitt, Patwardhan & Haberecht, 2000). A spectrum of cerebral specialization has been reported ranging from focal right parietal dysfunction to bilateral hemispheric deficits in the frontal and parietal lobes. The variability of cerebral lateralization in TS may be explained by a neurodevelopmental hypothesis proposed by Rovet (1990). This model suggests that TS individuals undergo aberrant neural development which results in altered cerebral lateralisation. Many factors that regulate neuronal migration or cellular organisation may influence the cognitive presentation in TS and may explain in part the inter-individual variability in cerebral and hemispheric specialisation (Reiss et. al, 2000).

As the TS cognitive profile displays many similarities to Rourke's Non-Verbal Learning Disability syndrome, Rourke's white matter hypothesis has also been used to explain the neurocognitive deficits observed in TS (Rovet, 1995). According to this hypothesis, visuo-spatial impairments result from white matter or myelin deficiencies. These deficiencies have a greater impact on the right rather than left hemisphere processing, as the right hemisphere has a greater proportion of white matter. Structural neuroimaging has not supported this hypothesis, demonstrating different regional distribution in both the grey and white matter (Rourke, 1995).

Hier and Crowley (1982) and Pennington et al. (1985) proposed an alternative hypothesis for the etiology of the cognitive profile of females with TS. Instead of supporting a model of right-hemisphere dysfunction, they proposed that the TS profile was more consistent with a pattern of diffuse brain abnormality. Pennington and his colleagues compared TS individuals with patients with left hemisphere lesions, right hemisphere lesions and the diffusely brain injured. When compared to controls, Pennington et al. found that TS females displayed a pattern of cognitive dysfunction which most resembled that of the head injured population. These results suggest that

TS individuals may have a wide variety of cognitive profiles without specific localised deficits in the right hemisphere.

MRI studies of girls with TS and female controls have revealed a smaller proportion of grey and white matter in the right parietal region (Brown et al., 2002; Reiss, Mazzocco, Greenlaw, Freund and Ross, 1995). White matter reductions were found in the right and left parietal lobes and increases in the right inferior parietal-occipital region.

Previous neuroimaging research in Turner syndrome (TS) has indicated parietal lobe anomalies, whilst anomalies in other brain loci have been less well substantiated. Haberecht et al. (2001) utilised functional MRI (fMRI) to investigate the neural substrates which underlie observed deficits in executive functioning and visuo-spatial processing in TS individuals. Eleven females with TS (aged 7-20) were compared to controls on fMRI whilst performing the 1-back and 2-back versions of a standard working memory task. On both tasks, TS females performed more poorly than controls. Compared with controls, TS females showed *increased* activation in the left and right supramarginal gyrus (SMG) during the 1-back task, and *decreased* activation in these regions when performing the 2-back task. This double dissociation in parietal activation was interpreted as TS females being unable to fully engage the parietal cortex during the more demanding 2-back working memory task, hence displaying a decrease in activation. In addition, decreased activation in the left and right dorsolateral prefrontal cortex (DLPRC) and caudate nucleus was observed in TS individuals as compared with controls during the 2-back task. It was proposed that activation differences localised in the SMG, in the inferior parietal lobe, may reflect deficits in visuo-spatial encoding and working memory storage mechanisms in TS. In addition, deficits in the DLPFC and caudate nucleus may be related to deficits in executive functioning during working memory performance. Altogether, the findings of Haberecht et al. point to deficits in the fronto-striatal and fronto-parietal circuits subserving multiple working memory functions in the TS population.

More recently, Tamm, Menon & Reiss (2003) evaluated 11 monosomic TS adolescents with age-matched controls on a 'Go/No Go' task while undergoing fMRI. The two groups did not differ on accuracy or reaction time, however the TS group activated more in the bilateral superior and middle frontal gyri than the control

subjects. Control subjects did not show increased activation in any region. The authors concluded that TS individuals compensated for executive dysfunction by recruiting additional prefrontal cortical regions involved in inhibition, attention and working memory functions necessary to perform the "Go/No Go' task successfully.

Positron emission tomography (PET) studies have also demonstrated atypical activation of left and right occipital and/or parietal cortices. Elliot, Watkins, Messa, Lippe and Chugani (1996) used PET to analyse differences in glucose metabolism in six girls with TS as compared with normal controls. Each of the participants also underwent neuropsychological examination. Five out of the six TS girls had some degree of cognitive or learning impairment. The five girls that had cognitive and learning impairments exhibited significantly lower parietal metabolism when compared with normal controls. Four TS girls had glucose metabolism at or below the 30^{th} percentile bilaterally in the parietal and lateral occipital cortical regions. The other two girls (one with limited cognitive impairment and one who was free from cognitive impairment) exhibited normal glucose metabolism in these regions. The results were generally consistent with those of Clark, Klonoff and Hayden (1990), who suggested bilateral parietal and occipital lobe dysfunction might contribute to cognitive impairments in TS.

Murphy et al. (1997) also investigated the link between cognitive ability and cerebral metabolic rates for glucose with PET in a sample of 16 TS adults and 13 age-matched controls. TS participants had a significant absolute hypermetabolism in most brain areas. However, normal metabolism was significantly lower in TS females when compared to controls in the insula, association neocortices and occipital cortices bilaterally, and the right hemisphere. Preliminary analysis demonstrated an X chromosome dosage effect in language ability and left temporal metabolism, asymmetry of right/left test scores and parietal metabolism. It was hypothesised that i) generalised brain hypermetabolism reflects global abnormalities in neuron packing ii) neuronal abnormalities occur in association neocortex that differ in nature and extent from whole brain and are associated with significant differences in normalised metabolism, iii) cognitive deficits are related to brain metabolic abnormalities and iv) social-behavioural problems may be related to abnormalities of brain metabolism.

In summary, these findings suggest neuroanatomical and neurophysiological abnormalities associated with TS, with primary emphasis on the occipital and parietal lobes in the right hemisphere, although bilateral cerebral deficits have been reported (Berch & Bender, 2000; Brown et al., 2004; Murphy et al., 1993; Rovet & Buchanan, 1999). These abnormalities are thought to have been the etiological substrate for the characteristic visual, spatial and perceptual dysfunction witnessed in TS individuals. There is also growing evidence to suggest involvement of the frontal circuitry with corresponding deficits in working memory ability (Haberecht et al., 2001; Tamm et al., 2003). These neurodevelopmental abnormalities may be genetically modulated, reflecting how much X chromosomal material is missing and the specific sites that are lost. However, functional differences also may be associated with hormonal dysfunction (Ross et al., 2003).

1.10 RATIONALE

There has been a gradual increase in the number of studies investigating the role of 'executive functioning' in TS females (eg. Temple et al., 1996; Romans et al., 1997) over the last decade. However, the literature thus far is somewhat limited and contradictory. There is evidence to suggest that TS females indeed do have difficulties on certain tasks thought to tap executive functioning, however the exact deficit/s remain/s elusive. Difficulties in executive functioning have been described in areas of verbal fluency (Romans et al., 1998; Temple, 2002; Temple et al., 1996; Waber, 1979) mental flexibility (Romans et al., 1998; Waber, 1979), organisation and planning (Buchanan et al., 1998; Romans et al., 1997; 1998), and visuo-spatial working memory (Buchanan et al., 1998; Romans et al., 1997). It remains unclear if executive skills in TS girls are domain independent, hence the possible explanation for the wide variability of results on neuropsychological tests.

While there have been numerous studies focusing on visuo-spatial impairments in TS, few have looked at the role of higher order executive functions and their potential role in mediating cognitive performance. Previous studies have suggested that the visuo-spatial deficits in TS may reflect a higher order of cognitive impairment in the area of executive functioning (Berch, 1996; Buchanan et al., 1998). Thus far, there has been a number of investigations which have suggested that the role of working memory in the TS population warrants further investigation (Buchanan et al., 1998; Ross et al.,

1995, Ross, 1996). There is also growing evidence to suggest the involvement of the frontal circuitry of the brain with corresponding deficits in working memory ability in the TS population (Haberecht et al., 2001; Tamm et al., 2003). It has been demonstrated that TS females have a reduction in brain volume in the right parietal, occipital and prefrontal cortices, when compared with controls (Elliot et al., 1996; Haberecht et al., 2001; Murphy et al., 1997; Reiss et al., 1995). As the previous research on working memory and its role in executive functioning in TS has been inconclusive, the current study aims to advance and expand previous knowledge and to determine the contributing role of executive functioning to the TS neurocognitive profile.

It has been suggested that further investigation using the conceptual frameworks employed in cognitive neuropsychology may assist in understanding the neurocognitive profile in TS (Berch & Bender, 2000; Buchanan et al, 1998; Nijhuis-van der Sanden; 2003; Eling & Otten, 2003). Models of working memory, such as that of Baddeley and Hitch (1974) are thought to be fruitful in providing a theoretical approach to the study of neuropsychological deficits in TS. As such, Baddeley and Hitch's 1974 model of working memory will be used in the current study, hopefully promoting further understanding of the theoretical underpinnings of the TS neurocognitive profile.

To date, there have been no Australian studies conducted on either executive or affective functioning in girls with TS. There is a need for a comprehensive, systematic study of Australian girls with TS, which is inclusive of cognitive, behavioural and socio-emotional measures. This sample should be representative of a variety of TS individuals from both urban and regional areas of Australia.

There has been a development of interest in the role of genomic imprinting in TS since Skuse et al.'s landmark paper in 1997, suggesting that TS females who had a paternally derived X chromosome (X^p) were significantly better adjusted, with superior verbal and higher order executive function skills. Since then, there has been a variety of studies relating to genomic imprinting in TS, producing mixed support for Skuse's hypothesis (Bishop et al., 2000; Donnelly et al., 2000; Ross & Zinn, 1999; Tsezou et al., 1999). The role of genomic imprinting in TS remains inconclusive; and further investigation is necessary to assess the relationships and relative contributions

of maternal versus paternal X chromosome inheritance on the physical and cognitive phenotypes in TS.

There have been no previous published studies that have attempted to investigate the relationship between executive abilities and social and behavioural functioning in the one sample. Although it has been demonstrated that TS females do poorly on some tests used to assess executive skills, there has been no inquiry as to whether these deficits on testing affect their ability to regulate their emotions, behaviour or function in everyday life. A reduction in attentional capacity has been reported, including difficulties associated with impulsivity ((McCauley et al., 1986; McCauley et al., 1995; Romans et al., 1997; Rovet & Ireland, 1994), however it is yet to be established how these attentional deficits interact with other cognitive and behavioural domains.

1.11 AIMS OF THE PRESENT STUDY

The aims of the current study are:

Aim 1: To investigate the role of executive functioning in a representative sample of Australian girls with TS aged between 6 and 16 years. TS girls will be examined on the Wechsler Intelligence Scale for Children (3rd ed.), Block Span Forward, Digit Span Forward, Controlled Oral Word Association Test, Controlled Animal Fluency Test, Rey-Osterrieth Complex Figure Test, Tower of London and the Wisconsin Card Sorting Test. Comparisons will be made with Australian normative data. In particular, this study will focus on the question of whether there is a specific TS visuo-spatial deficit or whether the difficulty is in fact due to an impairment of the higher order cognitive abilities of executive functions and working memory.

It is ***hypothesised*** that deficient performances on tests of visuo-spatial and executive functioning of TS girls are likely to result from reduced visuo-spatial working memory capacity and poorly developed higher order executive skills. These outcomes will be interpreted in the context of Baddeley's model of working memory.

Aim 2: To examine and compare the cognitive profile in a select subsample of TS girls with those of matched sibling controls. It is ***hypothesised*** that TS girls with perform more poorly than their non-affected sisters on non-verbal cognitive measures.

By using a matched sibling control group as a comparison group, family related variance will be minimised. TS girls and sibling controls will be examined on the Wechsler Intelligence Scale for Children (3rd ed.), the Behavioural Dyscontrol Scale (2nd ed.), the Rey-Osterrieth Complex Figure and the Wisconsin Card Sorting Test.

Aim 3. To assess social, emotional and behavioural functioning in Australian girls with TS. These areas of function will be measured by the Behaviour Assessment Scale for Children (Reynolds & Kamphaus, 1992) and the Social Cognition Questionnaire (Skuse et al., 1997). Further, this study will investigate whether there is a relationship between cognitive dysfunction and socio-emotional and behavioural functioning. It is ***hypothesised*** that girls with higher levels of social, emotional and behavioural problems will have poorer cognitive abilities.

Aim 4. To explore the concept of genomic imprinting, specifically, the concept of an X-linked locus for cognitive ability. Thus far, there have been few studies investigating the role of X origin on executive measures since Skuse's initial controversial finding in 1997. It is ***hypothesised*** that TS females whose X-chromosome is maternal in origin will have weaker executive and social skills than those who have a paternal X chromosome.

Aim 5: To investigate the potentially differing effects of X monosomy and non-45,X monosomy on cognitive, executive and behavioural measures. It is ***hypothesised*** that TS girls with X monosomy will perform more poorly than those of other cytogenetic TS variants on cognitive and behavioural measures.

2. METHOD

2.1 PARTICIPANTS

Participants with any neurological, metabolic, psychiatric or major systemic disorder (except for Turner's syndrome) were excluded from the study. Children with a Full Scale IQ below 70 points were also excluded. The participants in this study were 43 females with Turner's syndrome aged between 6 and 16 years 11 months. Of the 43, two participants were excluded after genetic and psychological testing. The first person excluded had a moderate intellectual disability and Insulin Dependent Diabetes Mellitus. The second person had a minute number of 45,X cells in the peripheral blood sample, and genetic testing revealed that her karyotype was not consistent with a diagnosis of TS. This then left 41 TS participants in the sample.

A subsample of 15 female siblings of the TS participants, aged between 6 and 16 years 11 months, was selected as a comparison group. Female siblings were chosen as a control group to try and control for genetic and environmental variance. Each of the 15 controls was compared with her TS sister on a selection of the assessment battery.

Participants with TS were recruited as part of a larger National Health and Medical Research Council (NHMRC) funded project entitled 'The genetic features of Turner's Syndrome: a family study'. Families were recruited from the Department of Endocrinology and Diabetes, Royal Children's Hospital, Parkville, Victoria; the Murdoch Children's Research Institute, Royal Children's Hospital; the Department of Endocrinology, Monash Medical Centre, Clayton, Victoria; the Women's and Children's Hospital, North Adelaide, South Australia; the Royal Hobart Hospital, Hobart, Tasmania. Further participants were recruited from the Victorian Turner's Syndrome Association and by referral from local General Practitioners and Paediatric Endocrinologists in all three states.

In all cases, Turner's syndrome was established by a thorough paediatric and genetic assessment including clinical interview, physical examination and chromosomal analysis. Participants were then required to undergo further sophisticated karyotype investigation as part of the NHMRC project to confirm the diagnosis of TS.

All participants spoke English as their first language. It is important to note that many females with Turner's syndrome experience a degree of hearing impairment as a result of recurrent otitis media. In this sample, parents reported that 74% of participants had experienced more than four episodes of otitis media and 46% had some degree of hearing difficulty. Despite this, no participant was excluded on the basis of poor hearing, as assessed by the clinician. None of the participants wore hearing aids and the reported hearing difficulties were not detectable in clinical interview or on assessment.

2.2 MATERIALS

2.2.1 Socio-Economic Status

Socio-economic status (SES) was measured using the Scale of Occupational Prestige (Daniel, 1983) which was developed and normed in Australia. This scale rates SES on parental occupation. It has an ordinal scale from 1 (indicating high prestige employment) to 7 (indicating low prestige employment). For example, a medical practitioner would rate a score of 1, while a factory worker would rate a score of 7. When a child had two working parents, the higher rated occupation was taken as an indicator of SES. In the case of parental separation, the occupation of the parent with whom the child resided was used to determine SES.

2.2.2 Neuropsychological Battery

General intellectual functioning was determined by administration of the Wechsler Intelligence Scale for Children - Australian Adaptation 3rd Edition (WISC-III) (Wechsler, 1992).

Visuo-spatial ability was measured by the Rey-Osterrieth Complex Figure (Anderson et al., 1995; Osterrieth, 1944; Rey, 1941; 1993).

Measures of executive function were assessed using the Behavioural Dyscontrol Scale 2nd Edition (Grigsby & Kaye, 1996); the Controlled Animal Fluency Test (Tucker, Ewing & Ross, 1996); the Rey-Osterrieth Complex Figure (Anderson et al., 1995; Osterrieth, 1944; Rey, 1941); the Tower of London Test (Anderson & Lajoie, 1996;

Shallice, 1982); Controlled Oral Word Association Test (Anderson, Lajoie & Bell, 1995; Benton & Hamsher, 1989); and the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Tally, Kay & Curtiss, 1993). Immediate attention and working memory were assessed with the Digit Span sub-test from the WISC-III and the Digit and Block Span subtests from the Neuropsychological Assessment of the School Aged Child (Anderson et al.; Milner, 1971).

Socio-emotional functioning was measured by the Behavioural Assessment System for Children (BASC) (Reynolds & Kamphaus, 1992) and the Social Cognition Questionnaire (Skuse et al. 1997).

Intellectual Functioning

WISC-III

The WISC-III was employed as a measure of intelligence because it provides a valid and reliable index of global intelligence (Wechsler, 1992). The scale provides separate intelligence quotients for verbal and non-verbal domains (VIQ and PIQ respectively), as well as an overall global intelligence score (FIQ). Each of these quotients has a mean of 100 and a standard deviation of 15. [Note: At the commencement of this study, the WISC-III was the current version of the Wechsler Intelligence Scale for Children. The WISC-IV was not in circulation].

The WISC-III is comprised of 13 sub-tests (10 core, 3 supplemental) which result in scaled scores with a mean of 10 and a standard deviation of 3 (Wechsler, 1992). In addition, the WISC-III generates four factor-based index scores that can be calculated from the sub-tests: the *Information*, *Similarities*, *Vocabulary* and *Comprehension* for the Verbal Comprehension Index (VCI); the *Picture Completion*, *Picture Arrangement*, *Block Design* and *Object Assembly* for the Perceptual Organisation Index (POI); the *Arithmetic* and *Digit Span* subtests for the Freedom from Distractibility Index (FDI); and the *Coding* and *Symbol Search* for the Processing Speed Index (PSI). The *Mazes* subtest is not included in the Index Scores.

Participants with TS were administered all ten core subtests of the WISC-III and one supplementary subtest *Digit Span*. The supplementary subtests of *Mazes* and *Symbol Search* were not used. As *Symbol Search* was not administered, the PSI was not calculated.

The WISC-III was used in this study to establish a cognitive baseline on which to compare other neuropsychological performances. It was administered according to standard procedures as outlined in the WISC-III manual (Wechsler, 1992).

Visuo-Spatial Ability

Rey-Osterrieth Complex Figure

The Rey-Osterrieth Complex Figure (RCF) is a copying and recall task that assesses visuo-spatial ability. Efficient completion of this test requires sound visuo-constructional ability (Spreen & Strauss, 1991), perceptual organisation (Lezak, 1995), sensori-motor co-ordination and grapho-motor skills (Kirk, 1985). Interscorer and test-retest reliabilities range from r =0.91 to 0.98 and r =0.60 to 0.76 respectively. The test requires the participant to copy a complex geometrical figure as accurately as she can from the stimulus design. After approximately a three minute interval and without previous forewarning, the subject is then asked to draw what they recall of the figure. The measures of performance that are derived include a copy score, which reflects the accuracy of the original copy, and is a measure of visuo-constructional ability, as well as three minute and thirty minute delayed recall scores, which assess the amount of information retained over time.

The RCF is a neuropsychological tool designed for adults that has been successfully employed with school-aged children. The task is appropriate for children aged 6 or older, and normative data indicates that it is sensitive to developmental changes (Akshoomoff & Stiles, 1995a; 1995b; Waber & Holmes, 1985; 1986). The RCF was administered and scored according to criteria outlined in the test protocol titled 'Neuropsychological Assessment of the School Aged Child' (Anderson et al., 1995). This version of the RCF has been developed, normed and standardised in Australia.

Executive Functioning

The executive tests outlined below were used to measure the functions of the 'central executive' in Baddeley's model of working memory.

Behavioural Dyscontrol Scale (2nd Edition).

The Grigsby Behavioural Dyscontrol Scale, 2nd Edition (BDS-2) is a measure adapted from the work of A.R. Luria (1966, 1980) by Grigsby and associates (Grigsby, Kaye, Baxter, Shetterly & Hamman, 1998; Grigsby, Kravcisin, Ayarbe & Busenbark, 1993; Kaye, Grigsby, Robbins & Korzun, 1990). It is comprised of functional items intended to assess the capacity for behavioural self-regulation in adults and children. This is thought to be a fundamental aspect of executive functioning (Fuster, 1997; Luria, 1980). The BDS-2 is a measure of motor planning, inhibition and working memory (Grigsby et al., 1992). It is of use in discriminating individuals who are unable to regulate their behaviour as a consequence of neural disorder or dysfunction from those who have the neurologic capacity for control, but demonstrate significant behavioural pathology for other reasons.

The scale consists of nine items and one insight measure. Seven items assess the ability to engage in simple motor tasks: repetitive bimanual tapping (Item 1), go-no-go (Item 2), motor procedural learning (Item's 3-6), and head-hand test, which involves imitation of the examiner's movements to point to various locations on the head and face (Item 7). Of the remaining two items, one measures working memory and the other attentional control (Item 8 & 10). The additional measure (Item 9) assesses the subject's insight into how she performed on the other nine tasks administered. The items are scored on an interval scale ranging from failure (0) thorough to successful performance (3). The total BDS-2 score is the sum of individual scores. The reliability (Grigsby et al., 1992) and validity (Grigsby et al., 1998; Kaye et al., 1990) of this measure have been documented in subjects aged from 4 to 70 years. The BDS-2 was administered according to the BDS-2 scoring system. See Appendix A for test protocol.

Controlled Animal Fluency Test

In a similar fashion to verbal fluency, animal fluency tasks require the participant to use organisational searching to generate a specific category of words. In this study, an Australian developed and normed animal fluency test called the Controlled Animal Fluency Test (CAFT) was used (Monti, 1984; Tucker, Ewing & Ross, 1996). The test has three conditions, as follows: first, the participant is required to produce as many animal names as she can (*Animal Automatic*). Then the participant is required to order the animal kingdom by size, beginning by naming the smallest and then gradually

moving towards the largest animal. Finally, the participant is asked to go through the alphabet and say an animal name for each of the twenty-six letters.

The participant was instructed as follows:

1. **Animals**

"Tell me as many different animals as you can, in any order, and keep going until I say 'stop'."

2. **Animals by Size**

"I want you again to tell me as many different animals as you can but this time I want you to put them in order of their size; that is, I want you to tell me the smallest animal you can think of first, then one just a little bit bigger, then a little bigger again and so on, making sure that each one is bigger than the one before it. Don't get too big too quickly or you'll run out. Keep going until I say 'stop'."

3. **Animals by Alphabet**

"Again I want you to tell me as many different animals as you can, but this time I want you to order them according to the alphabet; that is, the first one is to begin with A, the next with B, then C and so on. Only one animal for each letter and keep going until I say 'stop'."

For each of the conditions, the participant was allowed 60 seconds to complete the task. Scores were devised by adding up the totals of each category, with repetitions and rule breaks being excluded from the total (Tucker et al., 1996).

The first task was an "automatic network" task, in which the participant was asked to list as many words as possible in a given category – where the category was a well established (closely associated) grouping for most people. This task was used to establish the participant's ability to perform a fluency task and her repertoire within each category.

The second and third tasks were "regulation" tasks in which the participant was again asked to list as many words as possible in a given category, but (a) the words were

now to be ordered according to a given rule and (b) the category was not usually a closely associated network, i.e. it involved active search.

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT) is a verbal fluency task that requires the individual to use a self-generated strategy to enable organised searching (Temple et al., 1996). Verbal fluency tasks involve speeded lexical production, the promotion of automatic lexical access, and reflect efficient lexical organisation (Dunn, Gomes & Sebastian, 1996). There are thought to be two components of verbal fluency tests: (1) the linguistic component associated with left cerebral hemisphere function and (2) the ideational component associated with frontal lobe function. In addition, there is a working memory component, as children must retrieve new words whilst remembering previously retrieved words to avoid repetitive responses (Watson, Balota & Sergent-Marshall, 2001). Verbal fluency tests tap a number of abilities thought to measure executive functioning: organised searching (Milner, 1964), self-monitoring, initiation, shifting and response inhibition (Mahone et al., 2002). Verbal fluency has been consistently associated with frontal lobe efficiency in adult populations (Borkowski, Benton & Spreen, 1967; Butler, Rorsman, Hill & Tuma, 1993; Jones-Gotman & Milner, 1977; Tucha, Smely & Lange, 1999). These studies particularly implicate anterior, left prefrontal regions (Elfgren and Risberg, 1998; Milner, 1964; Pendleton, Heaton, Lehrman & Hulihan, 1982). Activation has also been found in the supplementary motor cortex, anterior cingulate cortex and the cerebellum (Ravnkilde, Videbech, Rosenberg, Gjedde & Gade, 2002).

The verbal fluency test used in this study employed the letters 'F', 'A' and 'S', as described in Anderson et al. (1995). Each participant has to produce as many words as possible which begin with the target letter (F, A and S). The task has a time limit of 60 seconds for each letter, and within the time constraint, the individual has to search her vocabulary to find relevant items. The task has two rules that must be adhered to whilst actively searching: no words that begin with capital letters and no repeats of words.

The COWAT was administered and scored according to criteria outlined in Neuropsychological Assessment of the School Aged Child, which was developed, normed and standardised in Australia (Anderson et al., 1995).

Rey-Osterrieth Complex Figure

The RCF was also used to assess complex visual planning and organisation, commonly regarded as executive skills. An accurate reproduction of the RCF is thought to require intact executive functioning (Anderson, Anderson & Garth, 2001). The organisational aspects of the task are sensitive to bilateral frontal lobe compromise. Because of the complexity of the figure, the RCF has been successfully used to evaluate the ability to plan, organise and assemble complex information (Akshoomoff & Stiles, 1995a; Waber & Holmes, 1985). A haphazard, fragmented mode of response suggests poor planning (Lezak, 1995).

A measure of organisational ability was derived from the scoring system devised by Waber and Holmes (1985) as outlined in Anderson et al., (1995). The system is composed of five levels of organisation, with Level 1 being poor organisation and Level 5 reflecting excellent organisation. An organisational scoring system was used, in addition to the accuracy scores, as a way of measuring planning and perceptual skills, without the influence of motor and coordination problems (Anderson et al.). Organisational strategies are also significantly associated with the quality of recall. Efficient organisational strategies enable better recall than fragmented, piecemeal or haphazard strategies (Akshoomoff & Stiles, 1995b; Bennett-Levy, 1984). Hence, it is important to be cognisant of organisational strategy when assessing visual memory with the RCF (Anderson et al., 2001).

In this administration, children were provided with a blank sheet of white paper and four pencils of different colours. A stimulus card depicting a complex geometrical design was placed in front of the child. They were handed a pencil and instructed to copy the figure exactly as they saw it. If the child indicated that they had made a mistake, they were instructed to correct it, but they were not allowed to start again.

After the child had completed a section of the drawing, the examiner handed her a second pencil of a different colour. This procedure was repeated two more times, until all four colours had been used. By recording the order in which the colours were used, the examiner could later establish the organisational strategies employed by the child. After administration of the COWAT, the child was presented with another blank sheet of white paper and a single pencil and asked to redraw the design from memory. If the

child hesitated, or stated that she could not remember the figure, she was encouraged to draw the parts that she did recall. Thirty minutes later the child was asked to reproduce the figure from memory again. There was no forewarning of the recall trials. As outlined previously, the RCF was scored according to the criteria in Neuropsychological Assessment of the School Aged Child (Anderson et al., 1995).

Tower of London

The Tower of London (TOL) (Shallice, 1982) is a test of executive function, which requires goal directed behaviour, step by step planning and problem solving. The test identifies problems in the higher order planning aspects of executive function (Shallice), with lower-order cognitive skills thought to be less essential for successful task completion (Anderson et al., 1996). Shallice reports that the lower order skills required to perform the TOL, such as visuo-motor co-ordination, spatial processing and short-term memory have little impact on performance, therefore implying a central role for problem solving and planning skills (Anderson et al.). Planning and problem solving require the integration of a number of inter-related skills, including focused and sustained attention, selection of appropriate goals, generation and implementation of plans and strategies for the achievement of these goals, and the ability to utilise feedback for the modification of unsuccessful strategies (Anderson et al., 1996; Glosser & Goodglass, 1990; Levin, 1990; Mateer & Williams, 1991; Stuss & Benson, 1987; Walsh, 1978).

An Australian developed, normed and standardised paediatric version of Shallice's original test was used in the present study (Anderson et al., 1995; 1996). The test was administered by showing the child a wooden peg board with three sticks of graded height and three differently coloured balls (blue, green and red). The child was told that they would be asked to move the balls from a starting pattern (which remains constant) to make a new pattern on a stimulus card. The subject must rearrange coloured balls on three sticks to form a target pattern while being constrained by a series of rules. There are 12 items to complete with each item requiring more complex planning skills as the test proceeds. After completion of each item, the subject must then rearrange the balls back to form the initial starting pattern. Successful task accomplishment demands anticipation and forward planning of moves towards a final target goal. Scores recorded for this test include planning time, solution time and the number of attempts to the correct solution for each of the 12 items. The test was

administered and scored according to the method described by Anderson, et al. (1995).

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) assesses the ability to form abstract concepts, to shift and maintain set, and to utilise feedback information to change strategy formulation (Chelune & Baer, 1986; Heaton et al. 1993). It involves planning, organised searching, goal-orientated behaviour, and the ability to regulate impulsive responses. These skills are thought to be mediated by the prefrontal areas in the cortex (Luria, 1980). The test requires the participant to have intact working memory for successful completion.

The test consists of four stimulus cards placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses and the fourth with four blue circles. Subjects are given two decks of response cards, which have designs similar to the stimulus cards, varying in colour, geometric form and number. The subject is then instructed to match each of the cards in the decks to one of the four key cards and is given feedback each time whether she is right or wrong.

The subject is first required to sort to colour, with all other responses being deemed 'wrong'. Once the ten consecutive correct responses have been achieved, the required sorting principle changes without warning, to form: colour responses are now incorrect. After ten consecutive responses to form, the sorting principle changes shifts to number, and then back to colour once more. The above procedure continues until the person has successfully completed six sorting categories (colour, form, number, colour, form, number) or until all 128 cards have been placed. The WCST was administered according to Heaton et al. (1993). It was scored using the WCST: Scoring Program IBM Version 4 (Heaton, 1990).

Immediate Attention and Working Memory

Digit Span

The 'Digits Forward' and the 'Digits Backward' components of the *Digit Span* subtest from the WISC-III (Wechsler, 1992) were used in this study and scored according to

the WISC-III manual. Various authors consider this subtest to be a measure of auditory attention and working memory (See Baron, 2004). It has a test-retest reliability of 0.85, when digits forwards and backwards are combined.

'Digits Forward' requires the child to verbally repeat a series of digits increasing in length as read out by the examiner. The digits are presented at a rate of one digit per second. Digits Forward is regarded as a measure of immediate auditory memory span (Sattler, 1992). Performance depends on a short-term, phonologically based storage system (Vallar & Baddeley, 1984). It is also considered a measure of efficiency of attention (Baron, 2004). Digits Forward was also individually scored according to criteria outlined in Neuropsychological Assessment of the School Aged Child (Anderson et al., 1995). Digits Forward was used as a measure of the 'phonological loop' in Baddeley's model of working memory (Vallar & Baddeley, 1984).

'Digits Backward' requires the child to repeat a series of increasing strings of digits in the reverse order to the examiner. The digits are read out to the child at the rate of one digit per second. The reversed digit span requirement of storing a few numbers briefly while rearranging them mentally is an activity requiring effort which calls upon working memory (Banken, 1985). Digits Backward was used as a measure of working memory in the current study.

Block Span

Block Span (Milner, 1971) is a test of immediate memory for visual information. Information about the reliability and validity is not available despite its wide use in clinical and normal populations. It has been proven to be a useful test of immediate spatial span in paediatric populations (Orsini, 1994). An Australian variation of Milner's original Corsi block-tapping test was used in this investigation (Corsi, 1972). This Block Span version is part of a school-aged assessment battery for Australian children (Anderson et al., 1995).

In this administration, a board on which nine identical blocks has been fixed was placed before the child (Milner, 1971). The child was asked to tap blocks in a sequence of increasing length, immediately after demonstration by the examiner. Two different sequences were presented at each level of difficulty. The test commenced with a sequence of three blocks, and continued up to nine blocks, or until the child

could no longer recall either of the sequences. The test was ceased once an individual had failed both trials on a certain block sequence. The final score was calculated for the maximum number of blocks tapped in a correct sequence on at least one of the two presentations. Block Span was scored according to criteria outlined in Neuropsychological Assessment of the School Aged Child (Anderson et al.). Block Span was used as a measure of the 'visuo-spatial sketchpad' in Baddeley's model of working memory as it is thought to reflect the child's span for visuo-spatial information.

2.2.3 Australian Normative Samples

The Australian normative samples used in this study were sourced from research conducted by the University of Melbourne and the Royal Children's Hospital, Melbourne, Australia. Normative data from the published test protocol titled 'Neuropsychological Assessment of the School Aged Child' (Anderson et al., 1995) was used for comparison on the following tests: Block Span, Digit Span, Rey Osterrieth Complex Figure, Tower of London and Verbal Fluency Test (COWAT).

As the normative sample in Anderson et al.'s (1995) assessment battery only included children aged from 7-13 years, another normative sample was used for children aged between 14 to 16 years. Anderson, Anderson, Northam, Jacobs and Catroppa (2001) administered a range of executive tests to assess the development of executive functions in adolescence and, in the process, provided Australian normative data for commonly used neuropsychological tests. This normative data was used for comparison in the following tests: Digit Span, Rey Osterrieth Complex Figure, Tower of London and Verbal Fluency Test (COWAT). See Appendix B for Anderson et al. (2001) normative data.

The Anderson et al. (2001) normative sample consisted of 138 children (69 boys, 69 girls) aged 11.0 years to 17.11 years. The participants were recruited from mainstream primary and secondary schools. Schools included in the study were randomly selected from those in the Melbourne metropolitan area, Victoria, Australia. Once schools had agreed to participate, schools were then selected, on the basis of demographic characteristics, to obtain a sample representative of the general population (Anderson

et al.). Daniel's Scale of Occupational Prestige (1983) was used to determine the SES demographics of the sample.

All participants spoke English as their first language and had no history of brain damage, sensory deficit, neurological abnormality or developmental disability. Children requiring special educational assistance were excluded from the sample, and all participants had a FSIQ greater than or equal to 80 points.

Unpublished normative data was used for comparison on the Controlled Animal Fluency Test (Tucker et al., 1996). Schools included in the study were randomly selected from those in the Melbourne metropolitan area, Victoria, Australia. This data was collected from 231 age stratified male and female students aged between six and seventeen years. All participants had a FSIQ greater than or equal to 80 points. See Appendix C for CAFT normative data.

2.2.4 Socio-Emotional and Behavioural Functioning

Behavioural Assessment System for Children

Socio-emotional functioning was measured by the Behavioural Assessment System for Children (BASC). The BASC Self-Report of Personality (SRP) is an omnibus personality inventory consisting of statements that are responded to as *True* or *False*. The SRP was used for both children and adolescents in the current study. The SRP has forms for two age ranges: child (8-11 years) and adolescent (12-18 years). The forms for each age range overlap considerably in scales, in structure and in individual items (Reynolds & Kamphaus, 1992). Both forms have identical composite scores: School Maladjustment, Clinical Maladjustment, Personal Maladjustment and an overall composite score, the Emotions Symptoms Index (ESI).

The form for children (SRP-C) has 12 scales and that for adolescents (SRP-A) has 14 scales arranged in composites. The SRP can be interpreted in reference to national age group norms (General, Female, and Male) or to Clinical norms. Special indexes are incorporated to assess the validity of the child's responses: the *F* index, the *L* ("fake good") index for the SRP-A only, and the *V* index designed to detect invalid responses due to poor reading comprehension, failure to follow directions, or poor contact with reality (Reynolds & Kamphaus, 1992). See Appendix D for SRP Scale definitions.

The Parental Rating Scale (PRS) was designed as a complementary measure of a child's adaptive and problem solving behaviours in the school, home and community settings. The PRS contain descriptors of behaviours that the parent is asked to rate. It uses a four-choice response format ranging from *Never* to *Almost always*.

The PRS has a form for each of three age ranges: preschool (4-5 years), child (6-11 years) and adolescent (12-18 years). The age levels of the PRS have a generally similar content and structure. The PRS assesses clinical problems in the broad domains of externalising problems, such as aggression and hyperactivity; internalising problems, such as depression and anxiety; and an adaptive skills score which looks at leadership qualities and social skills. The PRS has national age norms (General, Female and Male) and Clinical norms. The female normative group for both the SRP and the PRS were used in this study. The PRS includes an *F* ("fake bad") index, which is designed to detect a negative response set on the part of the parent doing the rating. Critical items may be interpreted individually. See Appendix E for PRS Scale Definitions.

Social Cognition Questionnaire

The Social Cognition Questionnaire (SCQ) (Skuse et. al, 1997) was used to determine whether TS females who had a paternally derived X chromosome (X^p) had better social cognitive skills than those with a maternally derived X chromosome (X^m). The questionnaire was devised by Skuse et al. as a measurement tool to summarise the main features of behaviour in TS females. Through pilot interviews and observations, Skuse et al. concluded that $45,X^m$ females in particular lacked flexibility and responsiveness in social interactions. The scale consists of twelve items and gives a brief indication of any socially maladaptive behaviour. The questionnaire is completed by parents and they are asked to rate their child's behaviour. The items are scored on an interval scale ranging from 0 (not at all true) to 1 (quite or sometimes true) or to 2 (very or often true). The internal consistency for the set of 12 items in the questionnaire was a standardised item alpha of 0.94 (Skuse et al.). Where possible, the questionnaire was completed by the mothers of the TS females. If the mother was unable to complete the questionnaire, the father was then asked to do so. The SCQ is outlined in Appendix F.

2.3 PROCEDURE

The recruitment of participants for this study took place over a three year period, from January 1999 to March 2002. The paediatric TS sample was recruited as part of the greater NHMRC project on Turner's syndrome. As such, for each TS female who participated, it was required that one or both of her parents underwent genetic testing and neuropsychological assessment. If possible, siblings were also encouraged to participate in the neuropsychological testing only. In exceptional circumstances, blood was required to be taken from participating siblings to establish parental X origin. All of this information was outlined to parents before consent was obtained, hence they were aware of the familial nature of the investigation.

The sibling controls were also recruited as part of the greater NHMRC project on Turner's syndrome. All female siblings of TS participants who participated in the larger study were selected as controls if they were aged between 6 and 16 years of age.

A diverse source of referrals was sought to try and minimise recruitment bias. As mentioned previously, the sample was recruited from across three states in Australia: South Australia, Tasmania and Victoria. Names of potential participants were supplied by specialist children's hospitals, suburban and rural general practitioners, paediatric endocrinologists, paediatricians, genetic ascertainment databases and state TS support group listings. Most females in Victoria and Tasmania who had been found to have a karyotype consistent with TS upon genetic testing were listed on the genetic ascertainment database at the Murdoch Children's Research Institute. The participants from this source included children who were being medically managed in their local community by a general practitioner, as well as those who were being cared for within the hospital system by an endocrinologist or paediatrician. Informed consent was obtained from the treating doctor to contact the families by letter.

Each participant and her family (parent/guardian) received a letter of introduction describing the purpose and requirements of the project. The letter requested that if the family did not want to be contacted about the study, they should send back the letter of introduction. Two weeks after sending the letter, a phone call was made to further explain the study and to invite the family to participate. If the family agreed, an

appointment was scheduled for testing either in the Psychology Department of the RCH or MMC, the Department of Endocrinology at the Women's and Children's Hospital, or in the participant's home. When possible, families were encouraged to attend the hospital for assessment to assist in maintaining a controlled environment. However, as a number of families lived in rural or remote areas across the three states, home visits were commonplace. Families were reimbursed for all travelling costs.

At the time of recruitment, it was explained to parents that a state-wide study of individuals with TS was taking place, and that the aim was to obtain as wide a spectrum of participants as possible to provide a representative sample for research into the condition. This was stressed to try and avoid obtaining a skewed sample population, consisting only of TS children in need of psychological assessment due to learning and/or behavioural difficulties. Parents were informed that one of the aims of the greater NHMRC study was to determine whether TS females who inherited their X chromosome from their mother differed from those who inherited their X chromosome from their father on behavioural, cognitive, social and physical measures.

There was a wide variety of reasons why families declined to participate. A significant proportion of them were surrounding the genetic nature of the larger NHMRC study and these reasons will be outlined in the discussion. Other reasons for refusing to participate included the time involved (usually one full day for the whole family), not wanting to bring up the past again and not wanting for their children to have to undergo blood extraction. Although exact data was not available, it is estimated that across the three states in Australia, approximately 50% of families approached declined to participate.

As part of the larger NHMRC project, comprehensive developmental, medical and psychiatric histories were obtained from family members at the time of assessment and verified with medical records. Physical measurements, a venous blood sample and fingerprints were also taken. The use of growth hormone and oestrogen therapy was recorded from parental and medical unit records.

Karyotype information was recorded from previous medical records as established at diagnosis, and was updated from recent chromosomal analysis completed as part of the larger NHMRC project. Parental origin of the X chromosome was determined by

the geneticists as part of the larger NHMRC project. Chromosomal analysis from blood lymphocytes was performed using standard as well as Fluorescence In Situ Hybridization (FISH) techniques in the Cytogenetics laboratory, Murdoch Children's Research Institute, Melbourne. DNA was extracted from venous blood samples of TS participants, siblings and their parent(s). Nineteen X-linked polymorphic microsatellite markers were scored in order to establish parental origin of the X chromosome. Polymerase Chain Reaction (PCR) and electrophoretic separations were performed at the Australian Genome Research Facility in Melbourne. Investigators were blind to both karyotype and X-origin at the time of assessment.

However, as the project was part of a larger NHMRC study that required DNA analysis, there were many families who were concerned about the potential ramifications.

Testing took place individually in a quiet, well-lit room for a duration of approximately three hours with scheduled breaks every hour. The break periods were to ensure fatigue was minimised. Clear articulation, increased volume and repetition where appropriate enabled all children with mild hearing difficulties to complete the psychological assessment to their full potential. Children were told to ask for further clarification if the instructions were not heard clearly. If children did not ask, but the examiner suspected poor auditory comprehension, the instructions were repeated. Although several parents reported that their child with TS had some degree of hearing difficulty, these difficulties were not detectable at the time of clinical assessment.

All participants with TS were administered a battery of neuropsychological tests. The test battery was administered in the following order: WISC-III, RCF Copy, COWAT, RCF 3' Delay, CAFT, Block Span, BDS-2, TOL, RCF 30' Delay, WCST. Children who were aged between 8 and 16 years also completed the BASC SRP. The 15 female sibling controls received a selected test battery due to time constraints. The control test battery was administered in the following order: WISC-III, RCF Copy, BDS-2, RCF 3' Delay, WCST, RCF 30' Delay. The mother of the TS female was asked to complete the BASC-PRS and the SCQ. In exceptional circumstances, the father completed these questionnaires. All tests were administered according to the procedure manuals. Verbal feedback was given on the day of assessment. At the conclusion of data collection, participants received a summary of their results in the form of a psychological report,

complete with recommendations. Referrals were provided on request for the person with TS, and her family.

3. RESULTS

3.1 DATA ANALYSIS

The SPSS Version 11.5 (2002) computer package was used to perform the statistical analyses. An overall alpha level of 0.05 was set for all statistical tests. Single sample t-tests were used to compare performances of TS individuals with normative samples. Where multiple comparisons were made, Bonferroni adjustments were used to control for Type 1 error inflation. Multivariate analysis of covariance was used to compare TS individuals and sibling controls on cognitive measures. Multivariate analyses of variance were used in the X –origin and karyotype analyses. Pillai's Trace criterion was used for multivariate analyses as it is considered to have acceptable power and to be the most robust statistic against violations of assumptions (Coakes & Steed, 2003). Scatter plots of socio-emotional and cognitive data revealed nonlinear monotonically increasing and decreasing relationships among variables. Spearman's rank order correlation was therefore used as a non-parametric alternative to the parametric bivariate correlation for analysing socio-emotional data. Reported significance levels were as given in SPSS output, to three decimal places.

3.2 DEMOGRAPHIC VARIABLES

The mean age for participants with TS was 12 years 1 month (range 6.00 – 16.11 years). Thirty-one participants were of British and Irish decent (75.6%), three of Greek origin (7.3%), two of Italian origin (4.9%), one of French origin (2.4%), one of Croatian origin (2.4%), one of Polish origin (2.4%), one of Russian origin (2.4%) and one from the Asia-Pacific region (2.4%). All TS participants spoke English as their first language. The mean socio-economic status rating for TS families was 4.16 (S.D. 1.51) (Daniel, 1983). Eight were left handed (19.5%), with the remaining thirty-three (80.5%) being right handed.

Participants with TS included 21 with 45,X karyotype, 8 with mosaicism (45,X/46,XX; 45,X/47XXX), 10 with deletions (46,X,i(Xq); 45,X/46,X,i(Xq), one with 45,X/46XY and one with a ring chromosome (See Table 3).

TABLE 3.

KARYOTYPE CLASSIFICATION BY PERCENTAGE (N=41)

Karyotype	*Percentage %*
Monosomy [45,X]	51.22
Mosaicism [45,X/46XX; 45,X/47XXX]	19.51
Deletions[46,X,i(Xq); 45,X/46,X,i(Xq)]	24.39
45,X/46XY	2.44
Ring chromosome	2.44

The origin of the X chromosome was unable to be determined for one participant hence she was excluded from the X-origin analyses. Of the remaining 40 participants, 29 had a maternally derived X chromosome, with the other 11 being of paternal derivation (See Table 4). These figures are consistent with those reported in Skuse et al. (1997) and are reflective of the general rate of X chromosome inheritance in the greater TS population.

TABLE 4.

PARENTAL ORIGIN OF X CHROMOSOME (N=40)

Origin of X Chromosome	*N*	*Percentage %*
Maternal [X^m]	29	72.50
Paternal [X^p]	11	27.50

From all peripheral blood cells analysed, the percentage with X-monosomy ranged from 10-100%. Half of the participants had 100% of their cells with X-monosomy (45,X). All girls with TS had short stature and 35 of the total 41 participants (85.4%) were currently receiving or had previously received growth hormone injections. Seven participants (17.1%) were receiving oestrogen replacement therapy at the time of testing. Eleven participants (26.8%) had required resuscitation at birth, or had undergone a traumatic delivery.

3.3 COGNITIVE FUNCTIONING

3.3.1 Data Screening

Prior to analysis, the cognitive and group variables were examined through SPSS data screening procedures for missing values, and the assumptions of univariate and multivariate analyses. Assumptions of normality were assessed via the Kolmogorov-Smirnov and Sharpiro-Wilks statistics, skewness and kurtosis values. All cognitive measures did not significantly differ from the normal distribution except for PIQ, which was positively skewed. However, as it is well documented that TS females consistently have lower PIQ scores than the normal population, and as transformation would have made interpretation difficult, this variable was not transformed. Results of evaluation of assumptions of normality, homogeneity of variance-covariance matrices, linearity, and multicollinearity were otherwise satisfactory.

3.3.2 Comparisons with Normative Data

Wechsler Intelligence Scale for Children (3rd Edition) (Australian Adaptation).

The Bonferroni alpha level for this analysis was 0.008.

Single sample t-tests were conducted to compare intellectual quotients (IQ) of TS females with population norms. A two-tailed t-test was used to determine whether differences existed between the Verbal and Performance IQ measures of the WISC-III for TS females.

Table 5 displays the mean IQ and Index scores for TS females and Figure 3 displays the distribution of IQ in the TS sample. Mean scores for *Full Scale IQ* [t(40)= -4.288, $p < 0.000$], *Performance IQ* [t(40)= -5.273, p=0.000] and *Perceptual Organisation* [t(40)= -4.563, p=0.000] were all significantly lower than the population mean of 100. Scores on measures of *Verbal IQ*, *Verbal Comprehension* and *Freedom from Distractibility Indices* did not significantly differ from the population mean [t(40)=-1.966, p=0.056; t(40)= -1.036, p=.306; t(40)= -2.490, p=0.017]. TS participants had significantly lower *Performance IQ* scores than *Verbal IQ* scores [t(40)= 3.302, p=0.002]. Thus in this study, TS individuals had stronger verbal than non-verbal intellectual abilities.

TABLE 5.

WISC III: MEAN IQ SCORES IN THE TS SAMPLE

IQ MEASURE[a]	*N*	*MEAN*	*SD*
Full Scale IQ	41	91.98	11.98
Verbal IQ	41	96.07	12.79
Performance IQ	41	89.27	13.03
Verbal Comprehension	41	97.98	12.51
Perceptual Organisation	41	91.02	12.60
Freedom from Distractibility	41	93.71	16.18

[a]Population Mean =100 SD=15

FIGURE 3.

WISC-III: IQ DISTRIBUTION IN THE TS SAMPLE

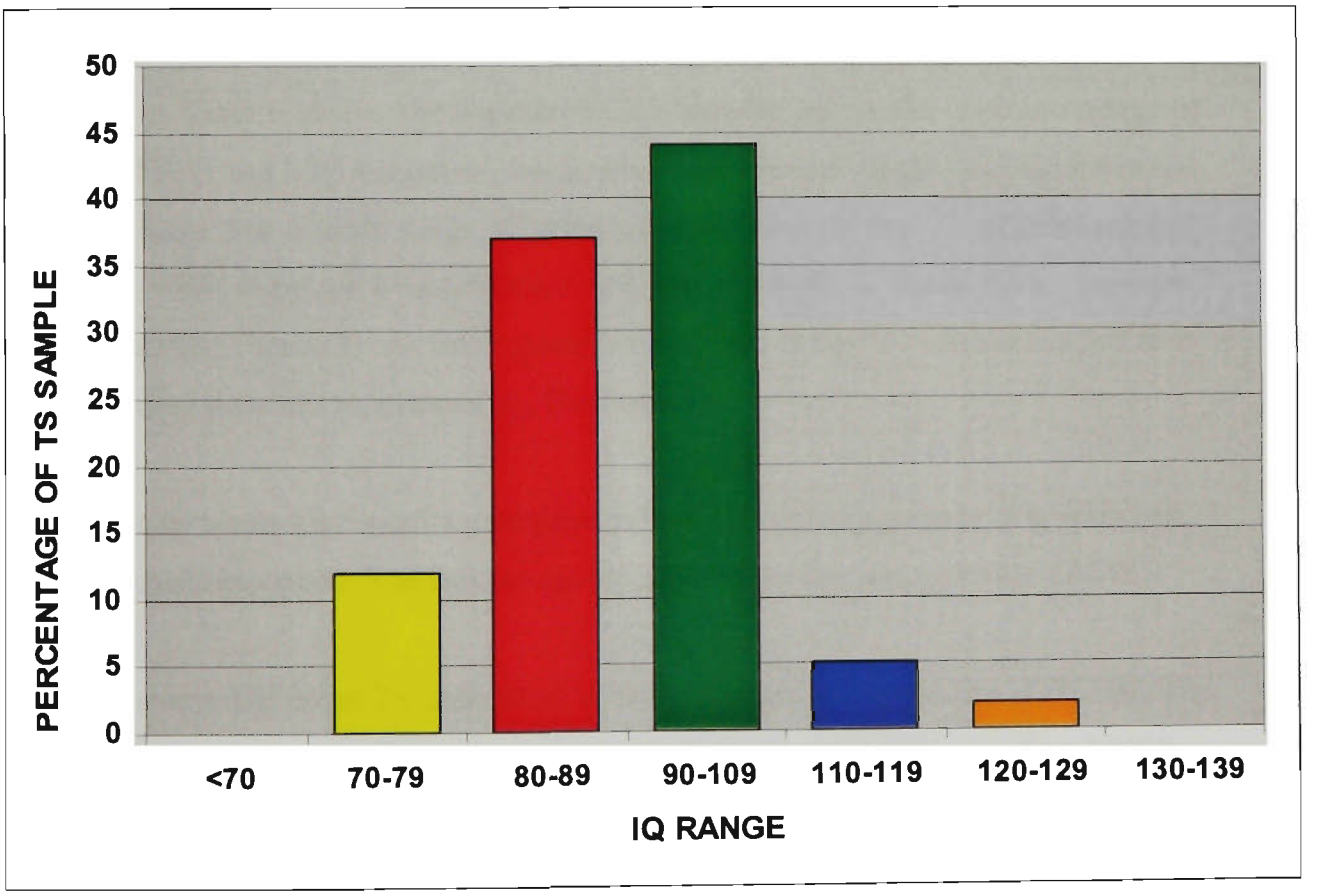


TABLE 6.

WISC-III: IQ DISTRIBUTION IN THE TS SAMPLE

IQ RANGE	*FSIQ (N)*	*FSIQ (%)*	*VIQ (N)*	*VIQ (%)*	*PIQ (N)*	*PIQ (%)*
Mild I.D.	0	0	1	2	1	2
Borderline	5	12	3	7	6	15
Low Average	15	37	7	17	18	44
Average	18	44	21	52	13	32
High Average	2	5	9	22	1	2
Superior	1	2	0	0	2	5
Very Superior	0	0	0	0	0	0
Total	41	100	41	100	41	100

As shown in Table 6 above, the majority of TS females fell in the 'average' range of ability on FSIQ and VIQ measures, but in the 'low average' range on PIQ measures. However, there was a wide range of intellectual abilities in the TS sample, ranging from girls with 'borderline' intellectual abilities through to those with 'superior' intelligence (See Figure 3). As participants with a FSIQ below 70 were excluded from the study, they were not represented in this Figure 3.

Single sample t-tests were used to compare individual subtest scores on the WISC-III with the population mean. The Bonferroni alpha level for this analysis was 0.0045.

Table 7 displays the mean TS individual subtest standard scores on the WISC-III. The WISC-III subtests scores of *Arithmetic* [t(40)= -4.536, p=0.000], *Coding* [t(40)= -4.476, p= 0.000], *Picture Arrangement* [t(40)= -5.889, p=0.000] and *Picture Completion* [t(40)= -4.370 p=0.000] were all significantly below the mean.

TABLE 7.

WISC III: MEAN SUBTEST STANDARD SCORES IN THE TS SAMPLE

SUBTEST[a]	N	MEAN	SD
Picture Completion	41	8.15	2.72
Information	41	9.83	2.65
Coding	41	7.85	3.07
Similarities	41	9.44	2.75
Picture Arrangement	41	7.66	2.55
Arithmetic	41	7.85	3.03
Block Design	41	9.00	3.29
Vocabulary	41	9.22	2.71
Object Assembly	41	8.85	2.68
Comprehension	41	9.76	3.36
Digit Span	41	9.37	3.32

[a]Population Mean=10 SD=3

Figure 4 is illustrative of the differences in general intellectual ability between TS participants and their immediate relatives. The graph is based on data collected as part of the larger NHMRC project. The present sample of TS girls (N=41) was compared on measures of IQ with participating adult parents, and male and female siblings between the ages of 6 and 16 years. While the FSIQ scores of family members fell largely within the average range of ability, fathers, mothers and siblings had significantly higher FSIQs than those of TS individuals [$F(3,132)=14.766$, $p=0.000$].

FIGURE 4.

FULL SCALE, VERBAL AND PERFORMANCE IQ SCORES:

TS GIRLS AND FAMILY MEMBERS

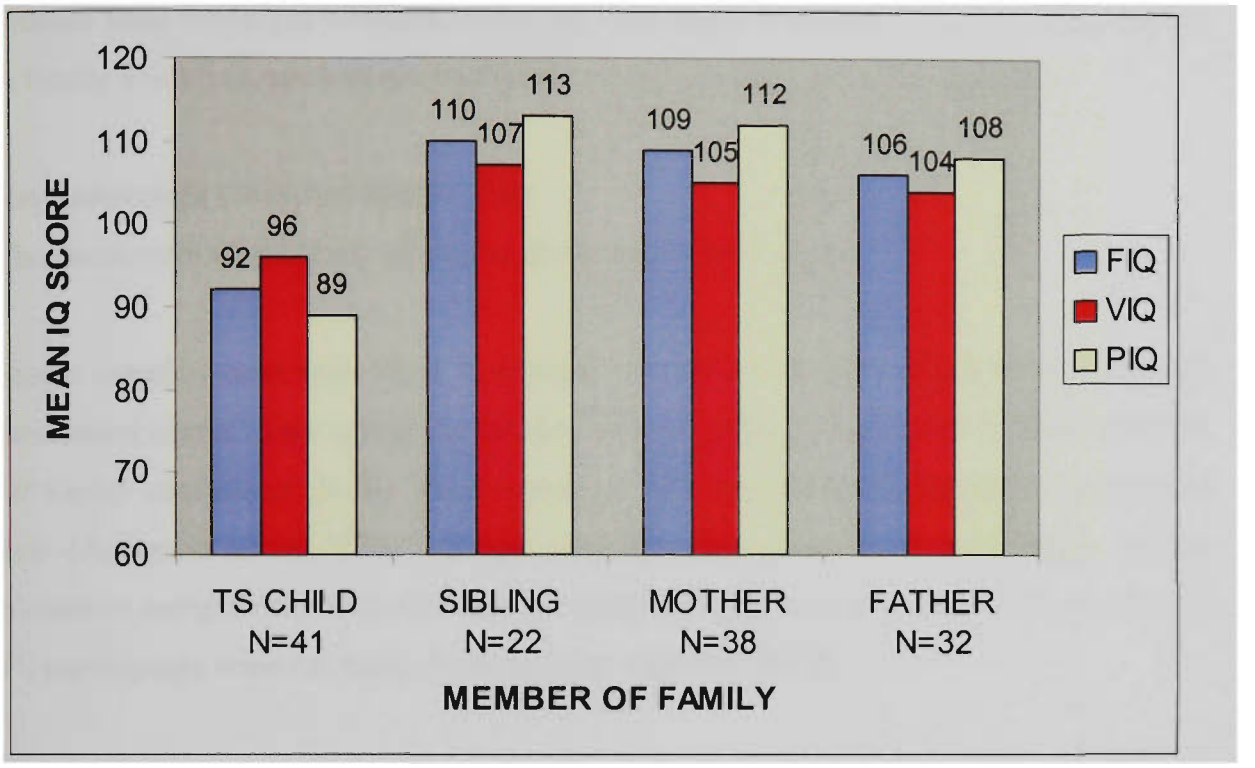
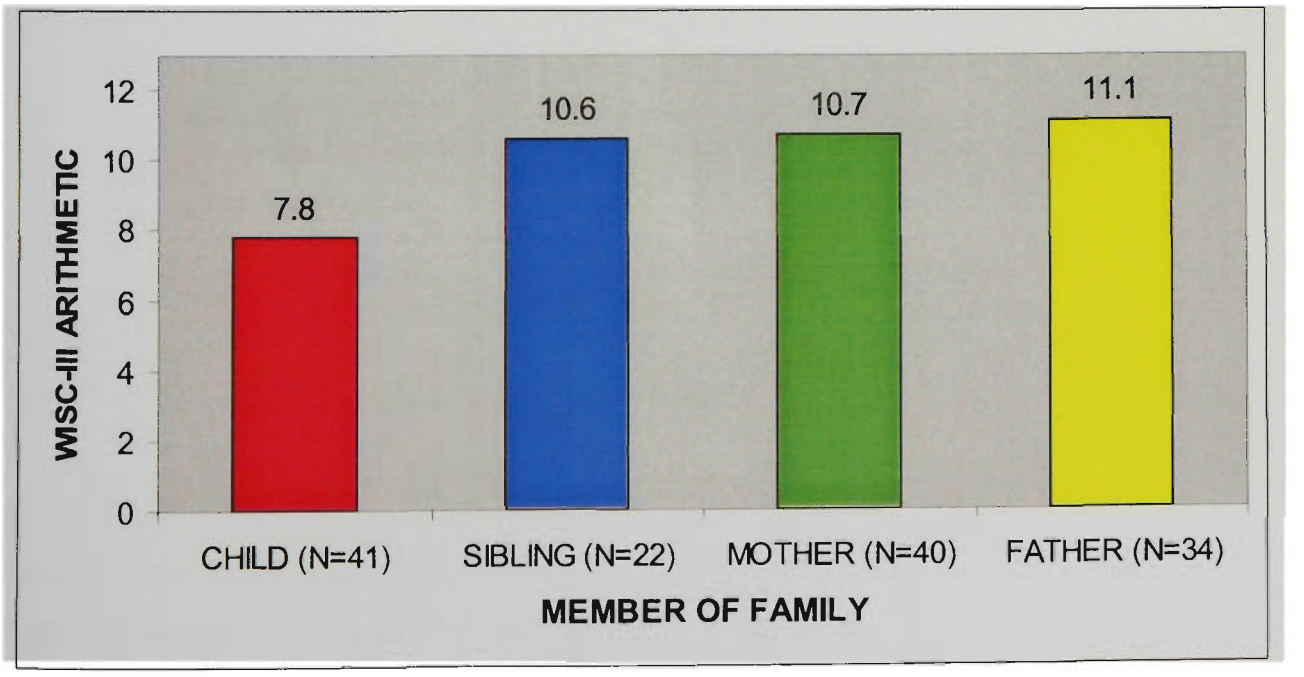


FIGURE 5.

WISC III: MEAN ARITHMETIC STANDARD SCORES WITHIN FAMILIES



As displayed in Table 7, TS individuals' lowest verbal subtest score was *Arithmetic*. For comparison, Figure 5 illustrates the difference in arithmetical ability of TS females and their family members (The parental and sibling data for Figures 3.1 and 3.2 were sourced from the larger NHMRC study on 'The genetic features of Turner's syndrome: A family study'; (Loesch et al., In Press).

Rey Osterrieth Complex Figure Test

The Bonferroni alpha level for this analysis was 0.0167.

Single sample t-tests were used to compare results of TS individuals with Australian population norms. Raw scores on the *Rey Accuracy* (Rey Copy), *Rey 3' Delay* and *Rey 30' Delay* conditions (0-36) were converted to Z-scores using Australian normative data (Anderson et al., 2001). Single sample t-tests were then undertaken. As the normative sample only included data for children aged 7-16 years olds, two 6 year old TS participants were excluded from the Rey analyses (N=39).

Participants with TS had significantly lower *Rey Accuracy* [t(38)= -6.098, p= 0.000], *Rey 3' Delay* [t(38)= -8.294, p=0.000] and *Rey 30' Delay* [t(38)= -8.058, p=0.000] scores on the Rey-Osterrieth Complex Figure Test than the Australian normative sample. See summary Table 8 below for means and standard deviations of all cognitive measures.

TABLE 8.

COGNITIVE MEASURES IN TS: MEANS AND STANDARD DEVIATIONS

COGNITIVE DOMAIN	*N*	*MEAN*	*SD*	*p Value*	*Signif. **
IMMEDIATE ATTENTION AND WORKING MEMORY					
Digit Span Forwards$_a$	39	-0.38	1.23	0.061	NS
Block Span$_a$	39	-1.03	1.13	0.000	S
VISUO-SPATIAL					
Rey Accuracy$_a$	39	-1.28	1.31	0.000	S
VISUAL MEMORY					
Rey 3' Delay$_a$	39	-1.73	1.30	0.000	S
Rey 30' Delay$_a$	39	-1.49	1.15	0.000	S
EXECUTIVE					
Tower of London$_b$	39	88.57	19.83	0.001	S
Tower of London: *Failed Attempts*$_a$	39	-0.39	1.27	0.062	N
CAFT$_a$					
CAFT- Automatic	41	-0.20	0.55	0.029	NS
CAFT - Size Order	41	-0.35	0.77	0.006	S
CAFT - Alphabet	41	-0.07	1.10	0.699	NS
COWAT$_a$ FAS Total:	39	-0.26	0.98	0.105	NS
WCST$_b$ WCST: Errors	41	104.15	18.50	0.159	NS
WCST:Perseverative Responses	41	101.24	17.12	0.644	NS
WCST: Perseverative Errors	41	103.56	19.47	0.249	NS
WCST: Nonperseverative Errors	41	104.12	16.76	0.123	NS
WCST: Conceptual Responses	41	103.14	19.39	0.305	NS

$_a$ Z Score $_b$ Standard Score. Population Mean = 100, SD = 15

*Significance with Bonferroni corrections

Tower of London

The Bonferroni alpha level for this analysis was 0.025

Single sample t-tests were used to compare results of TS females on the *Tower of London* with Australian population norms (Anderson et al., 1995; 2001). Raw summary scores were converted to standard scores using the method outlined in Anderson et al. (1996). The population standard scores have a mean of 100 and a standard deviation of 15. In addition, the number of failed attempts on the TOL was included in the analyses. The number of failed attempts was converted to Z Scores

using Australian normative data (Anderson et al., 1995; 2001). Single sample t-tests were then undertaken. As the normative sample only included data for children aged 7-16 years olds, two 6 year old TS participants were excluded from the Tower analyses (N=39).

Participants with TS had significantly lower standard scores on the *Tower of London* [t(38)= -3.599, p=0.001] than the Australian normative sample. The number of failed attempts was not significant [t(38)=-1.924, p=0.062]. This suggests that the TS sample were slow to complete the items on the TOL, hence they had difficulties reaching the correct solution within the sixty second time limit. However, they did not make an excessive number of failed attempts.

Digits Span Forwards and Block Span

The Bonferroni alpha level for this analysis was 0.025

Raw scores were converted to Z scores using Australian normative data (Anderson et al., 2001). As the normative sample only included data for children aged 7-16 years olds, two 6 year old TS participants were excluded from the Digit Span Forwards and Block Span analyses (N=39).

A single sample t-test was used to compare results of TS females on the *Digit Span Forwards* and *Block Span* tests with Australian population norms. TS females had significantly lower scores on the *Block Span* test [t(38)= -5.697, p =0.000] than did the Australian normative comparison group. No significant difference was found on the *Digit Span Forwards* test [t(38)= -1.928, p=0.061] indicating that TS individuals forward digit span length did not differ from the population norm.

Controlled Oral Word Association Test and the Controlled Animal Fluency Test

The Bonferroni alpha level for this analysis was 0.0125.

Single sample t-tests were used to compare results of TS females on the Controlled Oral Word Association Test (COWAT) and the Controlled Animal Fluency Test (CAFT) with Australian population norms. Raw scores were converted to Z scores using the Australian normative data. The number of words (*COWAT*), number of animals (*CAFT Automatic*), animals in size order (*CAFT Size*) and animals by alphabet (*CAFT Alphabet*) were examined. Performances on the *CAFT Size* [t(40)= -2.932, p= 0.006] condition were significantly lower than that of the Australian normative sample. No significant differences were found for *COWAT* [t(38)= -1.659, p=0.105], *CAFT Automatic* [t(40)= -2.266, p=0.029] or the *CAFT Alphabet* [t(40)=-0.390, p=0.699] conditions.

Wisconsin Card Sorting Test

The Bonferroni alpha level for this analysis was 0.01.

Single sample t-tests were used to compare the performance of TS females on the WCST with normative data (Heaton et al., 1993). TS females were compared on *Percent Errors, Percent Perseverative Responses, Percent Perserverative Errors, Percent Nonperseverative Errors and Conceptual Level Responses*. TS females did not significantly differ from the normative sample on any of the WCST measures. [t(40)=1.435, p=0.159; t(40)=0.465, p=0.644; t(40)=1.171, p=0.249; t(40)=1.574, p=0.123; t(40)=1.039, p=0.305].

3.3.3 Comparisons with Sibling Controls

Multivariate analysis of variance (MANOVA) was used to compare a select subsample of 15 TS individuals with 15 female sibling controls on a variety of cognitive measures. As previously outlined in the method, this control sample consisted of all of the available female siblings of TS participants between the ages of 6 and 16 years. There was no significant difference in age between the two groups [t(1,28)=1.070, p=0.294]. As each TS child lived with her sister, the children were matched for SES.

As illustrated in Table 9, girls with TS had significantly lower FSIQs than sibling controls [F(6,23)=6.510, p=0.000]. There was a statistically significant difference between TS females and sibling controls on all measures of IQ.

TABLE 9.

MEAN IQ MEASURES: TS AND SIBLING CONTROLS

IQ MEASURE	*TS MEAN (N=15)*	*CONTROL MEAN (N=15)*	*p Value*	*Signif.*
FSIQ	91.73 (9.63)	110.13 (12.70)	0.000	s
VIQ	95.40 (13.07)	107.13 (12.77)	0.019	s
PIQ	89.93 (9.99)	110.93 (10.67)	0.000	s
VC	96.93 (13.29)	107.07 (12.22)	0.038	s
PO	93.27 (11.56)	111.93 (12.13)	0.000	s
FD	93.33 (17.37)	107.40 (16.47)	0.031	s

The TS and control participants in the above group were compared on a selection of cognitive tests: *FSIQ*, *Arithmetic* (WISC-III), *Rey Accuracy*, *3' Delay*, *30' Delay* and *Organisational Score*, *BDS-2*, *Digits Forwards* and the *WCST: Percentage Errors* and *Categories Completed*. A significant main effect was found for *Group* (TS, Control) on measures of cognitive functioning [F(10,19)= 2.917, p=0.021]. See Table 10 for display of individual test means, standard deviations, F and P values.

TABLE 10.

TS VS CONTROLS: COGNITIVE MEASURES

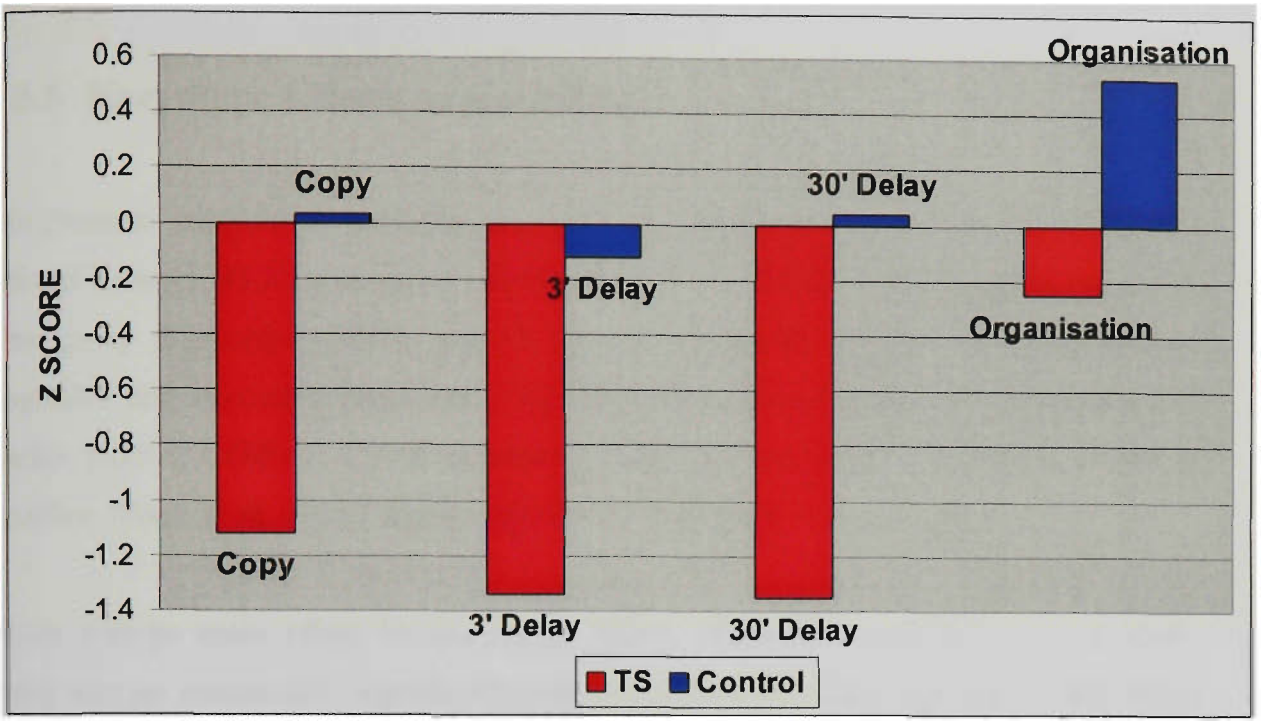
TEST	*TS MEAN (N=15)*	*CONTROL MEAN (N=15)*	*F Statistic*	*p Value*
FSIQ	91.73 (9.63)	110.13 (12.70)	19.979	0.000**
Arithmetic	7.40 (2.97))	11.27 (3.24)	11.606	0.002**
Rey Accuracy$_b$	-1.12 (1.25)	0.03 (1.07)	7.356	0.011*
Rey 3' Delay$_b$	-1.34 (1.33)	-0.12 (1.28)	6.631	0.016*
Rey 30' Delay$_b$	-1.35 (1.25)	0.04 (1.05)	10.897	0.003**
Rey Organisation$_b$	-0.25 (1.00)	0.53 (1.03)	4.383	0.045*
BDS-2$_a$	18.93 (4.79)	21.27 (5.96)	1.398	0.247
Digit Forwards$_b$	-0.51 (1.31)	-0.52 (1.44)	2.536	0.122
WCST: Errors$_c$	100.27 (20.54)	114.33 (13.91)	4.823	0.037*
WCST: Cat. Completed$_a$	4.67 (1.76)	6.00 (0.00)	8.615	0.007**

a: Raw Score b: Z Score c: Standard Score *p<0.05 **p<0.01

As shown in Table 10, the control group did significantly better than their TS siblings on the following measures: *FSIQ*, *Arithmetic, Rey Accuracy*, *Rey 3' Delay*, *Rey 30' Delay*, *Rey Organisational Score* and *WCST Categories Completed.* No differences were found on the *BDS-2* or *Digit Forwards*. Figure 6 below illustrates the differences between TS and controls on the Rey Complex Figure.

FIGURE 6.

REY COMPLEX FIGURE: TS vs. SIBLING CONTROLS



3.3.4 X-Origin and Cognition: Comparisons of X^m and X^p

Multivariate analysis of variance was used to investigate any group differences in TS individuals resulting from the origin of their X chromosome. The group *X Origin* had two levels: X^m and X^p (X^m=maternally inherited X chromosome and X^p= paternally inherited X chromosome). As genetic testing was unable to determine the X chromosome origin for one of the TS girls, the total number of TS participants in this analysis was 40. The following dependent variables were included in the MANOVA analysis: *VIQ, PIQ, Rey Accuracy, Rey 3' Delay, Rey 30' Delay, BDS-2, COWAT, CAFT Automatic, CAFT Size and CAFT Alphabet, Tower of London, Block Span, WCST Errors and WCST Categories Completed.* There was no main effect for *X Origin* on tests of cognitive functioning [F(14, 24)=0.709, p=0.745]. There was no significant difference in cognitive performance between X^m and X^p TS individuals.

As the above TS group consisted of both X monosomy and non 45,X individuals, another X origin analysis was undertaken for TS females with X monosomy (45,X) alone. The same variables were included in the MANOVA as outlined above. There was no main effect for *X Origin* (45,X) on tests of cognitive functioning [F(14, 5)=

0.669, p=0.746]. There was no significant difference in cognitive performance between monosomic (45,X) X^m and X^p TS individuals.

3.3.5 Karyotype Effects on Cognition

Multivariate analysis of variance was used to establish whether group differences existed between 45,X monosomy and non 45,X TS individuals on cognitive measures. The group *Karyotype (*45,X, non-45,X) was compared on the following general cognitive and executive measures: *VIQ, PIQ, Rey Accuracy, Rey 3" Delay, Rey 30' Delay, BDS-2, COWAT, CAFT Automatic, CAFT Size and CAFT Alphabet, Tower of London, Block Span, WCST Errors and WCST Categories Completed.*

There was no main effect for *Karyotype* [F(14, 24)=0.295, p=0.990]. In this study, there was no statistically significant relationship between karyotype and cognition in TS females.

3.4 SOCIO-EMOTIONAL AND BEHAVIOURAL FUNCTIONING

3.4.1 Data Screening

Prior to analysis, the BASC, SCQ and group variables were examined through SPSS data screening procedures for missing values, and the assumptions of univariate and multivariate analyses. Assumptions of normality were assessed via the Kolmogorov-Smirnov and Sharpiro-Wilks statistics, skewness and kurtosis values. Results of evaluation of assumptions of normality, homogeneity of variance-covariance matrices, linearity, and multicollinearity were generally satisfactory. Scatter plots of BASC, SCQ and cognitive data revealed nonlinear monotonically increasing and decreasing relationships among variables. Therefore, Spearman rank order correlations were used to examine the relationships between socio-emotional, behavioural and cognitive measures.

3.4.2 Comparisons with Normative Data

Behavioural Assessment Scale for Children (BASC)

BASC Parent Rating Scales

The Bonferroni alpha level for this analysis was 0.003.

One sample t-tests were used to compare the Parent Rating Scales (PRS) of TS individuals on the BASC with published female normative data (Reynolds & Kamphaus, 1992). Each PRS was computer scored and the raw scores were converted to standard T score prior to analyses. The PRS has three forms at three age levels: preschool (4-5 years), child (6-11 years) and adolescent (aged 12-18 years). In this study, the child and adolescent PRS were used and the data was summated across the two age ranges, as the forms are similar in content and structure (Reynolds & Kamphaus).

As outlined previously, the BASC PRF provides T scores for a variety of clinical scales, adaptive scales and composite scores. The clinical scales measure maladaptive behaviour. High scores on these scales represent negative or undesirable characteristics. The adaptive scales measure positive behaviours. High scores on these scales represent positive or desirable characteristics. The composite scores are helpful for summarising performance and for making broad conclusions regarding different types of maladaptive and adaptive behaviour. They represent behaviour dimensions that are distinct but not independent and measure problem behaviours that often occur together rather than individually. Table 11 below outlines the mean standard T scores on the clinical, adaptive and composite measures of the PRS. See Table 12 for scale and composite score classification and Appendix E for PRS Scale definitions and cut off levels of individual items.

All forty-one parents of the TS participants completed a PRS. Thirty-nine report forms were completed by the mother, while the other two were completed by the father. All BASC PRS variables were included in the analyses.

TABLE 11.

BASC PARENT RATING SCALE: MEAN T SCORES

SCALE[a]	N	MEAN	SD	p Value	Signif.*
CLINICAL					
Hyperactivity	41	55.73	14.00	0.012	N
Aggression	41	51.00	12.51	0.612	N
Conduct Problems	41	51.32	13.37	0.532	N
Anxiety	41	51.49	8.70	0.280	N
Depression	41	51.02	10.58	0.539	N
Somatization	41	52.32	10.37	0.160	N
Atypicality	41	54.76	11.41	0.011	N
Withdrawal	41	50.27	8.14	0.834	N
Attention Problems	41	60.32	11.38	0.000	S
ADAPTIVE					
Social Skills	41	48.37	10.00	0.302	N
Leadership	41	44.93	8.72	0.001	S
COMPOSITE					
Externalising Problems	41	53.12	13.13	0.136	N
Internalising Problems	41	52.05	9.30	0.166	N
Behavioural Symptoms Index	41	55.68	11.99	0.004	N
Adaptive Skills	41	46.44	9.41	0.020	N

[a] Population Mean = 50 SD = 10 * Significance with Bonferroni corrections

TS individuals had significantly different scores on the behavioural measures *Attention* [t(40)=5.806, p=0.000] and *Leadership* [t(40)=-3.723, p=0.001], as compared to the female normative population. TS females were rated by their parents as having higher levels of attentional problems than would be expected in the general female population. They also reported that their daughters did not possess the same leadership qualities as other females of the same age. No other parental report measures reached significance due to the stringent Bonferroni alpha level of <0.003; however, *Adaptive Skills* [t(40)=-2.424, p=0.020], *Atypicality* [t(40)=2.670, p=0.011], the *Behavioural Problems Composite* [t(40)=3.034, p=0.004] and *Hyperactivity* [t(40)=2.621, p=0.012] approached statistical significance, as can be seen in Table 11 above.

TABLE 12.

BASC: SCALE AND COMPOSITE SCORE CLASSIFICATION

Classification		
Adaptive Scales	**Clinical Scales**	**T-Score Range**
Very High	Clinically Significant	70 and above
High	At-Risk	60-69
Average	Average	41-59
At-Risk	Low	31-40
Clinically Significant	Very Low	30 and below

Figures 7, 8 and 9 below illustrates the percentage of the TS sample that fell into the 'Clinically Significant' or 'At-Risk' categories as reported by their parents on the clinical scales on the PRF. On the BASC, the term 'At Risk' indicates the presence of significant problems that, while requiring treatment, may not be severe enough to warrant a formal diagnosis. Alternatively, a score in the 'At-Risk' range may signify potential or developing problems that need to be monitored carefully. Scores in the 'Clinically Significant' range denote a high level of maladaptive behaviour (Reynolds & Kamphaus, 1992).

FIGURE 7.

BASC PARENT RATING SCALE: CLINICAL SCALES

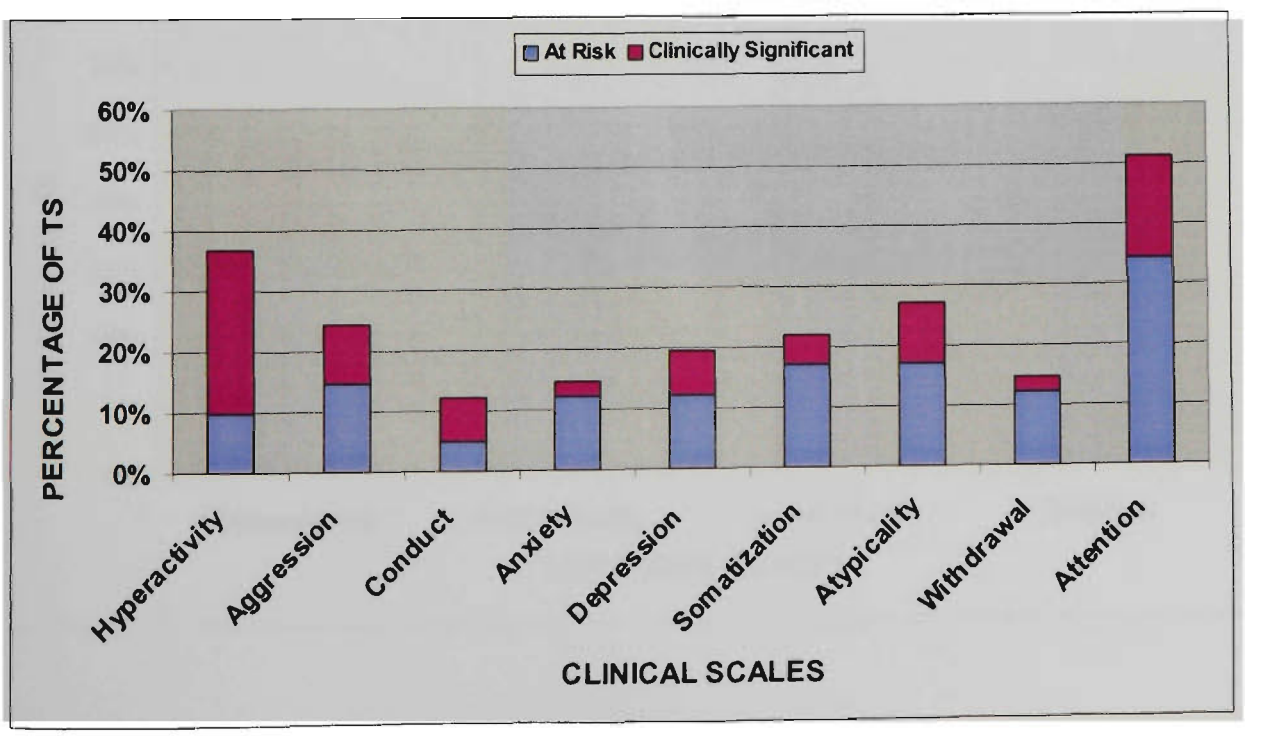


FIGURE 8.

BASC PARENT RATING SCALE: ADAPTIVE SCALES

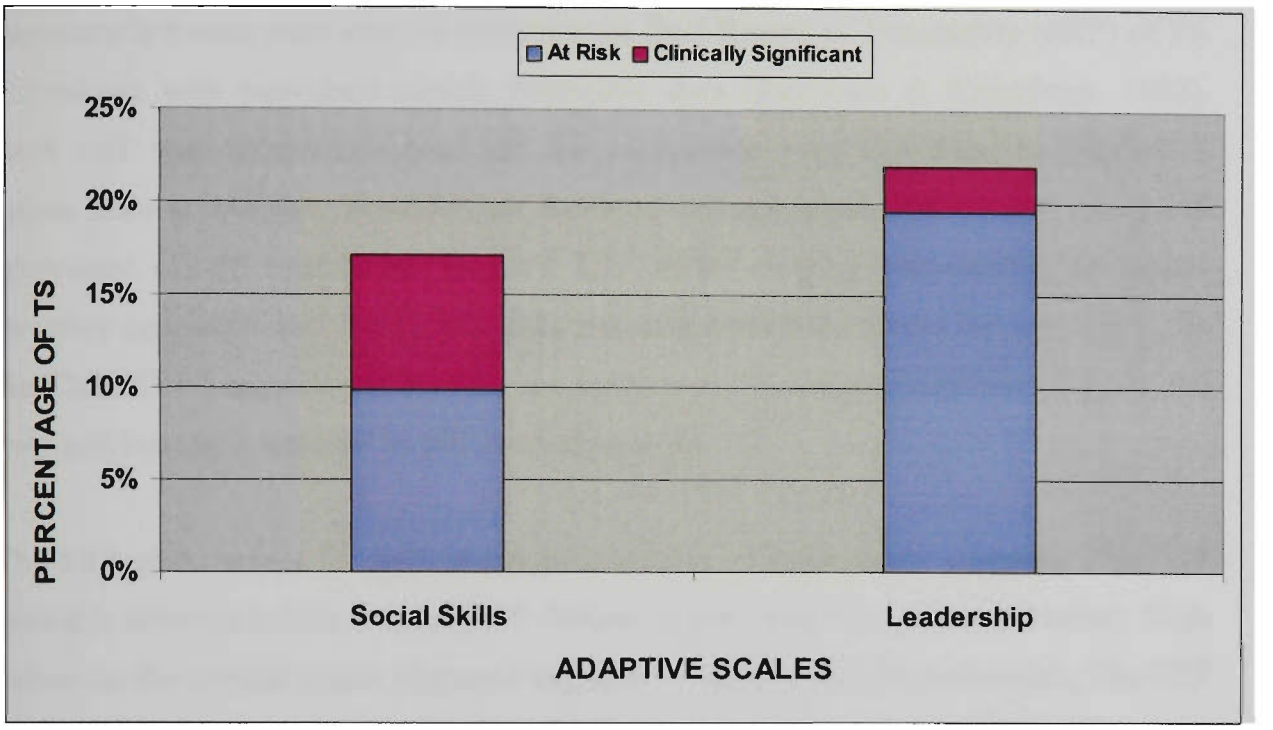
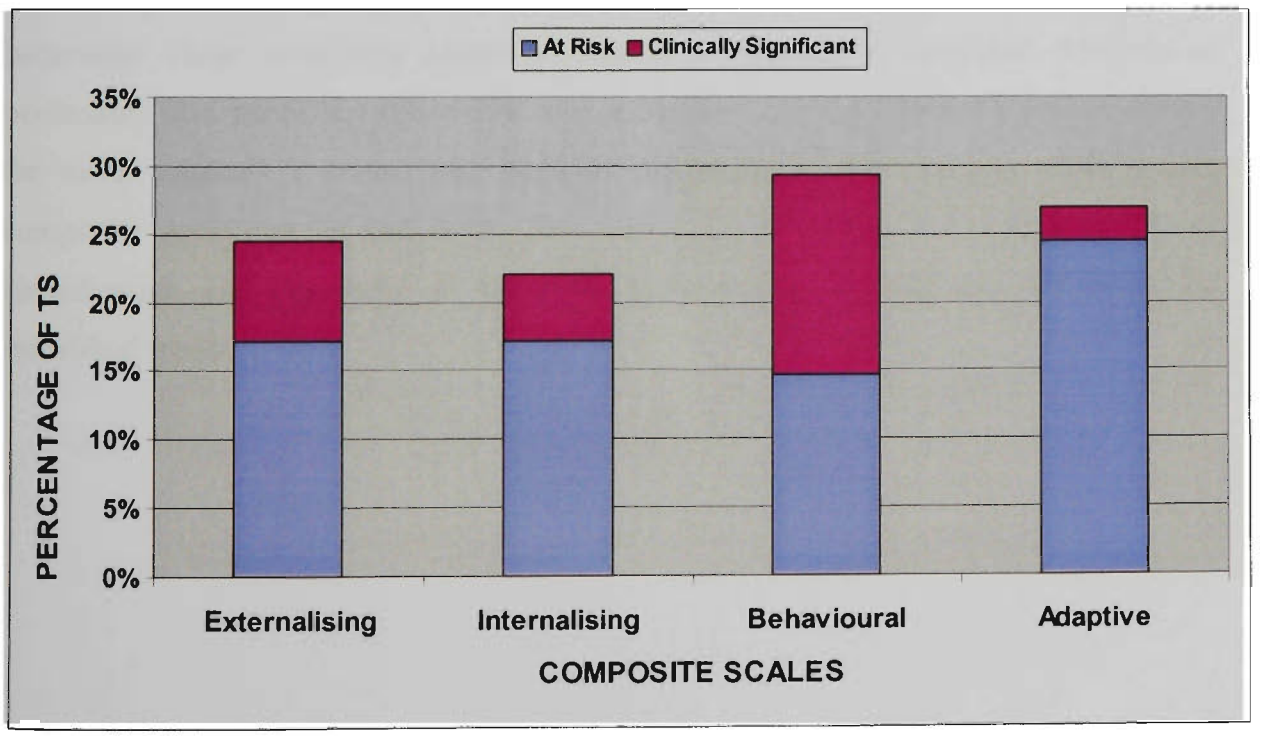


FIGURE 9.

BASC PARENT RATING SCALE: COMPOSITE SCALES



BASC Child Self Report Form

The Bonferroni alpha level for this analysis was 0.003.

One-sample t-tests were used to compare the Self-Report of Personality (SRP) of TS individuals with published female normative data (Reynolds & Kamphaus, 1992). Each SRP was computer scored and the raw scores were converted to standard T scores prior to analysis. The SRP has forms at two age levels: child (8-11 years) and adolescent (12-18 years). As the two SRP scales overlap considerably in scales, structure and individual items, this data was also summated across the age levels. As the Child SRP begins at age 8 years, the number of TS children who were 8 years and over and therefore included in this analysis was 36.

The SRP gives scores for individuals in a number of behavioural domains. The SRP provides information on a variety of clinical scales, measuring maladjustment. High scores on the clinical scales represent negative or undesirable characteristics. The SRP also provides information on a variety of adaptive sales measuring positive adjustment. On the adaptive scales, high scores represent positive or desirable characteristics. And, in a similar fashion to the PRF, the SRP provides composite scores, which are helpful for making broad conclusions regarding different types of adaptive and maladaptive behaviour. These composite scores provide good indications of global problems in personality and behaviour (Reynolds and Kamphaus, 1992). Table 13 below outlines the mean standard T scores and standard deviations on the clinical, adaptive and composite measures of the SRP. See Table 12 for scale and composite score classification and Appendix D for SRP Scale definitions and cut off levels for individual items.

TABLE 13.

BASC SELF-REPORT OF PERSONALITY: MEAN T SCORES

SCALE[a]	N	MEAN	SD	p Value
CLINICAL				
Attitude to School	36	48.22	10.65	0.324
Attitude to Teachers	36	47.89	7.60	0.104
Atypicality	36	46.50	9.43	0.032
Locus of Control	36	47.75	9.33	0.157
Social Stress	36	49.83	11.39	0.931
Anxiety	36	48.47	10.48	0.388
Depression	36	52.36	10.87	0.201
Sense of Inadequacy	36	50.33	10.15	0.845
ADAPTIVE				
Relations with Parents	36	50.61	10.90	0.739
Interpersonal Relations	36	44.19	17.17	0.050
Self-Esteem	36	46.28	9.63	0.026
Self-Reliance	36	46.94	13.39	0.180
COMPOSITE				
School Maladjustment	36	47.42	8.90	0.090
Clinical Maladjustment	36	47.83	9.70	0.189
Personal Adjustment	36	46.17	13.36	0.094
Emotional Symptoms Index	36	52.11	12.49	0.318

[a]Population Mean = 50 SD = 10

As shown in Figure 11, greater than 35% of TS girls fell within the 'Clinically Significant' or 'At Risk' range on measures of *Self-Esteem* [t(35)= -2.319, p=0.026]. TS girls also reported poorer *Interpersonal Relations* [t(35)=-2.028, p=0.05] and lower levels of *Atypicality* [t(35)= -2.227, p=0.032] than the female normative sample. Due to the stringent Bonferroni level, these results only approached clinical significance. No other behavioural variables reached a significance level of 0.05 or below. See figures 10 to 12 for illustration of the BASC Child Self Report.

FIGURE 10.

BASC SELF-REPORT OF PERSONALITY: CLINICAL SCALES

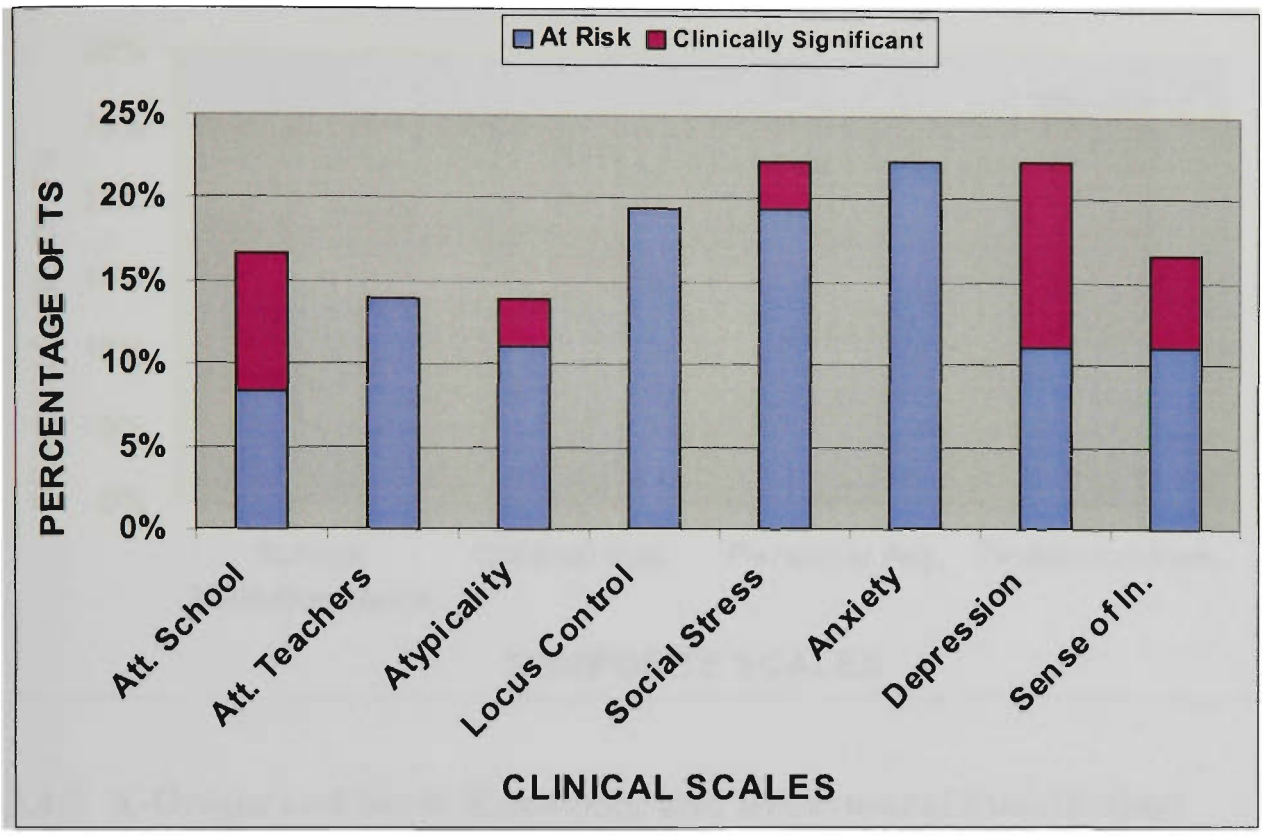


FIGURE 11.

BASC SELF-REPORT OF PERSONALITY: ADAPTIVE SCALES

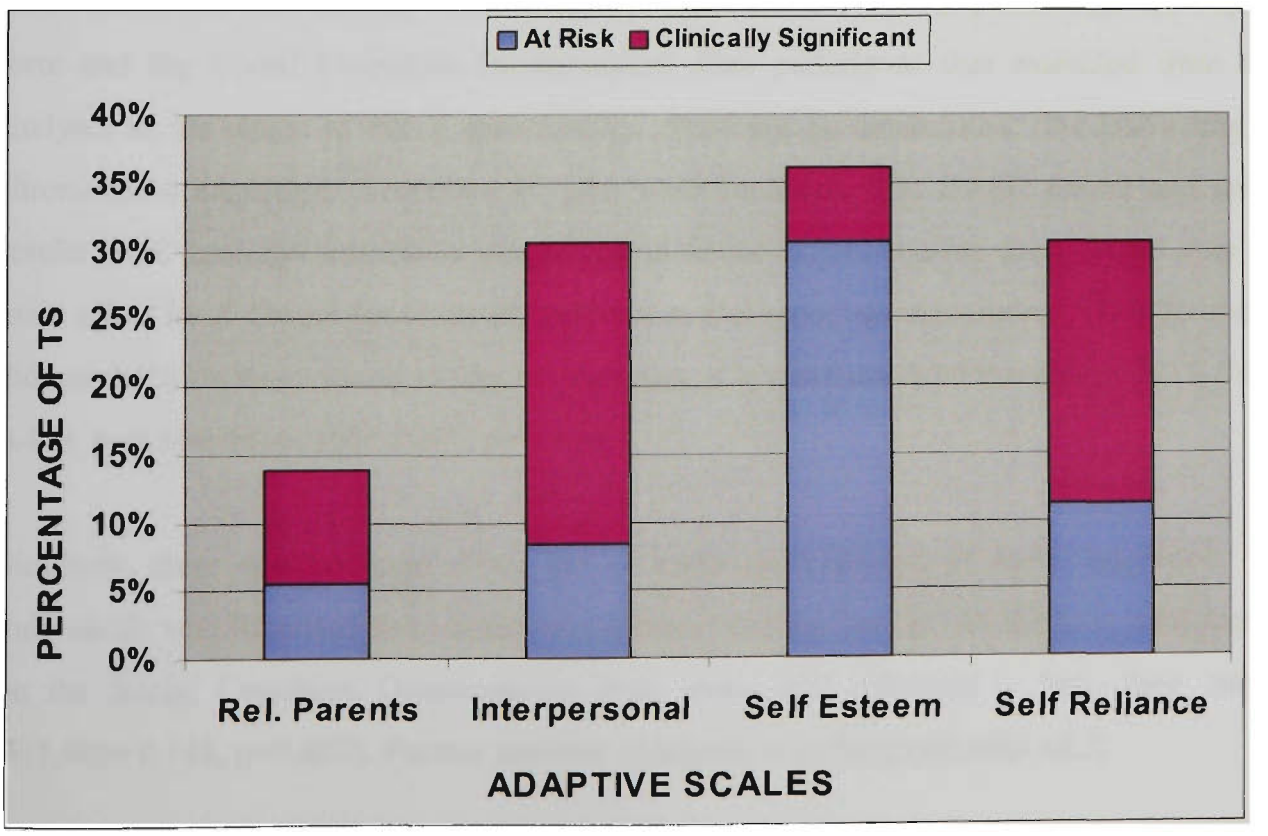
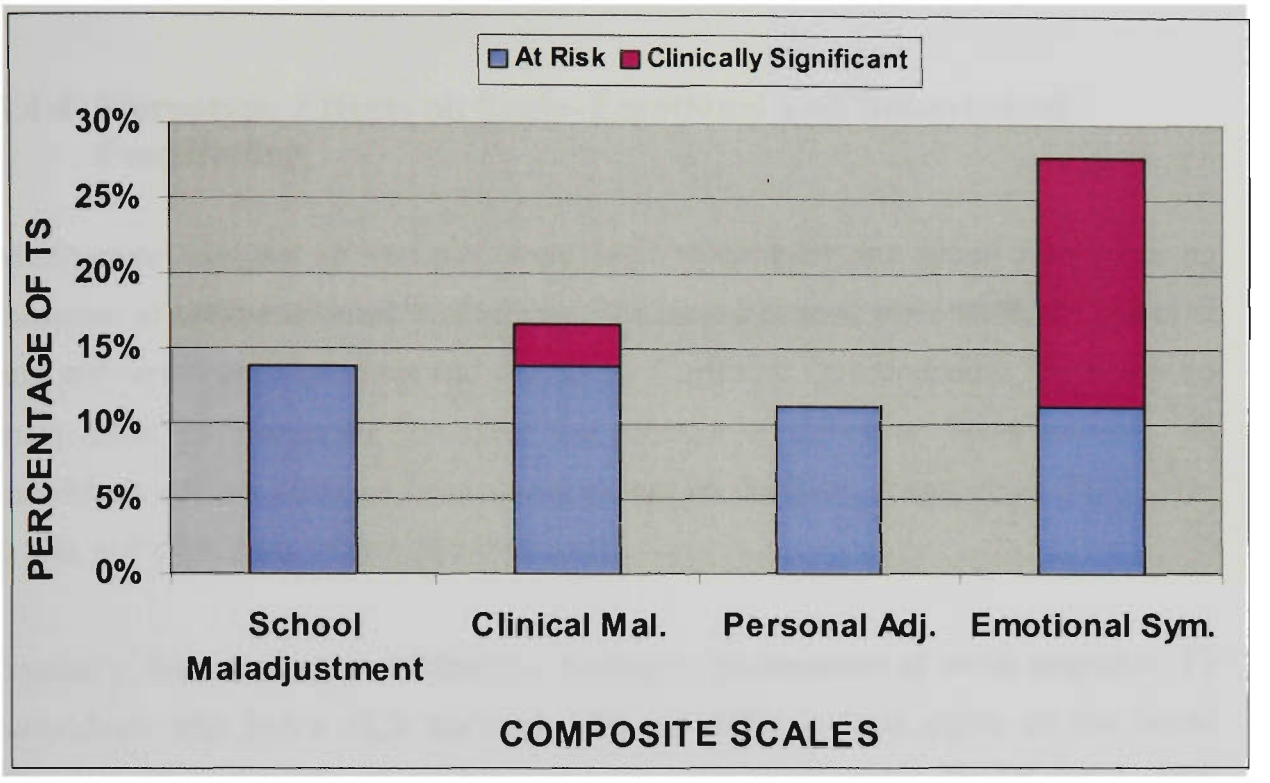


FIGURE 12.

BASC SELF-REPORT OF PERSONALITY: COMPOSITE SCALES



3.4.3 X-Origin and Socio-Emotional and Behavioural Functioning: Comparisons of X^m And X^p

Multivariate analyses of variance were used to compare the group *X Origin* on measures of socio-emotional functioning. These measures included the BASC parent and self-report form and the Social Cognition Questionnaire. One participant was excluded from the analyses as the origin of her X chromosome could not be determined. She had a ring X chromosome karyotype. Therefore 40 girls were included. The BASC parent and child results were analysed separately due to the different questionnaires used. There was no main effect for *X-Origin* for either the parental or self-report questionnaires. TS individuals did not differ on behavioural ratings on the basis of X chromosome inheritance [$F(15, 24)= 0.449$, $p=0.944$; $F(16, 19)= 1.207$, $p=0.344$].

Similarly, there was no main effect for *X-Origin* on measures of social cognition. TS individuals who inherited their chromosome from their mother did not differ in total scores on the Social Cognition Questionnaire from those who inherited it from their father [$F(1,40)= 0.148$, $p=0.863$]. Further analysis restricted to participants with 45,X

monosomy (X^m=15, X^p=5) did not reveal a main effect for X-origin [F(1, 18) = 0.086, p=0.773].

3.4.4 Karyotype Effects on Socio-Emotional and Behavioural Functioning

Multivariate analyses of variance were used to compare the group *Karyotype* on measures of socio-emotional functioning. The measures used were the BASC parental and self-report questionnaires and the Social Cognition Questionnaire. There was no main effect for *Karyotype* for either the parental or self-report questionnaires. TS individuals did not differ on behavioural ratings on the basis of karyotype [F(15, 24)= 0.890, p=0.583; F(16, 19)= 1.181, p=0.361].

Similarly, there was no main effect for *Karyotype* on measures of social cognition. TS individuals who had a 45,X karyotype did not differ in total scores on the Social Cognition Questionnaire from those who were not monosomic for TS [F(15, 24)= 0.879, p=0.557]. The TS individual's levels of social and emotional adjustment did not differ between 45,X monosomy and non 45,X monosomy conditions.

3.4.5 Cognition, Socio-Emotional and Behavioural Functioning

Spearman rank order correlations were used to examine the relationships between the cognitive, socio-emotional and behavioural variables in the TS population. A probability level of $p < 0.01$ was assumed to ensure against the increased risk of Type 1 statistical error. The BASC data obtained from the PRS and SRP questionnaires were again analysed separately.

As two of the BASC PRS variables were found to deviate significantly from normal in the analyses undertaken in Section 3.4.1, these variables were chosen for further examination. The variables *Attention Problems* and *Leadership* were correlated with the BASC, SCQ and previously examined cognitive variables reported in Section 3.3.2. *Hyperactivity* was also selected, as it approached statistical significance ($p < 0.012$) and was a commonly reported complaint by parents of TS girls.

The variable *Attention Problems* was significantly negatively correlated with scores on *FSIQ, VIQ, VC, FD, Arithmetic, BDS-2* and the *COWAT.* TS individuals who were reported to demonstrate high levels of inattention performed more poorly on tests of intelligence, arithmetic, and selected executive measures. See Appendix G for correlation matrices.

The variable *Attention Problems* was significantly positively correlated with the *SCQ.* TS individuals with attention difficulties scored higher on the SCQ, suggesting poorer social cognition. (*Note:* Low scores on the SCQ are suggestive of well-developed social cognition, high scores reflect poor social cognition).

The variable *Attention Problems* was significantly positively correlated with the following BASC PRS variables: *Hyperactivity, Depression, Atypicality, Behaviour Problems, Externalizing Problems, Aggression Problems* and *Conduct Problems. Attention Problems* was significantly negatively correlated with *Adaptive Skills* and *Leadership,* suggesting that TS children with attention problems have poorer adaptive skills and demonstrate reduced capacity for leadership. There were no significant associations between *Attention Problems* and BASC Child SRP variables.

High scores of the variable *Leadership* were significantly positively correlated with intelligence scores on the following WISC-III IQ measures: *FSIQ, VIQ, PIQ, VC,* and *PO. Leadership* was also positively correlated with scores on *Rey Figure Copy.* There was a significant statistical association between strong leadership skills and higher intelligence.

Leadership was negatively correlated with scores on the *SCQ.* TS females who were reported to have stronger *Leadership* skills had lower scores on the *SCQ,* suggesting better social adjustment.

Leadership had significant negative correlations with the BASC PRS variable *Behaviour Problems.* There was also a significant correlation between *Leadership* and the BASC Child SRP variable *Attitude to School.* So, TS girls who were rated by their parents as having good leadership skills had fewer behavioural problems, and a more positive attitude towards schooling.

Leadership was positively correlated with *Social Skills, Adaptive Skills* and *Adaptability.* Stronger leadership skills were positively associated with greater social skills and the ability to adjust flexibility to changes in routine.

Hyperactivity was negatively correlated with WISC-III attentional index, *Freedom from Distractibility (FD)*, but it did not correlate with any other IQ measure. There was a significant association between high levels of hyperactive behaviour and poor performance on cognitive tasks measuring distractibility. There were also negative correlations between *Hyperactivity* and the *BDS-2*, *SCQ* and *WCST: Perseverative Errors.* High levels of hyperactivity negatively affected performances on motor inhibition and working memory tasks and on social cognition measures. Hyperactive girls were also more likely to make perseverative errors on the WCST.

Hyperactivity was positively associated with the following BASC PRS variables: Depression, Externalising Problems, Aggression, and Behaviour Problems. Girls that were reported to have high levels of hyperactivity were more likely to suffer from depression and display a range of behaviour problems. There were no significant associations between *Hyperactivity* and BASC Child SRP variables.

The BASC Child SRP variable *Self Esteem* was the closest to approaching significance in the analyses undertaken in Section 3.4.1 (p= 0.026, Bonferroni corrected alpha = 0.003). This variable was chosen for further examination. *Self Esteem* was correlated with the BASC, SCQ and the previously examined cognitive variables reported in Section 3.3.2.

Self Esteem did not significantly correlate with any cognitive variables or the SCQ.

Self Esteem was negatively correlated with the following BASC SRP variables: *Attitude to Teachers, Locus of Control, Social Stress, Anxiety, Depression, School Maladjustment, Clinical Maladjustment* and *Emotional Symptoms Index. Self Esteem* also negatively correlated with the BASC PRS variable *Anxiety*. Girls with TS who reported lower levels of self esteem had a poorer attitude towards their teachers, an external locus of control, higher levels of social stress, higher levels of anxiety and depression and poorer clinical, school and emotional adjustment.

Self Esteem was positively correlated with the following BASC SRP variables: *Relations with Parents, Interpersonal Relations* and *Personal Adjustment.* Girls who had higher levels of self-esteem had stronger relationships with their parents, better interpersonal relations, more friends and higher levels of personal adjustment.

3.5 ILLUSTRATIVE CASE STUDIES

3.5.1 Case Study 1

'Kate'

Age: 11 years, 11 months

Background

Kate was born following a normal vaginal delivery with no perinatal complications. She weighed 2.9 kg. No lymphedema of the hands or feet was noted. She sat at 9 months, crawled at 13 months, walked at 22 months and spoke her first words at 12 months. Phrases were spoken at 21 months. Toilet training occurred at 30 months. Her gross motor milestones were normal. No behavioural problems were noted. During her early development she experienced frequent episodes of otitis media and had PE tubes (ear tubes) inserted at 15 months. Grommets were inserted at age 3 years. Kate had speech therapy in her preschool years to improve her articulation. Some balance and co-ordination problems were noted. Otherwise her early development was unremarkable.

She was diagnosed with TS when aged 6 years with a small distal deletion of the short arm of one X chromosome (karyotype 46,X deletion, (X) (p22.13 p22.32). All of her cells had this deletion. The deletion arose from the X chromosome inherited from her father. She presented with short stature and an increased carrying angle of her arms but no other physical stigmata were noted. Investigations revealed ovarian dysgenesis with an absence of renal and cardiac abnormalities. She began growth hormone treatment aged seven years.

Psychological assessment at aged 5 years revealed 'superior' verbal intellectual abilities (95%ile) and 'low average' nonverbal intellectual abilities (21%ile). Her Full Scale IQ fell within the 'high average' range.

During her primary school years, Kate had weekly maths tutoring. She made good progress at primary school and developed sound literacy skills. Her numeracy skills had significantly improved with tutoring assistance, but they remained below age expectation. Kate's teachers reported that she was a shy and somewhat anxious child who got teased at school. She required assistance in the classroom with writing as her handwriting was slow and laborious.

In her last year of primary school, Kate's teachers reported that she had specific learning and behavioural difficulties, which they thought would negatively impact on her ability to make a successful transition from primary to secondary school without specialist assistance. They reported that Kate had significant difficulties keeping up with the written work provided, organising her schoolwork and her daily routine, remembering to bring appropriate provisions to class and arriving at the appropriate lesson locations on time. Her teachers commented that she was a polite and conscientious child, who was simply unable to cope with the multiple complex demands of higher schooling. The school raised alternatives to mainstream education, with either the possibility of Kate attending a special needs school or alternating between the two school environments. Kate's mother was very distressed about the suggestion of specialist schooling and could not understand why this was suggested, considering her child had previously been of 'high average' intellect.

Current Assessment

At the time of assessment, Kate was eleven years and eleven months. She was in Grade 6 at a private school. Kate had two younger sisters, aged 8 and 6, with whom she attended school. She was then living with her mother, as her parents had separated a year earlier. Both parents were educated professionals and were working at the time of assessment. Kate's mother and her two sisters were also assessed as part of the NHMRC project.

Her mother reported that Kate experienced difficulties with orientation. One example of her poor orientation skills included getting lost on the way from one building to another in the school grounds. She demonstrated difficulties with reading simple maps, and found it difficult to navigate her way in a familiar hospital clinic setting, although she had visited the same clinic every three months for several years.

Her mother also outlined problems with forward thinking, organisation and planning. She believed Kate had difficulties organising her belongings for school, and was constantly forgetting to bring the necessary items. She was slow in getting ready for school and could not co-ordinate the various tasks necessary to be ready on time. She would frequently lose personal items and forget to tell her mother about upcoming events, such as school excursions. She had difficulty making friends, as she was sometimes oblivious to social cues, and her social interactions were somewhat awkward and immature. She was a shy child who was anxious about her scholastic ability.

To try and compensate for her disorganisation, Kate's mother ensured that her home routine was highly structured. She reported that a large daily wall planner was used at home to assist Kate with her day-to-day schedule planning. She assisted Kate with her activities of daily living by prioritising which tasks were the most important and breaking the tasks down into small manageable steps.

Kate presented as a quiet, attractive girl with short stature. Her walking was somewhat clumsy in style. She was very anxious on assessment and was concerned about her performance. Her speech was clear, but she did have a lisp with some words. Her handwriting was slow. She enjoyed art and maths but commented that she 'was not very good at them'. Neuropsychological test results are shown in Table 14.

TABLE 14.

KATE: NEUROPSYCHOLOGICAL TEST RESULTS

WISC- III	Raw Score	Standard Score	Percentile
Full Scale IQ	92	95	37
Performance IQ	42	90	25
Verbal IQ	50	100	50
Verbal Comprehension Index	43	104	61
Perceptual Organisation Index	38	97	42
Freedom from Distractibility Index	15	87	19
Picture Completion	23	12	75
Information	16	10	50
Coding	32	4	2
Similarities	18	11	63
Picture Arrangement	18	5	5
Arithmetic	15	7	16
Block Design	48	12	75
Vocabulary	36	12	75
Object Assembly	26	9	37
Comprehension	23	10	50
Digit Span	12	8	25
Rey Complex Figure Test			
Copy	24	NA	16
3' Delay	4.5	NA	0.4
30' Delay	2.5	NA	0.3
Organisational Score	Level 1	NA	4
Behavioural Dyscontrol Scale	18	NA	NA
Wisconsin Card Sorting Test			
Errors (%)	47	81	10
Perseverative Responses (%)	31	81	10
Perseverative Errors (%)	26	81	10
Nonperseverative Errors (%)	21	86	18
Conceptual Level Responses (%)	38	80	9
Categories Completed	2	NA	6-10

Tower of London	Raw Score	Standard Score	Percentile
Raw Score	54	NA	2
Standard Score	NA	68	2
Correct Items	8	NA	0.3
Failed Attempts	8	NA	66
Planning Time	53	NA	27
Controlled Animal Fluency Test			
Automatic	12	NA	14
Size Order	7	NA	21
Alphabet	2	NA	2
Rule Breaks	5	NA	NA
Repetitions	1	NA	NA
Block Span			
Forwards	4	NA	2
Backwards	2	NA	NA
Digit Span			
Forwards (number of digits consistently recalled)	4	NA	2
Backwards	3	NA	12

Kate's intellectual functioning fell within the 'average' range of ability, with stronger verbal than non-verbal intellectual abilities. This was a decline from previous levels and was thought to be due to the increasing 'executive' demands of the test over time. Her mother and her sisters also underwent intellectual assessment as part of the larger NHMRC project. Her mother and youngest sister fell within the 'very superior' intellectual range and her second sister in the 'high average' range.

Kate displayed particular weaknesses on the *Coding* and *Picture Arrangement* subtests of the WISC-III. The *Coding* score was consistent with Kate's reduced fine motor skills and laborious handwriting. Her poor score on Picture Arrangement suggested that she was having difficulty with visual sequencing and interpreting social cues.

She performed well on all verbal intellectual subtests, apart from *Arithmetic*. Her mental arithmetical skills were considerably weaker than her overall well-developed verbal abilities, suggesting difficulties in the working memory domain.

Kate's immediate auditory attention span fluctuated. She was able to recall 4 digits forwards consistently and 6 digits on one occasion. Her immediate visual span was reduced. She had difficulty remembering the location of the blocks tapped on the forward *Block Span* task. Her verbal and visual working memory, as assessed by her ability to reverse the sequence of digits and blocks, was similarly reduced.

FIGURE 13.

KATE: REY COMPLEX FIGURE COPY

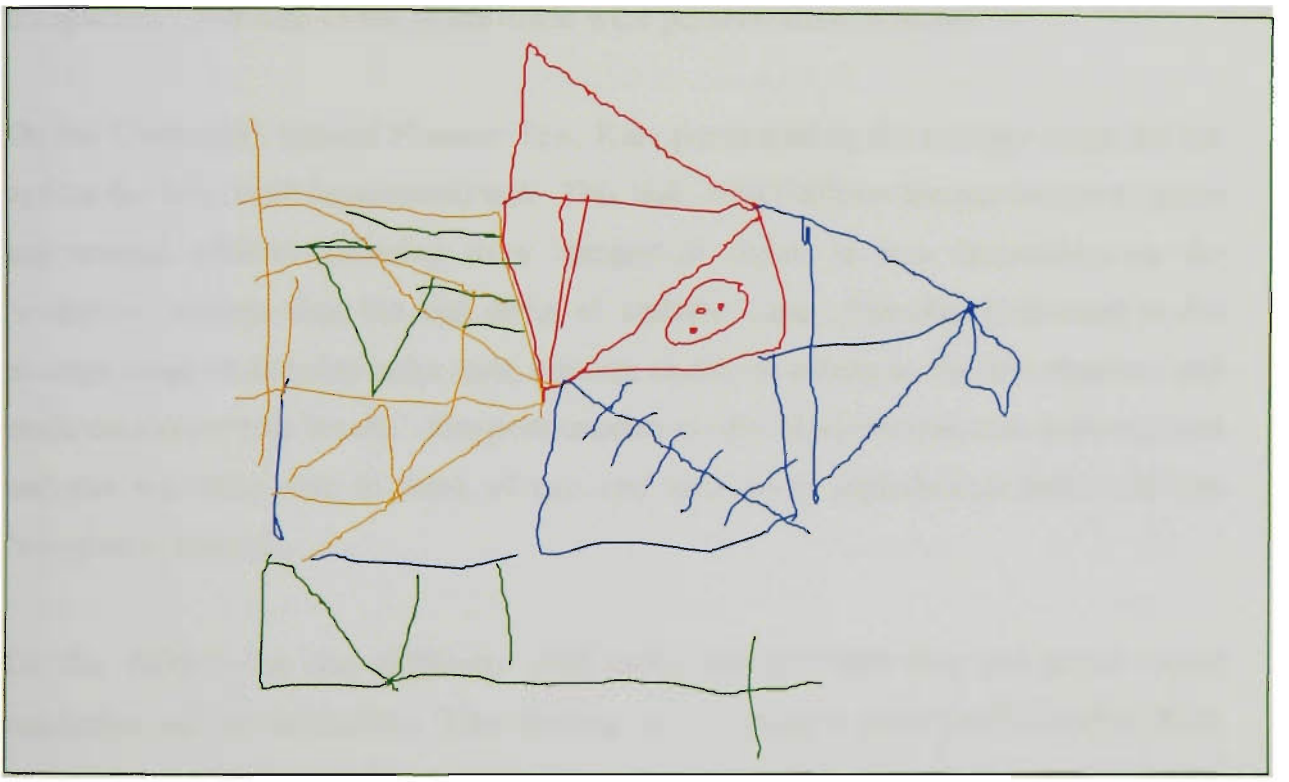


Figure 13 shows Kate's copy of the Rey Figure. She adopted a piece-meal strategy that resulted in poor integration of the elements of the figure. Her copying was slow and inefficient, taking her more than five minutes to copy the design. Her recollection of the figure, both immediate and delayed, demonstrated a significant degree of mental disorganisation, with each of the designs being difficult to recognise as a representation of the original. Her organisational score was ranked as Level 1, that is, in the impaired range. It was thought that her initial poor planning and organisation of the figure made it very difficult to remember the core structural details when it came to recalling it.

Kate's performance on the Tower of London was more than two standard deviations below the normal for her age. She found the task conceptually challenging, and was slow to complete each item. She was unable to complete the last four configurations in the time limit. She was not impulsive, and had few failed attempts. She reported that she simply could not plan ahead to be able to 'see' the correct configuration in her mind.

Her performance on the WCST fell within the mildly impaired range and she could not grasp the concept of category switching, which was required for successful test completion. Over half of the errors made were perseverative in nature.

On the Controlled Animal Fluency Test, Kate performed in the average range for her age on the free recall (automatic) task. This task, which allows the participant to name any animal without adhering to a categorical order, is less demanding on the 'executive' system than the size order or alphabet tasks. She also performed in the average range on the size order task, but was unable to adhere to the rule structure and made excessive 'rule breaks'. Her performance on the Alphabet task was impoverished and she was only able to think of two real animals in alphabetical order and one 'imaginary' animal.

On the BDS-2 she had difficulty with tasks that required fine and gross motor regulation and co-ordination. This finding was consistent with the difficulties Kate experienced with hand writing in the classroom. She made many perseverative errors on a task that required motor inhibition. She was unable to correctly 'mirror' hand actions of the examiner. She made three sequencing errors on a verbal task which required her to alternate numbers and letters until she reached the number twelve.

Results from the Parental Report on the BASC indicated clinically elevated levels on the scales of *Depression*, *Anxiety* and *Atypicality*. Her mother reported that she frequently worried about her school performance, was lacking in confidence, had few friends, and often forgot things. She also described somatic symptoms of anxiety, such as picking at her skin and pulling her hair. These results were consistent with reports from her school teachers and other allied health staff who had treated Kate at the hospital.

Kate's Self Report of Personality indicated that she was in the 'at risk' range on the scales of *Social Stress* and *Attitude to Teachers*, and on the *Emotional* and *Personal Symptoms* indices. She was in the 'clinically significant' range on the scales of *Sense of Inadequacy*, *Interpersonal Relations* and *Self-Reliance*. Responses included concerns about a lack of friends and relationships with school peers, poor school performance, difficulties with making decisions and organising schoolwork.

In summary, Kate was a child with marked executive impairment in the context of 'average' intellectual abilities. This meant she could not utilise her intellectual capacity unless the environment was highly structured, organised and based largely on routine. Although her mother was correct in assuming she did not have an intellectual disability, her day-to-day poor organisational and planning skills indicated very important cognitive deficits which would require a high level of assistance in the school and home environments. The combination of her short stature, cognitive and social difficulties made Kate more vulnerable to teasing and stigmatisation, as she was perceived as 'different' from her peers. Kate's parents were recommended to investigate alternative options to her current schooling, including a smaller, more accommodating mainstream school with the availability of specialist integration assistance. Strategies were provided for cognitive remediation. She was also referred for practical, supportive psychotherapy to assist with the transition from primary to high school. Kate was already an active member of a local TS support group and had made some close friends through this association.

3.5.2 Case Study 2

'Sarah'

Age: 11 years, 2 months

Background

Sarah was born following a normal delivery at 37 weeks. She weighed 6 pounds, 13 ounces. She was the first born child and her mother had had difficulties conceiving. Her mother suffered from morning sickness and vaginal bleeding during pregnancy. Her pregnancy was otherwise uneventful.

Sarah sat unsupported at 6 months and walked at 11 months. She spoke her first words at 6 months and was 1 year old before she could speak in sentences. She was breastfed until she was 9 months old and was toilet trained at 2 years. Sarah had recurrent bouts of otitis media throughout her childhood and chickenpox at 4 years. She had not experienced any other medical illnesses. Her mother reported that Sarah's motor skills had developed fairly normally, however she thought that she had experienced difficulties with co-ordination when learning to skip and ride a bike. Her hearing and vision had been tested and were reported to be normal.

Sarah was diagnosed at birth. Her karyotype was X monosomy (45, X) and she inherited her X chromosome from her mother. She had several physical stigmata of TS including short stature, broad chest, dystrophic nails, high arched palate, and cubitus valgus. She began growth hormone treatment aged five years.

Sarah's father was working as a labourer and had completed four years of secondary school. Her mother had completed six years of secondary school (Higher School Certificate) and was responsible for looking after her three children. Sarah had two younger sisters aged nine and eight. The nine-year old sister had an intellectual disability and attended a special school. Her younger sister was healthy and attended the same primary school as Sarah.

Current Assessment

At the current assessment, Sarah was eleven years and two months old. She was in Grade 5 at a local primary school in outer suburbia. She was currently living with her mother, father and two sisters. Sarah had volunteered to be a participant in the research study, however her other family members were not assessed, at their request.

Her mother reported that Sarah had found it difficult to make and maintain friends at school. She thought Sarah felt threatened when her friends talked to her youngest sister at school and therefore preferred to be alone with individual friends rather than in a group. Her mother said that she fought frequently with other playmates and feared not having any friends and not being liked. She thought Sarah was lacking in self-confidence and this was partly due to her difficulties making friends. She described her as an impulsive child who had a short attention span and was lacking in self control. She also thought she required a lot of extra parental attention and tended to over-react when faced with a problem.

When asked about her academic achievement, her mother reported that Sarah was a capable reader, but was a poorer speller. She thought Sarah had great difficulty grasping mathematics and was considerably behind her peers in this subject. She was otherwise performing well at school and enjoyed reading, art and music. She had not repeated any grades or received any specialist assistance in the classroom.

Sarah presented as an attractive, slightly chubby child who had golden curly hair and short stature. She appeared happy and bubbly, but made a number of self-deprecating comments throughout the assessment. She often giggled and talked to herself with statements such as 'think Sarah think' and 'stupid Sarah'. She required frequent reassurance that she was performing well and was quite concerned about 'failing'. Her manner was somewhat immature and she appeared nervous at times. Her levels of concentration fluctuated and she would often self-distract by singing to herself. Rapport was easily established. Neuropsychological test results are shown in Table 15.

TABLE 15.

SARAH: NEUROPSYCHOLOGICAL TEST RESULTS

WISC- III	Raw Score	Standard Score	Percentile
Full Scale IQ	82	88	21
Performance IQ	35	81	10
Verbal IQ	47	97	42
Verbal Comprehension Index	40	100	50
Perceptual Organisation Index	29	85	16
Freedom from Distractibility Index	15	87	19
Picture Completion	20	9	37
Information	16	10	50
Coding	36	6	9
Similarities	16	9	37
Picture Arrangement	21	6	9
Arithmetic	15	7	16
Block Design	36	9	37
Vocabulary	30	10	50
Object Assembly	16	5	5
Comprehension	23	11	63
Digit Span	12	8	25
Rey Complex Figure Test			
Copy	21	NA	5
3' Delay	5	NA	0.5
30' Delay	0	NA	<0.1
Organisational Score	Level 2	NA	24
Behavioural Dyscontrol Scale	16	NA	NA
Wisconsin Card Sorting Test			
Errors (%)	34	93	32
Perseverative Responses (%)	23	89	23
Perseverative Errors (%)	21	87	19
Nonperseverative Errors (%)	12	102	55
Conceptual Level Responses (%)	64	99	47
Categories Completed	6	NA	>16

Tower of London	Raw Score	Standard Score	Percentile
Raw Score	51	NA	0.7
Standard Score	NA	65	0.8
Correct Items	7	NA	<0.1
Failed Attempts	13	NA	24
Planning Time	41	NA	58
Controlled Animal Fluency Test			
Automatic	15	NA	34
Size Order	8	NA	31
Alphabet	11	NA	62
Rule Breaks	2	NA	NA
Repetitions	2	NA	NA
Block Span			
Forwards	4	NA	2
Backwards	2	NA	NA
Digit Span			
Forwards (number of digits consistently recalled)	4	NA	2
Backwards	3	NA	12
WRAT-3			
Reading	37	100	50
Spelling	27	90	25
Arithmetic	28	84	14

Sarah's intellectual functioning fell within the 'low average' range of ability with stronger verbal than non-verbal intellectual abilities. Her VIQ fell within the average range and her PIQ was in the low average with a significant difference of 16 points. A significant difference was also found between the Verbal Comprehension and Perceptual Organisation indices. She had particular difficulties on the *Coding*, *Picture Arrangement* and *Object Assembly* subtests of the WISC-III. Her psychomotor speed was reduced and she made two errors on *Coding*. She experienced marked visuo-spatial and organisational difficulties on the *Object Assembly* subtest and she was unable to construct the last two items in the time available. While she managed to correctly order a satisfactory number of the picture sequences on *Picture Arrangement*,

it took her a long time to interpret the nonverbal cues in the pictures and then re-arrange them successfully to tell a story.

Sarah's immediate attention span for both verbal and visual information was at the second percentile. She had a forward span of four items on *Digit Span* and *Block Span* and was unable to concentrate on these tasks. This difficulty in the attentional domain was consistent with corroborative reports from parents and teachers.

Her copy of the Rey Complex Figure was impulsively drawn and was poorly planned. She therefore had difficulties encoding the information in an organised fashion and could not recall any components after a 30 minute delay.

Sarah's performance on the Tower of London was more than two standard deviations below the normal for her age. She had 13 failed attempts and was unable to complete five of the configurations within the time limit. Sarah was impulsive, and reported that she could not stop herself from starting the task before she had properly thought about a possible solution. She therefore made many planning errors.

Her performance on the WCST was in the average range and she was able to complete the six categories. However, a high percentage of the errors made were perseverative in nature.

Sarah performed within normal limits on all three categories of the Controlled Animal Fluency Test, demonstrating sound verbal generativity. She made several impulsive errors, but was able to correct herself.

Sarah was quickly able to master the simple fine motor co-ordination tasks of the BDS-2. However, she had difficulties with both motor inhibition and initiation on a 'go no-go' task that required response inhibition and self-monitoring. She made a number of perseverative errors and was very impulsive. She was unable to 'mirror' the examiner's hand movements. She also experienced difficulty in a task of working memory that required alpha-numeric sequencing.

Sarah's literacy and numeracy skills were assessed using the Wide Range Achievement Test-Revision 3 (WRAT-3). She performed in the average range on a

word reading task. Her spelling was slightly weaker but still largely within normal limits. When questioned about her spelling, Sarah reported difficulty 'remembering what the word looked like' in her head. She had considerable difficulty when asked to complete the mathematical component of the task which required numerical computation using a pencil and paper. She could successfully complete the simple additions, subtractions and multiplications, but once the demands on working memory increased, she could not solve the problems. She also had difficulty successfully lining up the columns when doing mathematical problems and made a number of procedural errors.

Sarah's mother completed the Parental Report Form (PRF) of the BASC. The results indicated clinically elevated levels on the scales of *Hyperactivity* and *Attention Problems*. She reported that Sarah interrupted others, was overly energetic and impulsive, highly demanding of attention and had difficulties concentrating. She was said to be restless and easily distracted and did not adjust well to a changes in plan. She commented that her daughter was very sensitive to criticism and was worried what her parents thought of her. According to her mother's report, Sarah was also concerned about a lack of friends and children not liking her. Sarah was reported to be 'at risk' on the scales of *Aggression*, *Anxiety*, *Depression*, *Adaptability* and *Leadership Skills*.

Sarah's Self-Report of Personality (SRP) indicated clinically elevated levels on the scales of *Interpersonal Relations*, *Self-Esteem* and *Self-Reliance*. Sarah's SRP indicated she was 'at risk' on the scales of *Anxiety*, *Social Skills*, *Sense of Inadequacy* and the composite *School Maladjustment*. She reported that she had trouble getting along with other classmates and thought nobody liked her. She said that she had difficulties working independently and making decisions by herself. She reported that she could not stop herself making mistakes and gave up easily. She endorsed items which suggested a poor self-concept, including not liking her appearance and wishing she was someone else.

On the Social Cognition Questionnaire, Sarah's mother indicated that Sarah was oblivious to the effect her behaviour had on other members of the family and that her behaviour often disrupted normal family life. She said that Sarah was very demanding of people's time and was difficult to reason with when upset.

In summary, Sarah was a girl of average verbal intelligence who was experiencing difficulties in a number of cognitive domains. She had significantly stronger verbal than non-verbal intellectual abilities, and experienced particular difficulties on tasks that required intact visual abilities, including visual attention, sequencing, memory, problem solving, organisation and psychomotor speed. She also found it difficult to interpret non-verbal cues. Her presentation was suggestive of significant attentional difficulties, with impulsivity and rule breaking that was consistent with the results of the Parental Rating Scale. Sarah's Self-Report of Personality was of serious concern, with feelings of low self-worth, poor interpersonal relations and over-reliance on her parents. Her perception of herself was that she was 'different', and the combination of her cognitive, behavioural and emotional difficulties meant she was a child who was difficult to manage in the school and home environment. Sarah was referred on to a Clinical Psychologist for further assessment and treatment and the family was encouraged to seek family therapy.

4. DISCUSSION

4.1 COGNITIVE FUNCTIONING

4.1.1 Comparisons with Normative Data

The aim of the current study was to investigate the role of executive and behavioural functioning in a representative sample of Australian girls with TS. Girls with TS between the ages of 6 and 16 years were compared with a representative normative sample on general intellectual, attentional, visuo-spatial, executive and behavioural measures.

Consistent with past literature, there was a significant difference between verbal and non-verbal intellectual measures in the TS sample. Girls with TS had significantly lower Performance IQs (PIQ) and Perceptual Organisation Indices (POI) than the normative sample. The mean PIQ for the TS group fell at the upper end of the 'low average' range. This reduction in PIQ had the overall effect of lowering the mean TS Full Scale IQ (FSIQ) so that it fell at the lower end of the 'average' range of ability. Verbal IQ (VIQ), Verbal Comprehension (VCI) and the Freedom from Distractibility Indices (FDI) did not differ from normal.

The Verbal/Performance IQ discrepancy found in this study was consistent with previous research (Rovet, 1993; Shaffer, 1962) and suggests that while girls with TS generally have FSIQs in the average range of ability, their scores usually fall below that of normative populations due to a reduction in PIQ (Bender et al., 1993; Downey et al., 1989; Garron, 1977; Mazzocco et al., 1998; Money, 1973; Murphy et al., 1994; 1997; Pennington et al., 1982; 1985; Rovet & Netley, 1982; Rovet et al., 1994; Temple & Carney, 1993; Waber, 1979). In a literature review of 226 individuals with TS, the results from standardized intelligence tests demonstrated a mild lowering of FSIQ due to PIQs that were on average 12-15 points below VIQ (Rovet, 1990). The difference between PIQ and VIQ was not as marked in the present study, with a mean difference of 7 points.

There was wide variation in the TS sample on measures of generalized intelligence. Girls with TS were represented throughout the intellectual spectrum, from those with mild intellectual disabilities through to those with superior intellectual functioning.

However, there was more than the expected number of children in the low average range of ability.

Girls with TS performed particularly poorly on the WISC-III subtests of Picture Completion, Picture Arrangement and Arithmetic as compared to normative data. All other subtest performances did not differ from normal, including Digit Span. This WISC-III profile is largely consistent with previous research, which suggests that subtests with scores significantly below population norms, or controls, include Arithmetic, Digit Span, Picture Completion, Coding and Object Assembly (Garron, 1977; McGlone, 1985; Ross et al., 1995; Rovet, 1990; Silbert et al., 1977; Waber, 1979). The results of the current study agree with Lahood & Bacon (1985), McCauley et al., (1986), Silbert et al. (1977), Temple and Carney (1993; 1995), and Waber (1979) in finding no significant decrease in performance on the Block Design subtest.

TS performances on all verbal subtests were within the average range with the exception of Arithmetic. TS populations have consistently been found to be deficient in arithmetic, despite well-developed literacy and language skills (Alexander & Money; 1966; Bruandet, Molko, Cohen & Dehaene, 2004; Buchanan et al., 1998; Chen et al., 1981; Garron, 1977; Haberecht et al., 2001; Mazzocco, 1998; 2001; Rovet, 1993; 1995; Shaffer, 1962; Siegel et al., 1998; Van Borsel et al. 1999, Waber, 1979). It is thought that this difficulty may in part be related to the demands placed on the executive system when completing arithmetical problems.

Temple and Marriott (1998) examined a variety of mathematical skills in a group of eleven girls with TS, using a cognitive neuropsychological framework. Their results confirmed arithmetical difficulties in the TS population, which were not simply a consequence of spatial deficits. They reported that girls with TS had intact number processing on tasks of reading and writing Arabic numbers and number words, in copying Arabic numbers and in making magnitude judgments. However, the TS sample had impaired development of the calculation system. They were as accurate in their mathematical responses as the non-TS controls, but the TS girls were significantly slower to respond. This slowed response rate was consistent with previous research suggesting impaired development of speeded responding in the TS population (Temple et al., 1996). Temple and Marriott found that speeded access for retrieval was poor for addition facts and that there was a reduced flexibility in

responses in multiplication. They also reported that TS girls were less likely to attempt problems that could generate error. In addition, participants with TS also had procedural dyscalculia. In summary, Temple and Marriott's results suggested that the origin of dyscalculia in the TS population could be due to deficits in executive functioning, rather than in number and spatial processing alone. A number of recent studies have suggested that the role of visuo-spatial working memory is particularly important when solving mathematical problems (Bruandet et al., 2004; Bull & Scerif, 2001; Reuhkala, 2001; Kaufmann, 2002).

In this sample, there was no decrease in performance on the Digit Span subtest hence not supporting the theory of a reduction in immediate auditory attention in TS. This was in contrast to previous findings (Romans et al., 1997; 1998; Rovet, 1993; Silbert et al., 1977). Collaer, Geffner, Kaufman, Buckingham & Hines (2002) and Waber (1979) reported normal forward digit spans in TS females but decreased backward digit spans, suggesting impairment in working memory, rather than in immediate auditory attention.

By contrast, TS girls performed significantly more poorly than the normative sample on Block Span, suggesting a reduction in immediate visual attention and spatial working memory. This finding agrees with the work of Cornoldi et al. (2001), who found a reduction in forward and backward block spans in a sample of four adult women with TS.

On the RCF, girls with TS performed significantly more poorly than the normative sample on the Accuracy (Copy), 3' and 30' Delay conditions. The mean RCF Accuracy score was at the tenth percentile in the low average/borderline range, suggesting problems in visuo-constructional ability, spatial analysis, planning and organisation. Girls with TS had difficulty copying the figure in an organized, structured fashion and hence the end result was often piecemeal in approach.

The mean RCF 3' and 30' Delay scores were at the fourth percentile and the seventh percentile respectively, in the borderline range of ability. Girls with TS had significant difficulty recalling the complex figure after both a short and a long delay. However, their retention of visual information over time was sound. For the majority of the sample, TS girls were unable to accurately recall the figure after a short delay,

however they were able to retain what they had initially learned after a longer delay of 30 minutes. These results suggest that as the initial copy of the figure was poorly planned, girls with TS were not able to encode the visual information in an efficient manner, hence they had difficulties recalling it.

These results support the findings of Romans et al. (1997; 1998), Ross et al., (1997) and Waber (1979) who also found TS girls to be deficient on the RCF. Romans et al. (1997) suggested that TS girls' poor performance on the RCF may reflect a decreased ability to concentrate or attend to an abundance of information. For example, Romans suggested that TS girls could not process or integrate complex visual information simultaneously, hence concentrating on only a fraction at a time, leading to a piecemeal copying approach. In the current sample, many TS girls were unable to identify the large core structural elements of the figure (rectangle, diagonal cross, vertical and horizontal lines) and tended to focus on smaller details, hence losing sight of the overall organisation.

TS girls performed significantly more poorly than the normative sample on the TOL, suggesting a reduction in planning, problem solving and spatial working memory. The mean standard score on the TOL was in the low average range of ability. However, the TS sample did not make an excessive number of failed attempts. In this sample, TS girls had difficulty completing the more complex problems in the time limit provided. It was common for the older children to report that they could not mentally visualise the steps needed to obtain the finishing pattern, and therefore were slower to complete problems. Past studies have reported that TS girls perform more poorly on the Tower of Hanoi (Romans et al., 1997; 1998). The results of this study are consistent with those of Romans et al. who found that TS girls had reduced standard scores on the Tower of Hanoi and required more time to complete items than the control group. However, our results did not support the results of Temple et al. (1996), who found no effect on the TOL. The differences may be due to the varying sample sizes and ages. Temple et al. studied 16 TS girls ranging from 8 years to 12 years, while Romans et al. (1997) studied 105 girls aged between 7 and 16 years. In the current study, girls completing the TOL were also aged between 7 and 16 years, hence more closely representing Romans sample. Although the TOL and TOH are different tasks, the TOL was adapted from the TOH and the cognitive demands are thought to be reasonably similar.

No effect was found for TS females on the COWAT as compared with the normative sample. This result was surprising, considering the evidence from past studies to suggest that TS girls have reduced verbal generativity (Money, 1993; Romans et al., 1997; Temple et al., 1996; Waber, 1979). Our results were consistent with Pennington et al. (1985) who found that girls with TS did not differ from controls on phonemic fluency tasks.

TS girls performed more poorly than the normative sample on the Animal Size but not on the Animal Automatic or the Animal Alphabet conditions on the CAFT. As outlined previously, the CAFT has three conditions. In the first instance, girls are asked to name as many animals as they can. Second, the girls are asked to name as many animals as they can, in size order, starting from the smallest animal and working their way up to the largest animal. Then the girls are asked to name as many animals as they can in alphabetical order. The time limit for each condition is sixty seconds. Interestingly, it was only on the Animal Size condition that the TS sample differed from the normative sample.

To the best of our knowledge, the CAFT has not been used in TS populations previously. In previous studies, there have been reports of deficient performances on tests of animal fluency (Romans et al., 1998; Temple et al., 1996). The animal fluency test used in these studies was identical to the Animal Automatic condition in the CAFT. In our study, there was no difference between TS girls and the normative sample on the Animal Automatic condition. However, girls did perform more poorly on the Animal Size condition. The Animal Size condition requires the participants to firstly search the semantic category for different types of animals. It then requires the participant to hold the previously given animal names in working memory and mentally order them, from the smallest animal through to the largest. It is the most spatially demanding of the three conditions as it requires organized searching as well as reviewing size order and spatial sequencing.

Performances by TS girls on the WCST did not differ from the normative sample and fell well within the average range of ability. There were no differences found on any of the measures investigated, including the number of errors made, perseverative responses, nonperseverative responses or categories completed. This result is in

accordance with the majority of studies to date, which suggests that TS females do not have difficulties with cognitive flexibility and concept formation as measured by the WCST (McGlone, 1985; Pennington et al., 1985; Romans et al., 1997; 1998; Temple et al. 1996).

Baddeley's Model of Working Memory

The results of this study suggest that girls with TS have particular difficulties on tasks of executive function with complex spatial demands. TS performances were significantly below those of the normative sample on the following measures: FSIQ, PIQ, POI, Block Span, RCF, CAFT:Animal Size and TOL. No differences were found on executive tests with significant verbal demands. TS performances were at age expectation on measures of VIQ, VC, FD, Digit Forwards, COWAT, CAFT:Animal Automatic and Animal Alphabet and the WCST. These results support our hypothesis that girls with TS have reduced visuo-spatial working memory ability. They partially support the hypothesis that girls with TS have poorly developed higher order executive skills. The pattern of performance by TS individuals suggested that only spatially mediated higher order executive skills were affected in the TS population.

The results of cognitive assessment suggest that girls with TS have impairments in the visuo-spatial sketchpad and central executive but not the phonemic loop in Baddeley's model of working memory. Block Span, a measure of immediate visual attention and visuo-spatial working memory, is a task thought to measure the visuo-spatial sketchpad. The TS sample performed more poorly than the normative sample on Block Span, suggesting impairment in this subsystem of the working memory model. The TOL, WCST, COWAT, CAFT and RCF are tasks which have traditionally been viewed as 'executive' tasks or tasks which are sensitive to frontal system pathology. Within the framework of working memory model proposed by Baddeley and Hitch (1974), executive memory processes are assumed to be mediated by the central executive system. As the TS sample only performed more poorly on executive tests with complex spatial demands, one could conclude that the central executive system was impaired in TS, but the system was not acting as a single resource. Our findings support the notion of fractionation in the central executive.

Baddeley's model of working memory has been developed over the years (Baddeley, 1986; 1996). It is conceptualised that the central executive system strategically controls and manipulates the information coming from long-term memory and from the outside world into the two working memory slave systems: (1) the phonological loop, which is for the temporary storage of visual information, and (2) the visuo-spatial sketchpad, which is for the temporary storage of visual information. The question as to whether there is a single unitary executive system responsible for the different types of executive functions, or whether they are interacting, but independent multiple executive systems–remains unanswered (Baddeley, 1996). There are findings to suggest that the central executive is not acting as a single resource (Shallice & Burgess, 1993). Results from previous studies of executive functioning in TS support the hypothesis that the central executive is a multi-component system and that executive functions are fractionable (Romans et al., 1997; 1998).

Performance on the TOL has been demonstrated to be highly sensitive to disruptions in working memory. However, it has not been clear as to whether the planning requirements load verbal or visuo-spatial memory resources (Phillips, Wynn, Gilhooly, Della Sala & Logie, 1999). Questions have been asked as to whether people carry out the task by silently verbalising a plan of action (Morris et al., 1993), or by visualising a sequence of movements (Joyce & Robbins, 1991; Owen et al., 1990; Welsh, Cirerello, Cuneo & Brennan, 1995). Many authors have highlighted the role of visuo-spatial memory in the TOL, especially visuo-spatial working memory (Joyce & Robbins, 1991; Morice & Delahunty, 1996). Temple et al. (1996) suggested that it is difficult to verbalise the process involved in the TOL task, and suggested that visuo-spatial rehearsal must take place. Phillips et al. (1999) suggested that the locus of the executive component in the TOL is generating a mental plan of moves. Their findings suggested that visuo-spatial memory has a stronger role in TOL performance than verbal memory, and that the nature of the executive processing in the task related more to the execution and monitoring of on-line planning than the ability to form effective preplans of large sequences of moves. Our results are in support of Phillips et al. in suggesting that performance on the TOL is highly dependent on visuo-spatial as opposed to verbal working memory. In our TS sample, the girls regularly reported that they 'could not visualise' the next move and that they were unable to mentally manipulate the balls in their heads.

Our finding that visuo-spatial working memory is impaired in the TS population supports previous research (Buchanan et al., 1998; Romans et al., 1997). There has been a number of studies, each of which has tried to localise the neuroanatomical areas that subserve working memory in the TS population. Haberecht et al. (2001) found evidence to suggest that TS individuals had impaired frontal-parietal and fronto-striatal connections on tasks of visuo-spatial working memory and visuo-spatial orientation processing. Tamm et al. (2003) also demonstrated a relationship between inhibition, working memory and attention with the prefrontal cortex in a sample of TS females. Kesler et al. (2004) compared TS subjects and controls on a judgement of line orientation task. Kesler et al. reported that both TS and control subjects activated parietal-occipital regions involved in spatial orientation as observed on functional MRI. However there was significantly less activation in the TS group. As the task demands increased, controls recruited executive frontal areas whereas subjects with TS did not activate alternate brain regions to meet increasing demands. Kesler et al. concluded that the TS subjects demonstrated activation deficits in parietal-occipital and frontal regions during judgment of line orientation tasks. In summary, it appears that TS individuals demonstrate impairments on tasks of executive functioning and spatial functioning, and these results are supported by localisation studies revealing frontal system dysfunction.

In this TS sample, the operations of the phonological loop were intact. The actions of the phonological loop have been traditionally measured by tasks of immediate auditory attention, such as digit span. In the current study, TS females performed at age expectation on tests of digit span.

Recent research has suggested that tests of verbal fluency place demands on the phonological loop as well as the central executive, as interpreted in the context of Baddeley's model of working memory. Rende, Ramsberger and Miyake (2002) suggested that the phonological loop's ability to temporarily store and manipulate information was crucial for successful completion of the searching strategies utilised on tasks of verbal fluency. Similarly, the phonological loop has been thought to regulate the performance on novel tasks, such as on the WCST (Cinan & Tanor, 2002; Dunbar & Sussman, 1995). According to Dunbar and Sussman, the most likely explanation for the role of the phonological loop in WCST performance is that the executive process of updating the information about the sorting criterion requires the

use of the phonological store. If the phonological store is damaged, this would secondarily impair the executive function.

It is possible that the reason why the current sample performed in the normal range on the Digit Span, COWAT, Animal Automatic, Animal Alphabet and WCST tests was because these tests all require efficient functioning of the phonological loop for successful completion. This component of Baddeley's model was intact in this sample.

In summary, the current findings suggest that individuals with TS have specific difficulties on spatially demanding executive function tasks, particularly those demanding of visuo-spatial working memory. In the context of Baddeley's model of working memory, the phonological loop remains intact, however the visuo-spatial sketchpad and the central executive systems are impaired. Our results support the hypothesis that the central executive is a multi-function system, and is domain independent. The current results could be interpreted as supporting a distinction between spatial and verbal working memory resources at the level of the central executive.

4.1.2 Comparisons with Sibling Controls

Fifteen girls with TS were compared with fifteen female sibling controls on FSIQ, Arithmetic (WISC-III), RCF Accuracy, 3' Delay, 30' Delay and Organisational scores, BDS-2, Digit Forwards and the WCST: Percentage Errors and Categories Completed. There was a significant difference in performance on the majority of cognitive measures between TS participants and their sisters. Girls with TS performed more poorly than their sibling controls on all measures except for BDS-2 and Digit Forwards. There was a significant difference in generalized intelligence between the two groups. The mean sibling FSIQ was at the lower end of the 'high average' range of ability, while the mean FSIQ for TS individuals was at the lower end of the 'average' range. These results illustrate that while TS females usually have generalized intelligence scores in the average range of ability, they perform significantly below the level of their siblings. These differences in IQ were evident

even on verbal intellectual measures, although the differences were not as pronounced.

We hypothesised that TS girls and their non-affected sisters would only differ on non-verbal cognitive measures. This hypothesis was not supported. The TS sample performed below the level of sibling controls on verbal and non-verbal measures and this was interpreted as a reflection of the significant difference in FSIQ between the two samples.

The current findings corroborate the results of earlier studies in finding a general decrease in intellectual abilities in individuals with TS as compared with their non-TS sisters (Haverkamp et al., 2004; Mazzocco et al., 1998). The mean difference in FSIQ in our sample was 18 points, which was highly significant. Our results were similar to that of Mazzocco et al., who reported a significant difference in FSIQ (WISC-R) between TS and sibling controls of 23 points. Haverkamp et al. used the Kaufman Assessment Battery for Children (K-ABC) to assess intellectual and academic achievement scores in a group of 101 TS girls and 53 non-TS sisters. The total TS sample performed at a significantly lower level than the sisters on all subscales of the K-ABC.

In this sample of TS girls and female siblings, the TS group had significantly lower visuo-constructional, visual memory and spatial organisational skills as measured by the RCF Accuracy, Delay and Organisational scores (Waber & Holmes, 1985). This finding is clearly demonstrated in Figure 6. This result was predicted and extends the previous findings of Downey et al., who reported visuo-spatial and memory impairments in adult TS populations when compared with sibling controls on the Benton Visual Retention Test. Similar to the larger TS group, this selected sample of TS females had reduced accuracy and delayed recall scores on the RCF; however their retention of visual information over time was intact. It is likely that the poor planning and organisation of the initial copy of the figure affected the process of encoding and therefore the ability to recall the design after a delay. Although the amount of visual information recalled after a brief three minute delay was reduced, the TS sample was able to retain the information initially learnt and reproduce it after a thirty minute delay. This suggests that the cognitive pathway that is defective in the TS population

is the ability to accurately process and encode visual information, rather than the ability to remember it over time.

There was no difference between TS individuals and sibling controls on tests of forward digit span; indeed, the number of digits correctly recalled for each group fell within the average range of ability. This suggests that the cognitive differences found between the two groups could not be accounted for on the basis of differing auditory attention spans.

There was no significant difference between TS girls and sibling controls on the BDS-2. The BDS-2 was designed to assess behavioural self-regulation in adults and children. The BDS-2 is a measure of motor planning and inhibition and requires the subject to copy the examiner on a number of fine motor tasks. Although the TS group performed at a lower level on the BDS-2 than sibling controls, the difference was not statistically significant. In the larger NHMRC sample of TS females, parents and siblings, TS women had greater difficulties on this task as compared with their family members (Loesch et al., In Press). This suggests that in the current select sample, there were too few participants to detect a significant difference.

Although it is commonplace for TS parents to report difficulties with motor development and function, relatively few studies have investigated the role of motor function in the TS neuropsychological profile (Nijhuis-van der Sanden et al., 2003). There has been little consensus as to the exact nature of the motor difficulties in the TS population. Clark et al. (1990) did not find group differences in finger tapping tasks, in contrast to Bender et al. (1993) and McGlone (1985) who found a lowered movement velocity. McGlone proposed that motor control in TS subjects could be impaired irrespective of visuo-spatial deficits. Ross et al. (1996) found that TS girls (n=78) performed significantly worse than controls (n=145) on motor tasks with high visuo-spatial demands but not on simple motor tasks. In contrast, Nijhuis-van der Sanden and colleagues concluded that a problem in motor execution was present, independent of visuo-spatial perception problems (Nijhuis-van der Sanden, Smits-Engelsman & Eling, 2000; Nijhuis-van der Sanden, Smits-Engelsman, Eling, Nijhuis, & Van Galen, 2002). Further investigations are needed to clarify the relationship between cognitive and motor performance in the TS population.

There was a significant difference between TS girls and sibling controls on the WCST. Although the performance of TS girls on this test was in the average range, it was considerably lower than their sisters. This finding is most likely to be attributable to the significant difference in intelligence between the two groups.

Prior studies have confirmed that the IQ discrepancy between TS individuals and their female siblings persists into adulthood. Downey et al. (1991) reported significant differences in intelligence between adult women with TS and their siblings on the WAIS-R. Adult women had lower FSIQs and PIQs than their sisters, but the groups did not differ on measures of VIQ. TS females also performed more poorly on the Benton Visual Retention Test when compared with sibling controls. These differences were attributed to deficits in visuo-spatial processing, visual memory, visuo-constructional and arithmetic ability in the TS sample. Interestingly, TS individuals were comparable to their siblings in ratings of educational level, but had significantly lower occupational levels. So, although TS women had the same educational opportunities as their sisters, they were unable to obtain the same occupational status. The authors speculated that this lower level of occupational achievement in TS individuals may have been due to a combination of cognitive, behavioural and psychosocial factors affecting employment status.

The considerable intellectual differences between TS females, siblings, and their parents in the current study are illustrated in Figure 4. In this sample, the mean parent and sibling FSIQ was slightly higher than the average population. This may have been due to sampling bias, with more highly educated parents often being over-represented in research studies. However, the mean IQ scores for mothers and fathers were still in the average range of ability. The difference in non-verbal intellectual abilities between parents and their affected daughters was approximately 20 points, while the difference in verbal abilities was approximately 10 points. As shown in Figure 5, low scores on the Arithmetic subtest were partially responsible for the differences in verbal abilities between TS girls and their families.

While it is well documented that the general intellectual abilities of TS females usually fall within the average range, the current findings suggest that this level of ability is significantly below that of what would be expected based on familial heritability alone. These findings have significant implications for parents of children

with TS. While it is important for parents to encourage and support their daughters in their quest to achieve the highest educational and occupational outcome possible, it is also just as important that the family has realistic expectations about what their TS child could achieve.

In the larger NHMRC sample of TS families, it was commonplace for the adult women with TS to be employed, but the occupations the women held were usually less cognitively demanding than that of their siblings. For example, in one family interviewed, the father, mother and two adult siblings were employed in professional positions and had all completed postgraduate University qualifications. The adult sibling with TS was gainfully employed as a child care worker and had completed a two year TAFE course. When asked about family expectations when she was growing up, the woman reported that she has often felt inferior when compared with her siblings, even though her family had been very supportive and understanding. She reported that she made a number of close friends at school who were her intellectual equals, and these friends were of great assistance in boosting her self-confidence. However, she said it took her a number of years to accept the fact that she might never reach the same occupational status of her family members, and for her to adjust her expectations and be comfortable and proud of her achievements.

4.1.3 X-Origin and Cognition: Comparisons of X^m and X^p

It was hypothesised that TS females whose X-chromosome was maternal in origin would perform more poorly on executive measures than those who had a paternal X-chromosome. The current findings did not support this hypothesis. There was no main effect for X-origin and no significant difference was found on tests of cognitive functioning between X^m and X^p individuals. As the larger TS group consisted of both X monosomy and non-45,X individuals (X^m=28, X^p=11), further analyses were undertaken for TS females with X monosomy (45,X). Again there was no statistically significant difference in cognitive performance between monosomic X^m and X^p individuals (X^m=15, X^p=5). As the X-monosomy sample was small, these results certainly do not refute the possible role of genomic imprinting in the TS phenotype. The mean standardised test scores on intellectual and executive measures between X^m and X^p individuals were similar, however there was a consistent trend towards slightly

poorer performances in the X^m group. Our results are discrepant to those reported by Skuse et al. (1997) who found considerably weaker executive and social cognition skills in a sample of 55 monosomic TS females (X^m=55, X^p=25) who had maternal X inheritance. In support of our findings, Ross and Zinn (1999) also found no relationship between X- chromosome origin and intelligence in a sample of 30 monosomic individuals. In summary, our 45,X sample was not large enough to either support or refute the X-imprinting hypothesis.

There is still ongoing debate in the wider academic community as to whether imprinting is the mechanism responsible for the cognitive profile witnessed in TS females. Recent findings by Ross et al. (2000) provide convincing support for the haploinsufficiency hypothesis. Ross et al. compared visuo-spatial abilities in children and adults with non-mosaic deletions on the short arm of the X-chromosome (Xp). All individuals with poor visuo-spatial ability were missing the part of the chromosome within the pseudoautosomal dominant region (Xp22.3) known to escape X inactivation. They concluded that both copies of genes in this region must be present to express the trait properly. Ross et al. reported that the typical TS cognitive profile was observed in TS individuals regardless of whether their X-chromosome deletion was maternal or paternal in origin, indicating that X-imprinting was not the mechanism responsible for visuo-spatial deficits in TS females.

4.1.4 Karyotype Effects on Cognition

In this study, comparisons were made between 45,X monosomy and non 45,X individuals to investigate the potentially differing effects of karyotype on the TS neurocognitive profile. Twenty girls with a 45,X monosomy karyotype were compared with nineteen non-45,X girls on measures of intelligence, visuo-spatial, and executive measures. The non-monosomic group was comprised of individuals with either cell line mosaicism (e.g. 45,X/46,XX), isochromosome (e.g. 46,isoX^m) or, those with a deletion of one part of the X chromosome (e.g. 46,X,i(Xq)). Approximately half the non-45,X females had a karyotype consistent with mosaicism while the other half had a combination of X chromosome deletions and re-arrangements. It was hypothesised that girls with X-monosomy would do more poorly on cognitive measures than non-45,X TS girls. No significant statistical differences were found

between 45,X and non 45,X individuals on all cognitive measures, hence not supporting our hypothesis. Further analysis of group means *did not* reveal a trend towards poorer cognitive performances in 45,X individuals.

The current findings support the work of Chen et al. (1981), Garron (1977), Haverkamp et al. (2004) Rovet (1993) and Bender et al. (1990) who also reported no differences between monosomic and non-monosomic individuals on measures of cognitive function. However, our findings are in conflict with the commonly held view that girls who have a 'pure' 45,X monosomy karyotype (all cells missing the second sex chromosome) generally perform more poorly than those individuals with alternate cell line mosaicism, X-chromosome re-arrangements and/or deletions (Bender et al., 1984; 1993; Ross et al., 1997; Temple & Carney, 1995).

There has been increasing discussion in the literature about the difficulties associated with predicting the physical and cognitive phenotype on the basis of karyotype in TS individuals. Many associations have been proposed, but few have been universally supported (Sybert, 2002). Chromosomal mosaicism for monosomy X and a second or third cell line occurs in almost 50% of TS individuals and it is difficult to assess the relative contribution of each cell line to each organ system (Sybert). All females who are mosaic for TS do not share the same proportion of normal and abnormal cells in all tissues and the proportion in one tissue does not necessarily predict that in others. Occult mosaicism may mask differences conferred by the presence of cell lines with other X-chromosome or Y chromosome abnormalities in seemingly monosomic 45,X individuals. Most TS females are diagnosed with TS based on the results of karyotyping of only one tissue, usually that of peripheral blood. Therefore, mosaicism for a normal chromosome line or a different aneuploid cell line (e.g. 45,X) may remain undetected in the majority of cases (Sybert, 2002). Previous studies have suggested that a certain level of mosaicism is necessary for foetal survival because of the foetoprotective effect of more than one dose of locus/loci on the X-chromosome (Connor & Loughlin, 1989; Hassold, Pettay, Robinson & Uchida, 1992; Held et al., 1992; Hook & Warburton, 1983). In summary, there appears to be no definitive association between individual TS karyotypes and the physical and cognitive expressions of the condition. This may be in part due to the difficulties in the accurate detection and diagnosis of pure 45,X TS as opposed to non-45,X conditions.

4.2 SOCIO-EMOTIONAL AND BEHAVIOURAL FUNCTIONING

4.2.1 Comparisons with Normative Data

The Behavioural Assessment Scale for Children and the Social Cognition Questionnaire. were used to assess behavioural and socio-emotional functioning in forty-one individuals with TS. Parental report and self-report were examined separately by use of the BASC PRS and the SRP and the results were compared to published female normative data. The BASC measures provided standardized T scores for clinical scales, adaptive scales and composite scores.

Parents of TS females reported a high level of attention problems in the TS sample. This result was highly significant and the mean attention score was nearly a standard deviation above the expected level, in the 'At Risk' range. As mentioned previously, a score in the 'At Risk' range indicates the presence of significant problems and the 'Clinically Significant' range denotes a high level of maladaptive behaviour. Thirty-four percent of TS girls between the ages of 6 and 16 years were rated by their parents as being 'At Risk' for developing or experiencing significant attention problems. Seventeen percent had 'Clinically Significant' attention problems, at a level consistent with a formal diagnosis of attention deficit disorder. Attention problems were more prevalent in girls below the age of 12 years, with 44% falling in the 'At Risk' range and 22% having clinically significant levels of attention problems. These results are striking and agree with the findings from previous studies (Mazzocco et al., 1998; McCauley et al., 1986; 2001). McCauley et al. (2001) found a significantly higher rate of attention problems in their TS sample when compared to controls on the Diagnostic Interview for Children and Adolescents (DICA). According to their parents, girls met DSM-III criteria for attention deficit hyperactivity disorder (ADHD) more frequently than controls. This was particularly salient in the adolescent group in their sample.

TS girls were also more likely to experience poorer leadership skills when compared to the female normative sample. This finding was significant. However it is important to point out that the mean Leadership T Score was still in the average range. Parents reported that their daughters did not possess the same leadership qualities as other females of the same age. The variable Leadership in the BASC PRS is defined as the skills associated with accomplishing academic, social or community goals, including

the ability to work well with others (Reynolds & Kamphaus, 1992). Items on the PRS that comprise the leadership scale include statements such as 'is a self-starter', 'has lots of ideas', 'is good at getting people to work together', 'gives good suggestions for problem solving', is usually chosen as a leader', 'will speak up if the situation calls for it', 'works well under pressure' and 'makes decisions easily'. Interestingly, these questions appear to be assessing organisational, problem solving and decision making skills, skills which are thought to be reliant on intact executive functioning. The girls in this sample performed poorly on executive measures and on ratings of leadership, suggesting that the cognitive difficulties demonstrated on assessment do indeed affect the girls' social and adaptive functioning in the home and school environments.

No other BASC parental variables reached statistical significance due to strict Bonferroni adjustments. However the scales of Adaptive Skills, Atypicality, Hyperactivity and the Behaviour Problems composite all had alpha levels of $p<0.02$, suggesting significant difficulties in some TS individuals on these scales. The BASC Hyperactivity scale measures both hyperactivity and impulsivity, well known to be affected in TS populations (McCauley et al., 1986; 2001; Rovet, 1993). The Adaptive Skills scale is a composite of Adaptability, Social Skills and Leadership scales. High scores on this scale suggest difficulties with prosocial, organisational, study and other adaptive skills.

In our sample, TS girls were rated as having high scores on the Atypicality scale. However, this finding was not statistically significant and the mean T score was in the average range. The Atypicality scale can reflect a number of different problems, including thought disorder, psychosis, poor contact with reality and behavioural problems associated with developmental delay, such as rocking. A high score on this scale does not necessarily reflect psychotic behaviour and is relevant to several different interpretations. Questions comprising this scale include items such as 'daydreams', 'gets lost', 'has strange ideas', 'repeats one activity over and over', 'sings or hums to self', says ' I am afraid I will hurt someone' and 'picks at own hair, nails or clothing'. Some of the items are associated with behaviours seen in developmental delay, especially autism spectrum disorders. There have been associations made between TS and autism; in particular, girls who have a ring chromosome karyotype are more likely to exhibit behavioural disturbance similar to that witnessed in children with autism (El Abd et al., 1999). Further studies

comparing larger samples of children with a ring chromosome and those with autism may reveal interesting insights into both conditions.

On the BASC Self-Report of Personality, no individual scale reached statistical significance after Bonferroni adjustment. There was no significant difference between girls with TS and the female normative sample on behavioural and socio-emotional self report measures. The scales of Interpersonal Relations, Self-Esteem and Atypicality approached statistical significance with alpha levels ≤ 0.05. However, the mean T scores for each scale were clearly in the normal range. On the whole, girls with TS rated themselves as having sound socio-emotional adjustment. They were more likely to report lower levels of self-esteem than the normative population, but self-esteem was only marginally lower. This finding is consistent with the findings of Rovet (1993) who also found a mild decrease in self-esteem in the TS population, but for the majority of girls, self-esteem was in the average range.

In our sample, we observed a common behavioural presentation in young TS children. Very often, the TS children would exhibit inattentive, hyperactive and immature behaviours both in the clinic setting and in the home environment. The young children had a tendency to externalize their behaviour, and were usually very talkative and friendly with health professionals. Despite the initial impression of confidence, the children often reported poor peer relationships, with few friends and a tendency to socialize with younger children. At the group level, we noticed a marked change in behaviour as these girls approached adolescence. As teenagers, TS girls had a tendency to present as quiet, withdrawn, and were more self-conscious. In our sample, 26% of TS girls aged 12 and over fell into the 'At Risk' or 'Clinically Significant' range on scales of withdrawal. This was in distinct contrast to the under 12's where no girls experienced problems with withdrawal. Similarly, 52% of teenagers had 'At Risk' or 'Clinically Significant' levels of self-esteem on self-report measures, while only 8% of children fell into this range. Teenagers with TS were much more likely to have low levels of self–esteem than the age matched normative sample and TS children. However, as a whole group, the TS sample had only marginally lower levels of self-esteem than the normative sample.

The findings of this study suggest that the socio-emotional difficulties that parents and individuals with TS report differ, depending on their developmental stage. Group

analyses of socio-emotional variables on self-report measures suggest that the TS population see themselves as relatively 'normal' when compared with female normative samples. However, when the groups are broken down by age, more salient differences are noted. Children with TS (<12 years) were more likely to have significant problems with attention, hyperactivity and interpersonal relations than adolescents (> 12 years). Adolescents however, were more likely to suffer from low self-esteem and social withdrawal than TS children. The objective BASC data supported our subjective experience of developmental changes in presentation once a child reached early adolescent years. These changes may due to delays in pubertal and linear growth and cognitive development. Adolescence is always a risk period for girls with relation to self-esteem and body image, and girls with TS are at even greater risk than the normal population. As teenagers, they are faced with the reality of being shorter than their peers, even after growth hormone treatment. They also lack the normalizing experience of going through pubertal changes that characterise the transition from girl to womanhood. Even with oestrogen replacement therapy, for the majority of TS girls, fertility is reduced and having a family without the assistance of IVF technology is highly unlikely. TS girls, are more prone to weight gain than their peers and this may also negatively affect body image.

4.2.2 X-Origin and Socio-Emotional and Behavioural Functioning: Comparisons between X^m and X^p

No associations were found between parental X chromosome origin and behavioural or socio-emotional measures. Mean results on the Social Cognition Questionnaire were identical for X^m and X^p groups, hence not supporting the theory of an X-linked locus for social cognition. Our sample was not large enough to refute Skuse et al.'s 1997 findings of poorer social cognition in females whose X chromosome was maternal in origin; however, separate analyses of both mixed karyotype and monosomic TS females did not reveal any trends to suggest X imprinting. It is possible that with a larger sample, we may have found an effect. It is also possible that X-imprinting was not the mechanism responsible for social problems in our sample, and the combination of genetic, hormonal and environmental influences was more significant. To date, no studies have replicated the original findings of Skuse et al., although there has been a number of studies providing mixed support for the theory of imprinting (Bishop et al., 2000; Lawrence et al., 2003).

4.2.3 Karyotype Effects on Socio-Emotional and Behavioural Functioning

No associations were found between 45,X and non-45,X individuals on behavioural and socio-emotional measures. The one individual with a ring chromosome was excluded from the analyses so the non-45,X group consisted solely of individuals with mosaicism, deletions and re-arrangements of the X-chromosome. These findings do not support past research and likely reflect the heterogeneity of our non-45,X sample and the small sample size for each specific karyotype. Recent research has correlated social and behavioural syndromes with specific loci on the X-chromosome (Ross et al., 2000; Lawrence et al., 2003). Obviously, large samples of girls with specific X chromosome deletions are needed to replicate these findings. In a multi-centre Canada-wide trial of growth hormone therapy, Rovet and Ireland (1994) found that TS individuals with mosaicism were relatively unaffected on behavioural and socio-emotional measures, while those with a 45,X karyotype showed a moderate increase in the number of social problems. Children with X-chromosome deletions showed behavioural problems and children with an isochromosome showed social problems. One interpretation of these results is that different regions of the X-chromosome may be implicated in social versus behavioural problems (Rovet, 2004).

4.2.4 Cognition, Socio-Emotional and Behavioural Functioning

Correlational analyses were used to examine the relationship between the cognitive, behavioural and socio-emotional variables in the TS population. Only BASC variables that were found to be significant or to be approaching significance were correlated with cognitive measures. The variables Attention Problems, Leadership and Hyperactivity were selected from the BASC Parental Report Scales.

Attention problems were significantly negatively correlated with generalised intellectual measures, arithmetical skills, motor inhibition and planning and verbal generativity. TS individuals who were reported to have high levels of inattention had lower IQ's, and performed more poorly on test of arithmetic, motor inhibition and verbal fluency.

Attention problems had significant positive correlations with the Social Cognition Questionnaire. TS females whose parents reported difficulties with attention scored higher on the SCQ, suggesting poorer social cognition.

The BASC variable Leadership was significantly positively correlated with intelligence scores. Girls who were thought to possess strong leadership skills had higher levels of intelligence. Leadership was also positively correlated with copy performance on the Rey Complex Figure. Girls who had strong leadership skills were more likely to have strong visuo-spatial, constructional and organisational skills as measured by the RCF. Leadership was negatively correlated with scores on the SCQ. TS girls who were rated as having sound leadership skills had better social adjustment as measured by the SCQ.

There was a negative correlation between the BASC variable Hyperactivity and the Freedom from Distractibility Index on the WISC-III. There was a significant relationship between high levels of hyperactivity and cognitive distractibility. Hyperactivity did not correlate with any other intellectual measure. Hyperactivity negatively correlated with the BDS-2, the SCQ and the WCST: Perseverative Errors. Girls who were reported to have high levels of hyperactivity made more perseverative errors on the WCST. They also had difficulties with motor inhibition and working memory on the BDS-2. Social cognition was poorer in girls with excessive hyperactive behaviour.

As the BASC Self-Report variable Self-Esteem was the closest to approaching statistical significance, it was chosen for correlation with cognitive measures. There were no significant correlations between measures of self-esteem and cognitive measures. This suggests that problems with self-esteem are independent of the level of cognitive functioning.

The results of correlation analyses support our hypothesis that girls who experience high levels of behaviour problems have poorer cognitive abilities. The reverse was also true, in that girls who were rated as having excellent leadership qualities had higher levels of intelligence and better organisational skills. Poor attention had a significant impact on performances in other cognitive domains and negatively affected social cognition. It would appear that the behaviour problems associated with TS are

often the sequelae of the core neuropsychological difficulties. The neuropsychological deficits that may affect general adaptive functioning include visuo-spatial organizational deficits, deficits in social cognition, inefficient non-verbal problem solving, poor planning and reduced attentional skills. Girls with TS have difficulties reading non-verbal cues and therefore find it more difficult to understand body language and facial expressions in social interactions. This would likely impact on their ability to make friends and have good interpersonal relations.

These results have significant implications for remediation, and suggest that girls with TS need extra assistance in both the home and school environments. Interventions should be targeted at a combination of cognitive, socio-emotional and behavioural functions to maximise the chance of successful community integration and future occupational success. Girls may benefit from social skills training and cognitive behavioural therapies to enhance social adjustment and strengthen self-esteem and interpersonal relations.

4.3 Limitations and Future Directions

Although significant attempts were made to try and reduce sampling bias, it is possible that our sample was not necessarily representative of the larger TS population in Australia. As outlined previously, participants were recruited from across three states in Australia, and were not restricted to individuals who attended hospital clinics. Indeed, a number of our participants came from rural areas and were managed by local general medical practitioners. The TS sample was recruited from hospital clinic databases, GP's, paediatricians, endocrinologists and local support groups. We also had access to a state genetic database. The females on this database represented the majority of women who had presented for TS karyotyping in the states of Victoria and Tasmania. These individuals were not necessarily patients of a hospital, and they included foetuses that were initially screened for TS. We also tried to ensure that females who had two working parents or were from rural areas were not excluded from participating on the basis of time practicalities or geographic isolation. We visited many families in their home environments and often saw participants at weekends. Some of the more remote families had not had any contact with medical services since the initial diagnosis many years prior and had minimal information about TS. We spoke to a number of parents who had not gone on to have further

children as they incorrectly assumed that TS was an inherited condition. The geographical isolation of some families we visited meant that they had to drive for eight hours to the nearest clinic for specialist medical assistance and monitoring.

As the TS sample was recruited as part of a larger NHMRC research project on the role of genetic imprinting in TS, the study was explained to them in terms of how girls with TS may differ, depending on which parent from whom they inherited their X chromosome. This investigation raised many issues for a lot of the families involved, and a substantial number decided not to participate. The reasons for non-participation varied; for example, there were several parents who expressed concerns regarding the collection of DNA samples and were worried about the confidentiality of the results. They were concerned that this information might somehow be used by insurance companies in the future and could negatively impact their daughters' chances of being medically insured. We hypothesise that some mothers were also concerned about the possible revelation of non-paternity of the father for their children.

Other families reported that they did not want to know the origin of their child's X chromosome. Routinely, the results of this test were only offered at the parent's request. They were not released otherwise. The issue of blame was raised and families were concerned that if they knew which parent from whom their daughter had received the X chromosome, this parent may feel guilty and somehow responsible. As a number of families did not understand the complex genetics in TS, we were always faced with the quandary of how much information families should know before consenting to the research project. The ethics committees now demand that participants are fully informed about the possible pros and cons involved in research trials. We were not sure if this was a help or hindrance to recruitment. As a number of families we saw had been misinformed about the causes of TS, they often assumed that TS was an 'inherited' condition as it was labelled as 'genetic' as opposed to a spontaneous error at the point of conception. We clearly outlined the random nature of TS, and the varying genetic mechanisms responsible for the TS karyotype. However the long held belief by some families that TS was inherited, together with the complex genetic nature of the study certainly did have a negative impact on recruitment rates. There did not seem to be any particular trend in study refusal, and the families that refused to participate covered the spectrum of low to high socio-economic status. Therefore, although the sample may have been restricted, it was thought to be

reasonably representative of the general TS population. Certainly the demographics and the percentages of girls with 45,X versus non 45,X TS and maternal versus paternal X chromosome origin was highly consistent with the statistics reported in previous multi-centre studies.

One of the major limitations in our study was the relatively small sample size with regard to X-origin and karyotype analyses. Although the TS sample itself was of a reasonable size (considering that the median TS sample size reported by Rovet (1990) was twelve), it was not large enough to generate robust conclusions regarding the role of karyotype and X origin in the TS behavioural phenotype. Much larger studies of specific cytogenetic variants (e.g. 45,X, mosaicism, deletions, isochromosome, and ring chromosome) are needed to draw conclusions regarding cognitive, behavioural and socio-emotional functioning in TS individuals. The role of X imprinting is still being debated, and further studies are needed with large representative samples of 45,X monosomy individuals with both paternal and maternal X chromosome origin, to confirm or refute Skuse et al.'s (1997) initial findings. Considering the diverse cognitive and behavioural spectrum in TS, future directions could include grouping together TS individuals with similar cognitive, behavioural or socio-emotional profiles, and then attempting to correlate these results with either specific genetic loci and/or neuroanatomical and physiological correlates. Recent research correlating specific X chromosome deletions with cognitive performance has proven fruitful, and this research should be expanded to include more behavioural, social and emotional variables.

Another obvious limitation in this study was the absence of control subjects for the larger sample of TS girls. As we had initially anticipated a larger TS recruitment rate, we also predicted we would have a greater number of female sibling controls. Due to time constraints and the practicalities of assessing whole families in the one session, we were not able to administer all executive and behavioural measures to the control siblings that did participate. Future studies would benefit from using large control samples consisting of both female sibling and non-sibling controls.

In the current study, and in other studies of socio-emotional functioning in TS (e.g. McCauley et al., 2001) results of children's self-report measures did not reveal evidence of significant emotional distress. These results were in contrast to the reports

given by their parents, which suggested relatively high levels of behavioural and socio-emotional problems in their TS children. The role of insight has not been investigated in the TS population. The results from this study highlight the difficulties TS girls have on tasks of executive functioning. Poor executive skills have been linked to reduced levels of insight in many populations, especially in individuals with frontal lobe damage from brain injury. It is possible that the girls with TS did not report significant socio-emotional distress because they lacked insight into their condition. It is also possible that they were reporting in a way that was socially acceptable and minimizing actual difficulties. Or, it is possible that girls with TS are accurate at self-reporting their symptoms and they do not display significant socio-emotional problems. Future studies on the role of insight may assist in clarifying the nature of child self-report in the TS population.

In this study, we attempted to address the question as to whether deficits in general cognitive and executive functioning had a deleterious effect on behavioural and socio-emotional adjustment in TS females. The results suggest that indeed poorer cognition is associated with higher levels of maladaptive behaviour. However, it is not clear which comes first. Is it that inattention and hyperactivity cause a reduction in cognitive performance as they are part of the same disrupted neural pathway, or, is it that children with poor attentional skills and externalising behaviour have more difficulty learning and interacting with others, therefore not getting the opportunity to benefit from regular tuition and feedback from the environment? Further studies investigating the links between cognition, behaviour, socio-emotional functioning and adaptive living skills would be beneficial to try to clarify these issues.

Finally, enough progress has been made in our understanding of children with TS to develop and evaluate early intervention programs to minimize potential problems. Many of the cognitive and behavioural problems witnessed in TS individuals are similar to the pattern in non-verbal learning disability (Rourke, 1995). As a number of TS children also have executive dysfunction, cognitive remediation specifically targeting executive deficits is warranted. By using the guidelines suggested for children with non-verbal learning disabilities, programs could be tailored to fit the individual needs of children with TS.

4.4 Conclusions

The current study investigated the role of executive and behavioural functioning in a representative sample of Australian girls with TS. To the best of our knowledge, at the commencement of this study, there had been no published investigations of cognitive, behavioural and socio-emotional functioning in Australian girls with TS. More recently, there has been one small Australian study focusing on the role of the temporal lobes in the TS profile (Rae et al., 2004). Therefore, the current work is significant for the Australian TS population, and has important implications for TS families and local support groups.

The results of this study suggest that girls with TS have particular difficulties on tasks of executive function with complex spatial demands. The effect was domain dependent and no effect was found on verbally mediated executive tasks. As a group, TS individuals demonstrated significant problems on tasks assessing immediate visual attention, visuo-spatial working memory, planning, organisational skills and visuo-constructional skills. These specific cognitive deficits are thought to be responsible for lowering performance on non-verbal intellectual measures. Arithmetical skills were consistently reduced, with the reduction in part reflective of poor working memory ability. TS individuals performed within the expected range on tasks of immediate auditory attention and cognitive flexibility. These results were interpreted in the context of Baddeley's model of working memory, and suggested problems with the visuo-spatial sketchpad and the central executive, but not the phonological store.

The comparison of TS individuals with female sibling controls illustrated the difference in general intellectual ability between the two groups, regardless of spatial demands. TS girls did perform more poorly than controls on all spatial and executive measures. Performances on a task of cognitive flexibility (WCST) were lower than controls but still remained in the average range.

No differences were found between different TS cytogenetic groups and performances on cognitive, behavioural and social-emotional measures. Similarly, no differences were found between girls with a maternal versus paternal X chromosome.

In this sample, girls with TS were rated by the parents as having significant attention problems and this was more common in children under the age of twelve years. Leadership skills were also affected and parents viewed their daughters as lacking in the skills needed for successful leadership. This reduction in leadership ability was due to problems with decision making, organisation, assertiveness and reduced social competency. Parents also reported reduced adaptive living skills and behaviour problems in the TS population. It was common for teenagers with TS to report low levels of self-esteem. Parents rated their teenage TS daughters as more withdrawn in their teenage years. On the whole, TS self-report was generally sound and TS girls viewed themselves as having normal social and emotional functioning.

In conclusion, it is important to highlight the considerable variation observed among TS individuals. Results of studies such as this only reflect group trends and do not emphasise the wide variability in physical, cognitive, behavioural and socio-emotional functioning in the TS population. In the larger TS study, we saw an entire spectrum of functioning, from girls with severe intellectual disabilities, to those who were highly intelligent and had completed postgraduate degrees. On the whole, the cognitive changes observed in TS are mild, and most adult women with TS lead fulfilling and productive lives in their communities. It is important for parents to have realistic expectations about what their TS child can achieve. However, it is equally as important that the TS child is given the same opportunities, and is treated in the same manner as would be expected of other family members. Although there has been considerable progress made in determining the role of hormonal and genetic factors on the TS behavioural phenotype, the role of the environment is still largely unknown. In our experience, a well-adjusted, supportive and informed family can do much to help overcome the cognitive and social difficulties that are observed in some individuals with TS.

5. REFERENCES

Akshoomoff, N.A., & Stiles, J. (1995a). Developmental trends in visuo-spatial analysis and planning: I. Copying a complex figure. *Neuropsychology, 9(3)*, 364-377.

Akshoomoff, N.A., & Stiles, J. (1995b). Developmental trends in visuo-spatial analysis and planning: II. Memory for a complex figure. *Neuropsychology, 9(3)*, 378-389.

Albert, M.S., & Kaplan, E.F. (1980). Organic implications of neuropsychological deficits in the elderly. In L.W. Poon, J. Fozard, L. Cermak, D. Arenberg, & L.W. Thompson (Eds.), *New directions in memory and ageing: Proceedings of the George A. Talland Memorial Conference* (pp. 403-432). Hillsdale, NJ: Lawrence Erlbaum Associates Inc.

Alexander, D., & Money, J. (1966). Turner's syndrome and Gerstmann's syndrome: Neuropsychologic comparisons. *Neuropsychologia, 4*, 265-273.

Allport, A., Styles, E.A., & Hsieh, S. (1994). Shifting attentional set: Exploring the dynamic control of tasks. In C. Umilta & M. Moscovitch (Eds.), *Attention and performance XV* (pp. 421-452). Cambridge, MA: MIT Press.

Anderson, V. (1998). Assessing executive functions in children: Biological, psychological, and developmental considerations. *Neuropsychological Rehabilitation, 8*, 319-349.

Anderson, P., Anderson, V., & Garth, J. (2001). Assessment and development of organisational ability: The Rey Complex Figure Organisational Strategy Score (RCF-OSS). *The Clinical Neuropsychologist, 15(1)*, 81-94.

Anderson, P., Anderson, V., & Lajoie, G. (1996). The Tower of London Test: Validation and standardisation for paediatric populations. *The Clinical Neuropsychologist, 10(1)*, 54-65.

Anderson, V., Anderson, P., Northam, E., Jacobs, R., & Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology, 20*, 385-406.

Anderson, S.W., Damasio, H., Jones, R.D., & Tranel, D. (1991).Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. *Journal of Clinical and Experimental Neuropsychology,13,* 909-922.

Anderson, V., Lajoie, G., & Bell, R. (1995). *Neuropsychological assessment of the school-aged child*. Melbourne: Melbourne University Press.

Anderson, V., & Moore, C. (1995). Age at injury as a predictor of outcome following paediatric head injury. *Child Neuropsychology, 1*, 187-202.

Baddeley, A.D. (1986). *Working memory*. Oxford, Oxfordshire. Clarendon Press.

Baddeley, A.D. (1996). Exploring the central executive. *Quarterly Journal of Experimental Psychology, 49A*, 5-28.

Baddeley, A.D. (2002). Is working memory still working? *European Psychologist, 7(2)*, 85-97.

Baddeley, A.D., Della Sala, S., & Spinnler, H. (1991). The two-component hypothesis of memory deficit in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 13*, 372-380.

Baddeley, A.D., Eldridge, M., & Lewis, V. (1981). The role of subvocalisation in reading. *Quarterly Journal of Experimental Psychology*, *33A*, 439-454.

Baddeley, A.D., & Hitch, J.D. (1974). Working memory. In G.H. Bower (Ed.), *The psychology of learning and motivation.* (Vol. 8, pp. 47-90). San Diego, CA: Academic Press.

Baddeley, A.D., & Hitch, J.D. (1994). Developments in the concept of working memory. *Neuropsychology*, *8*, 485-493.

Baddeley, A.D., & Lieberman, K. (1980). Spatial working memory. In R. Nickerson (Ed.). *Attention and performance VIII* (pp. 521-539). Hillsdale, NJ: Erlbaum Associates.

Baddeley, A.D., & Wilson, B. (1988). Frontal amnesia and the dysexecutive syndrome. *Brain and Cognition*, *7*, 212-230.

Banken, J.A. (1985). Clinical utility of considering Digits Forward and Digits Backward as separate components of the Wechsler Adult Intelligence Scale-Revised. *Journal of Clinical Psychology, 41(5),* 686-691.

Barbas, H. (1992). Architecture and cortical connections of the prefrontal cortex in the rhesus monkey. In: *Advances in Neurology, 57*, Chauvel, P., Delgado-Escueta, A.V., Halgren, E. & Bancaud, J., (eds.), pp. 91-115. Raven Press, New York.

Baron, I.S. (2004). *Neuropsychological evaluation of the child.* New York: Oxford University Press, Inc.

Bell, M.A., & Fox, N.A. (1992). The relations between frontal brain electrical activity and cognitive development during infancy. *Child Development, 63*, 1142-1163.

Bender, B.G., Linden, M.G., & Robinson, A. (1993). Neuropsychological impairment in 42 adolescents with sex chromosome abnormalities. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 48*, 169-173.

Bender, B.G., Linden, M.G., & Robinson, A. (1994). Neurocognitive and psychosocial phenotypes associated with Turner syndrome. In S.H. Broman & J. Grafman (Eds.), *Atypical deficits in developmental disorders: Implication for brain function.* (pp. 197-216). Hillsdale, N.J. Lawrence Erlbaum Associates.

Bender, B.G., Puck, M.H., Salbenblatt, J.A., & Robinson, A. (1984). Cognitive development of unselected girls with complete and partial X monosomy. *Paediatrics, 73*, 175-182.

Bender, B.G., Puck, M.H., Salbenblatt, J.A., & Robinson, A. (1990). Psychoneuroendocrinology. In Holmes C.S. (Ed.). *Brain, Behaviour, and Hormonal Interactions*, New York: Springer, 138-163.

Bennett-Levy, J. (1984). Determinants of performance of the Rey-Osterrieth Complex Figure Test: An analysis, and a new technique for single-case assessment. *British Journal of Clinical Psychology, 23*, 109-119.

Benton, A. L., & Hamsher, K. de S. (1989). *Multilingual Aphasia Examination (2nd ed.)*. Iowa City: AJA Associates, Inc.

Berch, D.B. (1996). Memory. In J. Rovet (Ed.). *Turner syndrome across the lifespan.* (pp. 140-145). Toronto: Klein Graphics.

Berch, D.B., & Bender, B.G. (2000). Turner syndrome. In K.O. Yeates, M.D. Ris & H.G. Taylor (Eds.), *Paediatric Neuropsychology: Research, theory and practice.* New York: Guilford Press.

Berch, D.B., & Kirkendall, K.L. (1986). Spatial information processing in 45, X children. In A. Robinson (Chair). *Cognitive and psychosocial dysfunctions associated with sex chromosomes abnormalities*. Symposium presented at the meeting of the American Association for the Advancement of Science, Philadelphia.

Betts, P.R., Butler, G.E., Donaldson, M.D.C., Dunger, D.B., Johnston, D.I., Kelnar, C.J.H., et al. (1999). A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Archives of Disease in Childhood, 80(3)*, 221-225.

Bidlingmaier, F., Strom, T.M., Dorr, H.G., Eisenmenger, W., & Knorr, D. (1987). Estrone and estradiol concentrations in human ovaries, testes, and adrenals during the

first two years of life. *Journal of Clinical Endocrinology and Metabolism, 65(5)*, 862-867.

Bishop, D.V.M., Canning, E., Elgar, K., Morris, E., Jacobs, P.A., & Skuse, D.H. (2000). Distinctive patterns of memory function in subgroups of females with Turner syndrome: evidence for imprinted loci on the X-chromosome affecting neurodevelopment. *Neuropsychologia*, *38*, 712-721.

Bishop, P.M.F., Lessof, M.H., & Polani, P.E. (1960). Turner's syndrome and allied conditions. In Austin, C.R. (Ed.) *Sex Differentiation and Development*. Cambridge: Cambridge University Press.

Borkowski, J., Benton, A., & Spreen, O. (1967). Word fluency and brain damage. *Neuropsychologia*, *5*, 135-140.

Brandimonte, M.A., Hitch, G.J., & Bishop, D.V.M. (1992). Manipulation of visual mental images in children and adults. *Journal of Experimental Child Psychology*, *53*, 300-312.

Brown, C.J., Carrel, L., & Willard, H.F. (1997). Expression of genes from the human active and inactive X chromosomes. *American Journal of Human Genetics*, *60*, 1333-1343.

Brown, W.E., Kesler, S.R., Eliez, S., Warsofsky, I.S., Haberecht, M., Patwardhan, A., et al. (2002). Brain development in Turner syndrome: A magnetic resonance imaging study. *Psychiatry Research: Neuroimaging, 116*, 187-196.

Brown, W.E., Kesler, S.R., Eliez, S., Warsofsky, I.S., Haberecht, M., & Reiss, A.L., (2004). A volumetric study of parietal lobe subregions in Turner syndrome. *Developmental Medicine and Child Neurology*, 46(9), 607-609.

Bruandet, M., Molko, N., Cohen, L., & Dehaene, S. (2004). A cognitive characterisation of dyscalculia in Turner syndrome. *Neuropsychologia*, *42*, 288-298.

Bruner, J. (1973). Organisation of early skilled action. *Child Development*, *44*, 1-11.

Buchanan, L., Pavlovic, J., & Rovet, J. (1998). A re-examination of the visuo-spatial deficit in Turner syndrome: Contributions of working memory. *Developmental Neuropsychology, 14(2/3)*, 341-367.

Bull, R., & Scerif, G. (2001). Executive functioning as a predictor of children's mathematical ability: Inhibition, switching, and working memory. *Developmental Neuropsychology, 19(2)*, 273-293.

Butler, R.W., Rorsman, I., Hill, K.M., &Tuma, R. (1993). The effects of frontal brain impairment on fluency: Simple and complex paradigms. *Neuropsychology, 7*, 519-529.

Chelune, G.J., & Baer, R.A. (1986). Developmental norms for the Wisconsin Card Sorting Test. *Journal of Clinical and Experimental Neuropsychology, 8(3)*, 219-228.

Chen, H., Faigenbaum, D., & Weiss, H. (1981). Psychosocial aspects of patients with the Ullrich-Turner syndrome. *American Journal of Medical Genetics, 8*, 191-203.

Cinan, S., & Tanor, O.O. (2002). An attempt to discriminate different types of executive functions in the Wisconsin Card Sort Test. *Memory, 10(4)*, 277-289.

Clark, C., Klonoff, H., & Hayden, M. (1990). Regional cerebral glucose metabolism in Turner's syndrome. *The Canadian Journal of Neurological Science, 17*, 140-144.

Clement-Jones, M., Schiller, S., Rao, E., Blaschke, R.J., Zuniga, A., Zeller, R., et al. (2000). The short homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome. *Human Molecular Genetics, 9*, 695-702.

Clopper RR. (1990). Assessing the effect of replacement hormone treatment on psychosocial and psychosexual behavior in growth hormone deficient individuals. In: CS Holme, (Ed). *Psychoneuroendocrinology*. New York: Springer-Verlag; pp. 56–78.

Coakes, S.J., & Steed, L.G. (2003). *SPSS: analysis without anguish: version 11 for Windows*. Queensland: John Wiley & Sons Australia, Ltd,

Collaer, M.L., & Hines, M. (1995). Human behavioural sex differences: A role for gonadal hormones during early development? *Psychological Bulletin, 118(1)*, 55-107.

Connor, J.M., & Loughlin, S.A.R. (1989). Molecular genetics of Turner's syndrome. *Acta Paediatrica Scandinavia, 356*, 77-80.

Cornoldi, C., Marconi, F., & Vecchi, T. (2001). Visuo-spatial working memory in Turner's syndrome. *Brain and Cognition, 4*, 90-94.

Corsi, P.M. (1972). *Human memory and the medial temporal region of the brain*. Unpublished Ph.D. thesis, McGill University, Montreal Neurological Institute.

Daneman, M., & Carpenter, P.A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behaviour, 19*, 450-466.

Daneman; M., & Carpenter, P.A. (1983). Individual differences in integrating information between and within sentences. *Journal of Experimental Psychology: Learning, Memory, & Cognition, 9(4),* 561-584.

Daniel, A. (1983). *Power, privilege and prestige: Occupations in Australia*. Melbourne: Longman-Cheshire,

Dean, H. (1991). Growth hormone therapy in girls with Turner syndrome. *Birth Defects: Original Article Series*, 26(4), 229-234.

Della Sala, S., Gray, C., Baddeley, A., et al. (1999). Pattern span: a tool for unwelding visuo-spatial memory. *Neuropsychologia, 37*, 1189-1199.

Della Sala, S., & Logie, R.H. (2002). Neuropsychological impairments of visual and spatial working memory. In Baddeley, A.D., Kopelman, M.D., & Wilson, B.A. (Eds.), *The handbook of memory disorders*, John Wiley & Sons, Ltd.

Deloache, J.S., & Brown, A.L. (1984). Where do I go next? Intelligent searching by very young children. *Developmental Psychology, 20*, 37-44.

Denckla, M.B. (1996). A theory and model of executive function: A neuropsychological perspective. In G.R. Lyon & N.A. Krasnegor (Eds.), *Attention, memory, and executive function.* (pp 263-277). Baltimore: Brookes.

Dennis, M. (1989). Language and the young damaged brain. In T. Boll & B.K. Bryant (Eds.), *Clinical neuropsychology and brain function: research, measurement and practice* (pp. 89-123). Washington: American Psychological Association.

Dennis, M. (1991). Frontal lobe function in childhood and adolescence: A heuristic for assessing attention regulation, executive control, and the intentional states important for social discourse. *Developmental Neuropsychology*, 7, 327-358.

De Renzi, E., & Nichelli, P. (1975). Verbal and nonverbal memory impairment following hemispheric damage. *Cortex, 11*, 341-354.

Diamond, A., & Goldman-Rakic, P.S. (1989). Comparison of human infants and rhesus monkeys on Piaget's AB task: Evidence for dependence on the prefrontal cortex. *Experiment Brain Research, 74*, 24-40.

Donaldson, M.D. (1997). Growth hormone therapy in Turner syndrome-current uncertainties and future strategies. *Hormone Research, 48(suppl 5)*, 35-44.

Donnelly, S.L., Wolpert, C.M., Menold, M.M., Bass, M.P., Gilbert, J.R., Cuccaro, M.L. et al. (2000). Female with autistic disorder and monosomy X (Turner syndrome): Parent-of-origin effect of the X-chromosome. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 96*, 312-316.

Downey, J., Ehrhardt, A.A., Gruen, R., Bell, J.J., & Morishima, A. (1989). Psychopathology and social functioning in women with Turner syndrome. *Journal of Nervous and Mental Disease, 177(4)*, 191-201.

Downey, J., Ehrhardt, A.A., Morishima, A., Bell, J. & Gruen, R.A. (1987). Gender role development in two clinical syndromes: Turner syndrome versus constitutional short stature. *Journal of American Academy of Child and Adolescent Psychiatry, 26(4)*, 566-573.

Downey, J., Elkin, E.J., Ehrhardt, A.A., Meyer-Bahlburg, H.F.L., Bell, J.J., & Morishima, A. (1991). Cognitive ability and everyday functioning in women with Turner syndrome. *Journal of Learning Disabilities, 24(1)*, 32-39.

Dunbar, K., & Sussman, D. (1995). Toward a cognitive account of frontal lobe function: Simulating frontal lobe deficits in normal subjects. In J. Grafman, K.J. Holyoak, & F. Boller (Eds.), *Structure and functions of the human prefrontal cortex* (pp. 289-304). New York: The New York Academy of Science.

Duncan, J. (1986). Disorganisation of behaviour after frontal lobe damage. *Cognitive Neuropsychology, 3*, 271-290.

Dunn, M., Gomes, H., & Sebastian, M. (1996). Prototypicality of responses of autistic, language disordered, and normal children in a word fluency task. *Child Neuropsychology, 2*, 99-108.

El Abd, S., Patton, M.A., Turk, J., Hoey, H., & Howlin, P. (1999). Social, communicational, and behavioural deficits associated with ring X Turner syndrome. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 88*, 510-516.

El Abd, S., Turk, J., & Hill, P. (1995). Annotation: Psychological characteristics of Turner syndrome. *Journal of Child Psychology and Psychiatry, 36*, 1109-1125.

Elfgren, C., & Risberg, J. (1998). Lateralized blood flow increases during fluency tasks: Influence of cognitive strategy. *Neuropsychologia, 36*, 505-512.

Elgar K, Campbell R, Skuse D. (2002). Are you looking at me? Accuracy in processing line-of-sight in Turner syndrome. *Proceedings Royal Society of London Basic Biological Science, 269*, 2415-22.

Elliott, T.K., Watkins, J.M., Messa, C., Lippe, B., & Chugani, H. (1996). Positron emission tomography and neuropsychological correlations in children with Turner's syndrome. *Developmental Neuropsychology*, *12*, 365-386.

Fernandez, R., Mendez, J., & Pasaro, E. (1996). Turner syndrome: A study of chromosomal mosaicism. *Human Genetics, 98*, 29-35.

Fryer, S.L., Kwon, H., Eliez, S., & Reiss, A.L. (2003). Corpus callosum and posterior fossa development in monozygotic females: A morphometric MRI study of Turner syndrome. *Developmental Medicine and Child Neurology, 45(5)*, 320-324.

Fuster, J.M. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe* (3rd ed.). Philadelphia: Lippincott-Raven

Fuster, J.M. (1993). Frontal lobes. *Current Opinion in Neurobiology*, *3*, 160-165.

Fuster, J.M. (1999). Cognitive functions of the frontal lobes. In B.L. Miller & J.L. Cummings (Eds.), *The human frontal lobes* (pp. 187-195). New York: The Guild Ford Press.

Garron, D.C. (1977). Intelligence among persons with Turner's syndrome. *Behaviour Genetics, 7(2)*, 105-127.

Gathercole, S.E. (1994). Neuropsychology and working memory: A review. *Neuropsychology*, *8(4)*, 494-505.

Gathercole, S.E., & Baddeley, A.D. (1989). Evaluation of the role of phonological STM in the development vocabulary in children: A longitudinal study. *Journal of Memory and Language*, *28*, 200-213.

Gioia, G.G., Isquith, P.K., Retzlaff, P., & Espy, K.A. (2002). Confirmatory factor analysis of the BRIEF in a clinical sample. *Child Neuropsychology, 8*, 249-257.

Glosser, G., & Goodglass, H. (1990). Disorders in executive control functions among aphasic and other brain damaged patients. *Journal of Clinical and Experimental Neuropsychology, 12*, 485-501.

Grafman, J., Jonas, B., & Salazar, A. (1990). Wisconsin Card Sorting Test performance based on location and size of neuroanatomical lesion in Vietnam veterans with penetrating head injuries. *Perception and Motor Skills, 71,* 1120-1122.

Goldberg, M.B., Scully, A.L., Soloman, I.L., & Steinbach, H.L. (1968). Gonadal dysgenesis in phenotypic female subjects. *American Journal of Medicine, 45*, 529-543.

Good, C.D., Elgar, K., Kuntsi, J., Akers, R., Price, C.J., Ashburner, J., et al. (2001). Gene deletion mapping of the X chromosome [Abstract]. *Neuroimage, 13*, S793.

Gravholt, C. H., Svenstrup, B., Bennett, P., & Christiansen, J.S. (1999). Reduced androgen levels in adult Turner syndrome: Influence of female sex steroids and growth hormone status. *Clinical Endocrinology, 50*, 791-800.

Grigsby, J., & Kaye, K. (1996). Behavioural Dyscontrol Scale Manual (2nd edition).

Grigsby, J., Kaye, K., Baxter, J., Shetterly, S.M., & Hamman, R.F. (1998). Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. *Journal of American Geriatrics Society, 46*, 590-596.

Grigsby, J. Kaye, K., & Robbins, L.J. (1992). Reliabilities, norms and factor structure of the Behavioural Dyscontrol Scale. *Perceptual and Motor Skills, 74*, 883-892.

Grigsby, J., Kravcisin, N., Ayarbe, S.D. & Busenbark, D. (1993). Prediction of deficits in behavioural self-regulation among persons with Multiple Sclerosis. *Archives Physical Medicine and Rehabilitation, 74*, 1350-1353.

Grumbach, M.M., Van Wyck, J.J., & Wilkins, L. (1955). Chromosomal sex in gonadal dysgenesis relationship to male pseudohermaphroditism and theories of human sex differentiation. *Journal of Clinical Endocrinology, 15*, 1161-1193.

Gungor, N., Boke, B., Belgin, E., & Tuncbilek, E. (2000). High frequency hearing loss in Ullrich-Turner syndrome. *European Journal of Paediatrics. 159(10),* 740-744

Haberecht, M.F., Menon, V., Warsofsky, I.S., White, C.D., Dyer-Friedman, J., Glover, G.H., et al. (2001). Functional neuroanatomy of visuo-spatial working memory in Turner syndrome. *Human Brain Mapping, 14*, 96-107.

Haddad, H.M., & Wilkins, L. (1959). Congenital anomalies associated with gonadal aplasia: review of 55 cases. *Paediatrics, 23*, 885-902.

Hall, J.G., & Gilchrist, D.M. (1990). Turner syndrome and its variants. *Paediatric Clinics of North America, 37*, 1421-1440.

Hall, J.G., Sybert, V.P., Williamson, R.A., Fisher, N.L., & Reed, S.D. (1982). Turner's syndrome. *Western Journal of Medicine, 137*, 32-44.

Hassold, T.J. (1986). Chromosomal abnormalities in human reproductive wastage. *Trends in Genetics, 2*, 105-110.

Hassold, T., Pettay, D., Robinson, A., & Uchida, I. (1992). Molecular studies of parental origin and mosaicism in 45,X conceptuses. *Human Genetics, 89*, 647-652.

Haverkamp, F., Zerres, K., Rietz, C., Noeker, M., & Ruenger, M. (2004). Risk analyses for the cognitive phenotype in Turner's syndrome: Evidence of familial influence as a decisive factor. *Journal of Child Neurology, 19*, 183-190.

Heaton, R.K., Chelune, G.J., Tally, J.L., Kay, G.G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test manual: Revised and expanded.* Psychological Assessment Resources, Inc.

Heaton, R.K. (1990). *Wisconsin Card Sorting Test Scoring Program: IBM Version 4 for Windows (WCST: CV4) Research Edition*. Florida: Psychological Assessment Resources, Inc.

Hecker, R., & Mapperson, B. (1997). Dissociation of visual and spatial processing in working memory. *Neuropsychologia, 35*, 599-603.

Held, K.R., Kerber, S., Kaminsky, E., Singh, S., Goetz, Seemanova, E., et al. (1992). Mosaicism in 45, X Turner syndrome: Does survival in early pregnancy depend on the presence of two sex chromosomes? *Human Genetics*, *88*, 288-294.

Henn, W., & Zang, K.D. (1997). Mosaicism in Turner's syndrome. (Letter) *Nature, 390*, 569.

Hier, D.B., & Crowley, W.F. (1982). Spatial ability in androgen deficient men. *New England Journal of Medicine*, *306*, 1202-1205.

Hitch, G.J. (1980). Developing the concept of working memory. In G. Claxton (Ed.), *Cognitive psychology: New directions* (pp. 156-196). London: Routledge & Kegan Paul.

Hook, E.B., & Warburton, D. (1983). The distribution of chromosomal genotypes associated with Turner's syndrome: Livebirth prevalence rates and evidence for diminished foetal mortality and severity in genotypes associated with structural abnormalities or mosaicism. *Human Genetics, 64*, 24-27.

Hsu, L.Y. (1994). Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. *American Journal of Medical Genetics, 53(2)*, 108-140.

Huisman, J., Slijper, F.M., Sinnema, G., Akkerhuis, G.W., Brugman-Boezeman, A., Feenstra, J., et al. (1993). Psychosocial effects of two years of human growth hormone treatment in Turner syndrome. The Dutch Working Group: Psychologists and Growth Hormone. *Hormone Research, 39*, Suppl 2:56-59.

Hultcrantz M. (2003). Ear and hearing problems in Turner's syndrome. *Acta Oto-Laryngologica. 123(2),* 253-257.

Jacobs, P. Dalton, P., James, R., Mosse, K., Power, M., Robinson, D., et al. (1997). Turner syndrome: A cytogenetic and molecular study. *Annals of Human Genetics, 61,* 471-483.

Johnson, R., Rohrbaugh, J.W., & Ross, J.L. (1993). Altered brain development in Turner's syndrome. *Neurology, 43,* 801-808.

Jones-Gotman, M., & Milner, B. (1977). Design fluency: The intervention of nonsense drawings after focal cortical lesions. *Neuropsychologia, 15,* 653-674.

Joyce, E.M., & Robbins, T.W. (1991). Frontal lobe function in Korsakoff and non-Korsakoff alcoholics: Planning and spatial working memory. *Neuropsychologia, 29(8),* 709-723.

Kagan-Krieger, S. (1998). A phenomenological study of women with Turners syndrome: A maturational and developmental perspective. *Journal of Adult Development.*, *5*, 125-135.

Kahneman, D., Treisman, A., & Gibbs, B.J. (1992). The reviewing of object files: Object-specific integration of information. *Cognitive Psychology*, *24*, 175-219.

Kaufmann, L. (2002). More evidence for the role of the central executive in retrieving arithmetic facts – A case study of severe developmental dyscalculia. *Journal of Clinical and Experimental Neuropsychology*, *24*, 3, 302-310.

Kaye, K., Grigsby, J., Robbins, L.J., & Korzun, B. (1990). Prediction of independent functioning and behaviour problems in geriatric patients. *Journal of American Geriatric Society, 38*, 1304-1310.

Kesler, S.R., Blasey, C.M., Brown, W.E., Yankowitz, J., Zeng, S.M., Bender, B., et al. (2003). Effects of X-monosomy and X-linked imprinting on superior temporal gyrus morphology in Turner syndrome. *Biological Psychiatry, 54*, 636-646.

Kesler, S.R., Haberecht, M.F., Menon, V., Warsofsky, I.S., Dyer-Friedman, J., Neely, E.K., et al. (2004). Functional neuroanatomy of spatial orientation processing in Turner syndrome. *Cerebral Cortex*, 14, 174-180.

Keverne, E.B. (1997). Genomic imprinting in the brain. *Current Opinion in Neurobiology*, *7*, 463-468.

King, J., & Just, M.A. (1991). Individual differences in syntactic processing: The role of working memory. *Journal of Memory and Language*, *30*, 580-602.

Kirk, U. (1985). Hemispheric contributions to the development of graphic skills. In C. Best (Ed.), *Hemispheric function and collaboration in the child* (pp. 193-228). Orlando FL: Academic Press.

Kuntsi, J., Skuse, D., Elgar, K., Morris, E., & Turner, C. (2000). Ring-X chromosomes: their cognitive and behavioural phenotype. *Annals of Human Genetics, 64*, 295-305.

Lagrou, K., Xhrouet-Heinrichs, D., Heinrichs, C., Craen, M., Chanoine, J.P., Malvaux, P., et al. (1998). Age-related perception of stature, acceptance of therapy, and psychosocial functioning in human growth hormone-treated girls with Turner's syndrome. *Journal of Clinical Endocrinology and Metabolism, 83(5)*, 1494-1501.

Lahood, B.J., & Bacon, G.E. (1985). Cognitive abilities of adolescent Turner's syndrome patients. *Journal of Adolescent Health Care, 6*, 358-364.

Lawrence, K., Campbell, R., Swettenham, J., Terstegge, J., Akers, R., Coleman, M., et al. (2003). Interpreting gaze in Turner syndrome: impaired sensitivity to intention and emotion, but preservation of social cueing. *Neuropsychologia, 41*, 894-905.

Lawrence, K., Kuntsi, J., Coleman, M., Campbell, R., & Skuse, D. (2003). Face and emotion recognition deficits in Turner syndrome: A possible role for X-linked genes in amygdala development. *Neuropsychology, 17(1)*, 39-49.

Leao, J.C., Voorhess, M.L., Schlegel, R.J., & Gardner, L.I. (1966). XX/XO mosaicism in nine preadolescent girls: short stature as a presenting complaint. *Paediatrics, 38*, 972-981.

Levin, B.E. (1990). Organisational deficits in dyslexia: Possible frontal lobe dysfunction. *Developmental Neuropsychology, 6*, 95-110.

Levin, H.S., Culhane, K.A., Hartmann, J., Evankovich, K., Mattson, A.J., Harward, H., et al. (1991). Developmental changes in performance on tests of purported frontal lobe functioning. *Developmental Neuropsychology, 7*, 377-395.

Lewandowski, L., Costenbader, V., & Richman, R. (1985). Neuropsychological aspects of Turner syndrome. *International Journal of Clinical* Neuropsychology, 7, 144-147.

Lezak, M.D. (1988). IQ: R.I.P. *Journal of Clinical and Experimental Neuropsychology, 10(3),* 351-361.

Lezak, M.D. (1993). *Neuropsychological assessment*. New York: Oxford University Press.

Lezak, M.D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Lindsten, J. (1963). *The nature and origin of X-chromosome aberrations in Turner's syndrome*. Stockholm: Almist and Wiksell.

Lippe, B.M., Westra, S.J., & Boechat, M.I. (1993). Ovarian function in Turner syndrome: Recognizing the spectrum. In I. Hibi & K. Takano (Eds.), *Basic and clinical approach to Turner syndrome* (pp. 117-122). Amsterdam, Netherlands: Elsevier Science Publishers.

Loesch, D.Z., Bui, Q.M., Kelso, W., Huggins, R.M., Slater, H., Warne, G., et al. (In Press). Effect of Turner's syndrome and X-linked imprinting on cognitive status: analysis based on pedigree data. *Brain and Development.*

Logie, R.H. (1986). Visuo-spatial processing in working memory. *Quarterly Journal of Experimental Psychology, 38A*, 229-247.

Luria, A.R. (1966). *Higher cortical functions in man.* New York: Basic Books.

Luria, A.R. (1973). *The working brain: An introduction to neuropsychology.* New York: Basic Books

Luria, A.R. (1980). *Higher cortical functions in man* (2nd ed.). New York: Basic Books.

MacDonald, M.C., Just, M.A., & Carpenter, P.A. (1992). Working memory constraints on the processing of sentence ambiguity. *Cognitive Psychology, 24*, 56-98.

Maeda. T., Ohno, M., & Matsunobu, A. (1991). A cytogenetic survey of 14836 consecutive liveborns. *Japanese Journal of Human Genetics, 36*, 117-129.

Mahone, E.M., Cirino, P.T., Cutting, L.E., Cerrone, P.M., Hagelthorn, K.M., Hiemenz, J.R., et al. (2002). Validity of the Behaviour Rating Inventory of Executive Function in children with ADHD and/or Tourette syndrome. *Archives of Clinical Neuropsychology*, 17, 643-662.

Mambelli, M.C., Perulli, L., Casella, S., Levetaki, R., Perini, C. Gozzi, G., et al. (1995). Difficulties and experiences in dealing with the needs of patients with Turner syndrome and their families: The usefulness of the multidisciplinary approach. In Rovet J (Ed.), *Turner syndrome across the lifespan* (pp. 108-112). Ontario: Klein Graphics.

Mani K., & Johnson-Laird P.N. (1982). The mental representation of spatial descriptions. *Memory and Cognition, 10(2)*, 181-187.

Mateer, C.A., & Williams, D. (1991). Effects of frontal lobe injury in childhood. *Developmental Neuropsychology, 7*, 359-376.

Mathisen, B., Reilly, S., & Skuse, D. (1992). Oral-motor dysfunction and feeding disorders of infants with Turner syndrome. *Developmental Medicine and Child Neurology, 34*, 141-149

Mathur, A., Stekol, L., Schatz, D., MacLaren, N.K., Scott, M.L., & Lippe, B. (1991). The parental origin of the single X chromosome in Turner syndrome: Lack of correlation with parental age or clinical phenotype. *American Journal of Human Genetics, 48(4)*, 682-686.

Matsumoto, A., Arai, Y., Urano, M., & Hyodo, S. (1991). Androgen regulates gap junction mRNA expression in androgen-sensitive motor neurons in the rat spinal cord. *Neuroscience Letters, 131*, 159-162.

Mazzocco, M.M.M. (1998). A process approach to describing mathematics difficulties in girls with Turner syndrome. *Paediatrics, 102(2)*, 492-6.

Mazzocco, M.M.M. (2001). Math learning disability and math LD subtypes: Evidence from studies of Turner syndrome, fragile X syndrome, and neurofibromatosis type 1. *Journal of Learning Disabilities, 34(6), 520-533.*

Mazzocco, M.M.M., Baumgardner, T., Freund, L.S., & Reiss, A. (1998). Social functioning among girls with Fragile X or Turner syndrome and their sisters. *Journal of Autism and Developmental Disorders, 28(6)*, 509-517.

McCauley, E. (1990). Psychosocial and emotional aspects of Turner syndrome. In B.G. Bender & D.B. Berch (Eds.), *Sex chromosome abnormalities and behaviour: Psychological studies* (pp. 79-99). Boulder, Colorado: AAAS/Westview Press.

McCauley, E., Feuillan, P., Kushner, H., & Ross, J.L. (2001). Psychosocial development in adolescents with Turner syndrome. *Journal of Developmental and Behavioural Paediatrics, 22(6)*, 360-365.

McCauley, E., Ito, J., & Kay T. (1986). Psychosocial functioning in girls with Turner's syndrome and short stature: Social skills, behaviour problems, and self-concept. *Journal of the American Academy of Child Psychiatry, 25(1),* 105-112.

McCauley, E., Kay, T., Ito, J., & Treder, R. (1987). The Turner syndrome: Cognitive deficits, affective discrimination, and behaviour problems. *Child Development, 58*, 464-473.

McCauley, E., Ross, J., Kushner, H., & Cutler, G. Jr. (1995). Self-esteem and behaviour in girls with Turner syndrome. *Journal of Developmental Behavioural. Paediatrics., 16*, 82-88.

McCauley, E., Sybert, V.P. & Ehrhardt, A.A. (1986). Psychosocial adjustment of adult women with Turner syndrome. *Clinical Genetics, 29*, 284-290.

McEwen, B.S., Jones, K.J., & Pfaff, D.W. (1987). Hormonal control of sexual behaviour in the female rat: Molecular, cellular and neurochemical studies. *Biology of Reproduction, 36*, 37-45.

McGlone, J. (1985). Can spatial deficits in Turner's syndrome be explained by focal CNS dysfunction or atypical speech lateralization? *Journal of Clinical and Experimental Neuropsychology, 7*, 375-394.

Mega. M.S. & Cummings, J.L. (2001). In Salloway, S.P., Malloy, P.F., & Duffy, J.D. *The frontal lobes and neuropsychiatric illness*, Washington, American Psychiatric Publishing, Inc.

Mesulam, M. M. (2000). *Principles of Behavioral and Cognitive Neurology*. New York: Oxford University Press.

Midtbo, M., Wisth P.J., & Halse, A. (1996). Craniofacial morphology in young patients with Turner syndrome. *European Journal of Orthodontics, 18*, 215-225.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J. Warren & K. Akert (Eds.). *The frontal granular cortex and behaviour* (pp. 313-331). New York: McGraw-Hill

Milner, B. (1971). Interhemispheric differences in the localisation of psychological processes in man. *British Medical Bulletin, 27,* 272-277.

Money, J., (1973). Turner's syndrome and parietal lobe functions. *Cortex, 9*, 387-393.

Money J. (1993). Specific neuro-cognitive impairments associated with Turner (45,X) and Klinefelter (47,XXY) syndromes: a review. *Social Biology. 40(1-2),* 147-51

Money, J. & Alexander, D. (1966). Turner's syndrome: Further demonstration of the presence of specific cognitional deficiencies. *Journal of Medical Genetics, 3*, 47-48.

Money, J. & Granoff, D. (1965). IQ and the somatic stigmata of Turner's syndrome. *American Journal of Mental Deficiency, 70*, 69-77.

Monti, J.A. (1984). *The neurocognitive mechanisms underlying perseveration.* Unpublished doctoral dissertation, Victoria University, Toronto, Canada.

Morice, R., & Delahunty, A. (1996). Frontal/executive impairments in schizophrenia. *Schizophrenia Bulletin, 22,* 125-137.

Morris, R.G., Ahmed, S., Syed, G.M., & Toone, B.K. (1993). Neural correlates of planning ability: Frontal lobe activation during the Tower of London test. *Neuropsychologia, 31(12),* 1367-78.

Morris, R. G., & Baddeley, A. D. (1988). Primary and working memory functioning in Alzheimer-type dementia. *Journal of Clinical and Experimental Neuropsychology, 10(2)*, 279-296.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*, 257-267.

Murphy, D.G.M., Allen, G., Haxby, J.V., Largay, K.A., Daly, E., White, B.J., et al. (1994). The effects of sex steroids, and the X chromosome, on female brain function: A study of the neuropsychology of adult Turner syndrome. *Neuropsychologia, 32(11)*, 1309-1323.

Murphy, D.G.M., DeCarli, C., Daly, E., Haxby, J.V., Allen, G., White, B.J. et al. (1993). X-chromosome effects on female brain: A magnetic resonance imaging study of Turner's syndrome. *Lancet, 342*, 1197-1200.

Murphy, D.G.M., Mentis, M.J., Pietrini, P., Grady, C., Daly, E., Haxby, J.V., et al. (1997). A PET study of Turner's syndrome: Effects of sex steroids and the X chromosome on brain. *Biological Psychiatry, 41*, 285-298.

Naumova, A.K., Leppert, M., Barker, D.F., Morgan, K., & Sapienza, C. (1998). Parental origin-dependent, male offspring-specific transmission-ratio distortion at loci on the human X chromosome. *American Journal of Human Genetics*, *62*, 1493-1499.

Netley, C., & Rovet, J. (1983). Atypical hemisphere lateralization in Turner's syndrome. *Cortex*, *18*, 377-384.

Neisser, U. (1967). *Cognitive psychology*. Englewood Cliffs, NJ: Prentice-Hall.

Nielsen, J., & Sillesen, I. (1981). Turner's syndrome in 115 Danish girls born between 1955 and 1966. *Acta Jutlandica 56*, Medicine Series 22, Aarhus.

Nielsen, J., & Wohlert, M. (1991). Chromosome abnormalities found among 34910 newborn children: results from a 13-year incidence study in Aarthus, Denmark. *Human Genetics, 87*, 81-83.

Nigg, J.T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin, 126*, 220-246.

Nijhuis-van der Sanden, M.W.G., Eling, P.A.T.M., & Otten, B.J. (2003). A review of neuropsychological and motor studies in Turner syndrome. *Neuroscience and Biobehavioural Reviews*, 27, 329-338.

Nijhuis-van der Sanden, R.W.G., Smits-Engelsman, B.C.M., & Eling, P.A.T.M. (2000). Motor performance in girls with Turner syndrome. *Developmental Medicine and Child Neurology, 42*, 685-690.

Nijhuis-van der Sanden, R.W.G., Smits-Engelsman, B.C.M., Eling, P.A.T.M., Nijhuis, B.J.G., & Van Galen, G.P. (2002). Low elementary movement speed is associated with poor motor skill in Turner syndrome. *Developmental Medicine and Child Neurology, 3*, 643-670.

Norman, D., & Shallice, T. (1980). *Attention to action: Willed and automatic control of behaviour* (CHIP Report No. 99). University of California, San Diego.

O'Neill, S., Ghelani, K., Rovet, J., & Chitayat, D. (2000). *Physical and psychological development in individuals prenatally diagnosed with 45,X/46,XX.* Presented at the American Society of Human Genetics Meeting. Philadelphia, PA.

Orsini, A. (1994). Corsi's block-tapping test: Standardisation and concurrent validity with WISC-R for children aged 11 – 16. *Perceptual and Motor Skills, 79*, 1547-1554.

Osterrieth, P. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie, 30*, 206-356.

Osterrieth, P. (1993). The complex figure copy test. *The Clinical Neuropsychologist, 7*, 3-21.

Owen, A.M., Downes, J.J., Sahakian, B.J., Polkey, C.E., & Robbins, T.W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28(10),* 1021-1034.

Park, E., Bailey, J.D., & Cowell, C.A. (1983). Growth and maturation of patients with Turner's syndrome. *Paediatric Research, 17*, 1-7.

Parker, D.M., & Crawford, J.R. (1992). Assessment of frontal lobe dysfunction. In J.R. Crawford, D.M. Parker, & W.W. McKinlay (Eds.), *A handbook of neuropsychological assessment* (pp. 267-294). Hove, UK: Lawrence Erlbaum Associates Ltd.

Pasquino, A.M., Passeri, F. Pucarelli, I., Segni, M., & Municchi, G. (1997). Spontaneous pubertal development in Turner's syndrome. *Journal of Clinical Endocrinology and Metabolism, 82*, 1810-1813.

Pavlidis, K., McCauley, E., & Sybert, V.P. (1995). Psychosocial and sexual functioning of adult women with Turner syndrome. *Clinical Genetics, 47*, 85-89.

Pendleton, M.G., Heaton, R.K., Lehman, R.A., & Hulihan, D. (1982). Diagnostic utility of the Thurstone Word Fluency Test in neuropsychological evaluations. *Journal of Clinical Neuropsychology, 4*, 307-317.

Pennington, B.F., Bender, B., Puck, M., Salbenblatt, J., & Robinson, A. (1982). Learning disabilities in children with sex chromosome anomalies. *Child Development, 53(5),* 1182-92.

Pennington, B.F., Heaton, R.K., Karzmark, P., Pendleton, M.G., Lehman, R., & Shucard, D.W. (1985). The neuropsychological phenotype in Turner syndrome, *Cortex, 21*, 391-404.

Pennington, B.F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 37*, 51-87.

Perry, R.J., & Hodges, J.R. (1999). Attention and executive deficits in Alzheimer's disease: A critical review. *Brain, 122*, 383-404.

Phillips, L.H., Wynn, V., Gilhooly, K.J., Della Sala, S., & Logie. R.H. (1999). The role of memory in the Tower of London task. *Memory, 7(2)*, 209-231.

Pidcock, F.S. (1984). Intellectual functioning in Turner syndrome. *Developmental Medicine and Child Neurology, 26*, 539-545.

Plotnick, L., Attie, K., Blethen, S., & Sy, J. (1998). Growth hormone treatment of girls with Turner syndrome: The National Cooperative Growth Study experience. *Paediatrics, 102(2)*, 479-481.

Polani, P.E. (1960). Chromosomal factors in certain types of educational subnormality. In Bowman, P.W. & Mautner, H.B. (Eds.) *Mental Retardation*. New York: Grune and Stratton.

Polani, P.E. (1961). Turner's syndrome and allied health conditions. *British Medical Bulletin, 17*, 200-205.

Rabinowicz, T. (1976). Morphological features of the developing brain. In M.A.B. Brazier & F. Coceani (Eds.), *Brain dysfunction in infantile febrile convulsions* (pp.1-23). New York: Raven.

Rae, C., Joy, P., Harasty, J., Kemp, A., Kuan, S., Christodoulou, J. et al., (2004). Enlarged temporal lobes in Turner syndrome: An X-chromosome effect? *Cerebral Cortex*, 14, 156-164.

Ranke, M.B., & Grauer, M.L. (1994). Adult height in Turner syndrome: Results of a multinational survey. *Hormone Research, 42(3)*, 90-94.

Ranke, M.B., Pflüger, H. Rosendahl, W., Stubbe, P., Enders, H., Bierich, J.R., et al. (1983). Turner's syndrome: Spontaneous growth in 150 cases and review of the literature. *Paediatrics, 141*, 81-88.

Rao, E., Weiss, B., Fukami, M., Rump, A., Niesler, B., Mertz, A. et al. (1997). Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner's syndrome. *Nature Genetics, 16*, 54-63.

Ravnkilde, B., Videbech, P., Rosenberg, R., Gjedde, A., & Gade, A. (2002). Putative tests of frontal lobe function: A PET-Study of brain activation during Stroop's test and verbal fluency. *Journal of Clinical and Experimental Neuropsychology, 24*, 534-547.

Reiss, A.L., Eliez, S., Schmitt, J.E., Patwardhan, A., & Haberecht, M. (2000). Brain imaging in neurogenetic conditions: Realizing the potential of behavioural neurogenetics research. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*, 186-197.

Reiss, A.L., Freund, L., Plotnick, L., Baumgardner, T., Green, K. Sozer, A.C., et al. (1993). The effects of X monosomy on brain development: Monozygotic twins discordant for Turner's syndrome. *Annals of Neurology, 34*, 95-107.

Reiss, A.L., Mazzocco, M.M.M., Greenlaw, R., Freund, L.S., & Ross, J.L. (1995). Neurodevelopmental effects of X monosomy: A volumetric imaging study. *Annals of Neurology, 38*, 731-738.

Rende, B., Ramsberger, G. & Miyake, A. (2002). Commonalities and differences in the working memory components underlying letter and category fluency tasks: A dual-task investigation. *Neuropsychology, 16(3)*, 309-321.

Reuhkala, M. (2001). Mathematical skills in ninth-graders: Relationship with visuo-spatial abilities and working memory. *Educational Psychology, 21*, 4, 387-399.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie, 28*, 286-340.

Rey, A. (1993). Psychological examination of traumatic encephalopathy (translation). *The Clinical Neuropsychologist*, 7, 3-21.

Reynolds, C.R., & Kamphaus, R.W. (1992) (Eds.). *Behaviour Assessment System for Children: Manual. American Guidance Service, Inc. USA*

Robinson, A., Bender, B.G., Borelli, J. Puck, M. Salbenblatt, J., & Winter, J. (1986). Sex chromosome aneuploidy: Prospective and longitudinal studies. In S. Ratcliffe & N. Paul (Eds.), *Prospective studies on children with sex chromosome aneuploidy* (pp. 23-73). New York: Alan R. Liss,.

Romans, S.M., Roeltgen, D.P., Kushner, H., & Ross, J.L. (1997). Executive function in girls with Turner's syndrome. *Developmental Neuropsychology, 13(1)*, 23-40.

Romans, S.M., Stefanatos, G., Roeltgen, D.P., Kushner, H., & Ross, J.L. (1998). The transition to young adulthood in Ullrich-Turner syndrome: Neurodevelopmental changes. *American Journal of Medical Genetics, 79*, 140-147.

Rosenfeld, R.G., & Grumbach, M.M. (Eds.). (1990). *Turner syndrome*. New York: Marcel Dekker.

Rosenfeld, R.G., McCauley, E., Albertsson-Wikland, K., Asch, R., Irvine, J.C., Conte, F., et al. (1994). Recommendations for diagnosis, treatment, and management of individuals with Turner syndrome. *The Endocrinologist, 4(5)*, 351-358.

Ross, J.L. (1990). Disorders of the sex chromosomes: Medical overview. In C.S. Holmes (Ed.), *Psychoneuroendocrinology: Brain, behaviour, and hormonal interactions* (pp.127-137). New York: Springer-Verlag.

Ross, J.L. (1996). Oestrogen therapy in the treatment of Turner's syndrome. In J. Rovet (Ed.), *Turner syndrome across the lifespan* (pp. 93-96).Toronto: Klein Graphics.

Ross, J.L., Kushner, H., & Roeltgen, D. (1996). Developmental changes in motor function in girls with Turner syndrome. *Paediatric Neurology, 15*, 317-322.

Ross, J.L., Kushner, H., & Zinn, A. R. (1997). Discriminant analysis of the Ullrich-Turner syndrome neurocognitive profile. *American Journal of Medical Genetics, 72*, 275-280.

Ross, J.L., Roeltgen, D., & Cutler, G.B. (1995). The neurodevelopmental transition between childhood and adolescence in girls with Turner syndrome. In Albertsson-Wikland, K. & Ranke, M. (Eds.), *Turner syndrome in a life-span perspective*. Elsevier Science, USA.

Ross, J.L., Roeltgen, D., Feuillan, P., Kushner, H., & Cutler, G.B. (1997). Absence of growth hormone effects on cognitive function in girls with Turner syndrome. *Journal of Clinical Endocrinology and Metabolism, 82(6)*, 1814-1817.

Ross, J.L., Roeltgen, D., Feuillan, P., Kushner, H., & Cutler, G.B. (1998). Effects of oestrogen on non-verbal processing speed and motor function in girls with Turner's syndrome. *Journal of Clinical Endocrinology and Metabolism, 83*, 3198-3204.

Ross, J.L., Roeltgen, D., Feuillan, P., Kushner, H., & Cutler, G.B. (2000). Use of oestrogen in young girls with Turner Syndrome: Effects on memory. *Neurology*, 54, 164-170.

Ross, J.L., Roeltgen, D., Kushner, H., Wei, F., & Zinn, A. (2000). The Turner syndrome-associated neurocognitive phenotype maps to distal Xp. *American Journal of Human Genetics, 67*, 672-681.

Ross, J.L., Roeltgen, D., Stefantatos, G.A., Feuillan, P., Kushner, H., Bondy, C. & Cutler, Jr G.B. (2003). Androgen responsive aspects of cognition in girls with Turner syndrome. *Journal of Clinical Endocrinology and Metabolism*, 88(1), 292-296.

Ross, J.L., Stefanatos, G.A., Kushner, H., Zinn, A., Bondy, C., & Roeltgen, D. (2002). Persistent cognitive deficits in adult women with Turner syndrome. *Neurology, 58(2)*, 218-225.

Ross, J.L. & Zinn, A. (1999). Turner syndrome: Potential hormonal and genetic influences on the neurocognitive profile. In: Tager-Flusberg, H (Ed.), *Neurodevelopmental Disorders* (pp. 251-268). A Bradford Book, The MIT Press, Massachusetts, USA.

Ross, J.L., Zinn, A., & McCauley, E. (2000). Neurodevelopmental and psychosocial aspects of Turner syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*, 135-141.

Rourke, B.P. (1989). *Nonverbal learning disabilities: The syndrome and the model.* New York: Guilford Press.

Rourke, B. (1995). *Syndrome of nonverbal learning disabilities.* New York, NY, Guilford Press.

Roush J., Davenport, M.L., & Carlson-Smith, C. (2000). Early-onset sensorineural hearing loss in a child with Turner syndrome. *Journal of the American Academy of Audiology. 11(8)*, 446-453

Rovet, J.F. (1990). The cognitive and neuropsychological characteristics of females with Turner syndrome. (pp. 38-77). In D.B. Berch & B.G. Bender (Eds.), *Sex chromosome abnormalities and human behaviour.* Boulder: Westview Press.

Rovet, J.F. (1993). The psychoeducational characteristics of children with Turner syndrome. *Journal of Learning Disabilities, 26(5)*, 333-341.

Rovet, J.F. (1995). Turner syndrome. In B.P. Rourke (Ed.), *Syndrome of non-verbal learning disabilities: Neurodevelopmental manifestations* (pp.351-371). New York: Guilford Press.

Rovet, J.F. (2004). Turner Syndrome: Genetic and hormonal factors contributing to a specific learning disability profile. *Learning Disabilities, Research and Practice, 19(3)*, 133-145.

Rovet, J.F., & Buchanan, L. (1999) Turner syndrome: A cognitive neuroscience approach. In: Tager-Flusberg, H. (Ed.), *Neurodevelopmental Disorders*. Massachusetts: A Bradford Book, The MIT Press

Rovet, J., & Ireland, L. (1994). Behavioural phenotype in children with Turner syndrome. *Journal of Paediatric Psychology., 19*, 779-790.

Rovet, J., & Netley, C. (1982). Processing deficits in Turner's syndrome. *Developmental Psychology, 18*, 77-94.

Rovet, J, Szekely, C., & Hockenberry, M.N. (1994). Specific arithmetic calculation deficits in children with Turner syndrome. *Journal of Clinical and Experimental Neuropsychology, 16*, 820-839.

Sattler, J.M. (1992). *Assessment of Children: Revised and Updated* (3rd ed.). San Diego, CA: Jerome M. Sattler, Publisher, Inc.

Sculerati, N., Ledesma-Medina, J., Finegold, D.N., & Stool, S.E. (1990). Otitis media and hearing loss in Turner syndrome. *Archives of Otolaryngology – Head and Neck Surgery, 116*, 704-707.

Shaffer, J.W. (1962). A specific cognitive deficit observed in gonadal aplasia (Turner's syndrome). *Journal of Clinical Psychology, 18*, 403-406.

Shallice, T. (1982). Specific impairments in planning. *Philosophical Transcripts of the Royal Society of London, 298*, 199-209.

Shallice, T. (1988). *From neuropsychology to mental structure*. Cambridge, England: Cambridge University Press.

Shallice, T., & Burgess, P.W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain, 114*, 727-741.

Shallice, T., & Burgess, P.W. (1993). Supervisory control of action and thought selection. In A. Baddeley & L. Weiskrantz (Eds.). *Attention: Selection, awareness, and control* (pp. 171-187). Oxford: Oxford University Press.

Siegel P.T, Clopper, R., & Stabler, B. (1991). Psychological impact of significantly short stature. *Acta Paediatric Scandinavia, 377(suppl)*, 14-18.

Siegal, P.T., Clopper, R., & Stabler, B. (1998). The psychological consequences of Turner syndrome and review of the National Cooperative Growth Study psychological substudy. *Paediatrics, 102*, 488-491.

Silbert, A., Wolff, P.H., & Lilienthal, J. (1977). Spatial and temporal processing in patients with Turner's syndrome. *Behaviour Genetics, 7(1)*, 11-21.

Skuse, D.H., Good, C.D., Elgar, K., Thomas, N.S., & Morris, J.S. (2001). *Gene-brain mechanisms in Turner syndrome*. Paper presented at the Genesis conference.

Skuse, D.H., James, R.S., Bishop, D.V.M., Coppin, B., Dalton, P., Aamodt-Leeper, G., et al. (1997). Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature, 387*, 705-708.

Smith, E.E., & Jonides, J. (1996). Working memory in humans: Neuropsychological evidence. In M. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 1009-1020). Cambridge, MA: MIT Press.

Spreen, O., Risser, A.H., & Edgell, D. (1995). *Developmental neuropsychology*. New York: Oxford University Press.

Spreen, O., & Strauss, E. (1991). *A compendium of neuropsychological tests*. New York: Oxford.

SPSS Inc. (2002). *SPSS Graduate Pack 11.5 for Windows*. USA: SPSS Inc.

Stuss, D.T. (1992). Biological and psychological development of executive functions. *Brain and Cognition, 20*, 8-23.

Stuss, D.T., & Alexander, M.P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research, 63*, 289-298.

Stuss, D.T., & Benson, D.F. (1986). *The frontal lobes*. New York: Raven Press.

Stuss, D.T., & Benson, D.F. (1987). The frontal lobes and control of cognition and memory. In E. Perecman (Ed.), *The frontal lobes revisited.* (pp.141-158). New York: IRBN Press.

Swillen, A., Fryns, J.P. & Kleczkowska, A., Massa, G., Vanderschueren-Lodeweyckx, M., & Van den Berghe, H. (1993). Intelligence, behaviour, and psychosocial development in Turner's syndrome. *Genetic Counseling, 4(1),* 7-18.

Sybert, V.P. (2002). Phenotypic effects of mosaicism for a 47, XXX cell line in Turner syndrome. *Journal of Medical Genetics, 39*, 217-221.

Tamm, L., Menon, V., & Reiss, A.L. (2003). Abnormal prefrontal cortex during response inhibition in Turner syndrome: Functional Magnetic Resonance Imaging evidence. *Biological Psychiatry, 53*, 107-111.

Temple, C. M. (2002). Oral fluency and narrative production in children with Turner's syndrome. *Neuropsychologia, 40*, 1419-1427.

Temple, C.M., & Carney, R.A. (1993). Intellectual functioning of children with Turner syndrome: A comparison of behavioural phenotypes. *Developmental Medicine and Child Neurology, 35*, 691-698.

Temple, C.M., & Carney, R.A. (1995). Patterns of spatial functioning in Turner's syndrome. *Cortex, 31*, 109-118.

Temple, C.M., Carney, R.A., & Mullarkey, S. (1996). Frontal lobe function and executive skills in children with Turner's syndrome. *Developmental Neuropsychology, 12(3)*, 343-363.

Temple, C.M., & Marriott, A.J. (1998). Arithmetical ability and disability in Turner's syndrome: A cognitive neuropsychological analysis. *Developmental Neuropsychology, 14(1)*, 47-67.

Thatcher, R.W. (1991). Matruation of the human frontal lobes. Physiological evidence for staging. *Developmental Neuropsychology, 7*, 397-419.

Thatcher, R.W. (1992). Cyclical cortical re-organisation during early childhood. *Brain and Cognition, 20*, 24-50.

Thompson, J.A. (1983). Is continuous visual monitoring really necessary in visually guided locomotion? *Journal of Experimental Psychology: Human Perception and Performance, 9*, 427-443.

Thompson, M.W., McInnes, R.R., & Willard, H.F. (Eds.) (1991). *Thompson & Thompson: Genetics in Medicine. Fifth Edition.* USA: W.S. Saunders Company.

Tsezou, A., Hadijiathanasiou, Ch., Gourgiotis, D, Galla, A., Kavazarakis, Em., Pasparaki, A., et al. (1999). Molecular genetics of Turner syndrome: Correlation with clinical phenotype and response to growth hormone therapy. *Clinical Genetics, 56*, 441-446.

Tucha, O., Smely, C., & Lange, K.W. (1999). Verbal and figural fluency in patients with mass lesions of the left or right frontal lobes. *Journal of Clinical and Experimental Neuropsychology, 21*, 229-236

Tucker, A., Ewing. J., & Ross, N. (1996, September). *Animal Fluency: A new test of executive functioning: Normative data and clinical experience*. Paper presented at the College of Clinical Neuropsychologists Second Conference, Sydney, Australia.

Vallar, G. & Baddeley, A. (1982). Short-term forgetting and the articulatory loop. *Quarterly Journal of Experimental Psychology, 34*, 53-60.

Vallar, G. & Baddeley, A. (1984). Fractionation of working memory: Neuropsychological evidence for a phonological short-term store. *Journal of Verbal Learning and Verbal Behaviour*, 23, 151-161.

Van Borsel, J., Dhooge, I., Verhoye, K., Derde, K., & Curfs, L. (1999). Communication problems in Turner Syndrome: A sample survey. *Journal of Communication Disorders*, 32, 435-446.

Van Gemund, J.J., & Van Geldern, H.H. (1961). Gonadal dysgenesie bij kinderen. *Nederlands Tijdschrift voor Geneeskunde, 105*, 1678-1683.

Waber, D.P. (1979). Neuropsychological aspects of Turner's syndrome. *Developmental Medicine and Child Neurology, 21*, 58-70.

Waber, D., & Holmes, J. (1985). Assessing children's copy productions of the Rey-Osterrieth Complex Figure. *Journal of Clinical and Experimental Neuropsychology, 7*, 264-280.

Waber, D., & Holmes, J. (1986). Assessing children's memory productions of the - Osterrieth Complex Figure. *Journal of Clinical and Experimental Neuropsychology, 8*, 563-580.

Walsh, K. W. (1978). *Neuropsychology: A clinical approach*. New York: Churchill Livingstone.

Walsh, K., & Darby, D. (1999). *Neuropsychology: A clinical approach*. (4th ed.). New York: Churchill Livingstone.

Watson, J., Balota, D.A., & Sergent-Marshall, S.D. (2001). Semantic, phonological, and hybrid veridical and false memories in healthy older adults and in individuals with dementia of the Alzheimer type. *Neuropsychology, 15*, 254-267.

Wechsler, D. (1992). Wechsler Intelligence Scale for Children: Third Edition (WISC-III) Australian Adaptation. USA: Psychological Corporation.

Welsh, M.C., Cicerello, A., Cuneo, R., & Brennan, M. (1995). Error and temporal patterns in Tower of Hanoi performance: Cognitive mechanisms and individual differences. *Journal of General Psychology, 122*, 69-81.

Welsh, M.C., & Pennington, B.F. (1988). Assessing frontal lobe functioning in children: Views from developmental psychology. *Developmental Neuropsychology, 4*, 199-230.

Welsh, M.C., & Pennington, B.F., & Groisser, D.B. (1991). A normative-developmental study of executive function: A window on prefrontal function in children. *Developmental Neuropsychology, 7*, 131-149.

White, B.J. (1994). The Turner syndrome: Origin, cytogenetic variants, and factors influencing the phenotype. In S.H. Broman & J. Grafman (Eds.), *Atypical deficits in developmental disorders: Implication for brain function.* (pp. 183-195). Hillsdale, N.J.. Lawrence Erlbaum Associates.

Yakovlev, P.I., & Lecours, A.R. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Minkiniwski (Ed.), *Regional development of brain in early life.* (pp. 3-70). Oxford, UK: Blackwell.

Yeates, K.O., Ris, M.D., & Taylor, H.G. (Eds.) (2000). *Paediatric neuropsychology. Research, theory, and practice.* New York: Guilford Press.

Zinn, A.R., & Ross, J.L. (1998). Turner syndrome and haploinsufficiency. *Current Opinion in Genetics and Development, 8*, 322-327.

Zinn, A.R., Tonk, V.S., Chen, Z., Flejter, W., Gardner, A., Guerra, R., et al. (1998). Evidence for a Turner syndrome locus or loci at Xp11.2-p22.1. *American Journal of Human Genetics, 63*, 1757-1766.

6. APPENDICES

APPENDIX A

BEHAVIOURAL DYSCONTROL SCALE-2 (2nd Edition)

Name:_____

Date:_____

1. Tap twice with right hand and once with left in a series. (10 repetitions)

3 – No errors, performed rapidly, learned quickly
2 – Smooth performance, no more than 1 or 2 perseverative errors
1 – Three or 4 perseverative errors, or poor timing and slow or effortful performance with fewer errors
0 – Poor performance, 5 or more perseverative errors

2. Tap twice with left hand and once with right in a series. (10 repetitions)

3 – No errors, performed rapidly, learned quickly
2 – Smooth performance, no more than 1 or 2 perseverative errors
1 – Three or 4 perseverative errors, or poor timing and slow or effortful performance with fewer errors
0 – Poor performance, 5 or more perseverative errors

3. If I say "red", squeeze my hand. If I say "green", do nothing. (15 repetitions)

3 – No errors, rapid responses to verbal stimuli
2 – No more than 1 error
1 – Two to 4 errors, including false starts
0 – More than 4 errors of inhibition or initiation

4. If I tap twice, you tap once. If I tap once, you tap twice. (10 repititions)

3 – No errors, rapid responses to stimuli
2 – No more than 1 error
1 – Two or 3 echopraxic or perseverative responses
0 – More than 3 errors

5. Alternate touching of thumb and fingers (5 full repetitions after practice)

3 – Rapid performance, no errors, quickly automatic
2 – Learns task with few errors, becomes relatively automatic with practice
1 – Difficulty in learning task, many errors, never automatic, best performance remains effortful
0 – Failure to learn task

6. Fist-Edge-Palm

3 – Rapid performance, no errors or hesitancy, quickly automatic
2 – Learns task with minimal errors, becomes relatively automatic with practice
1 – Difficulty in learning task, many errors, never automatic, effortful performance throughout
0 – Failure to learn task

7. Head's Test (Correct first mirroring error)
a) left fist behind head;
b) right hand points to right eye;
c) left hand vertical, right horizontal, form a "T";
d) right hand with bent fingers under chin;
e) left hand to left ear

3 – no errors
2 – one error
1 – Two or 3 errors
0 – More than 3 errors

8. Alphanumeric Sequencing

1 a 2 b 3 c 4 d 5 e 6 f 7 g 8 h 9 i 10 j 11 k 12 l

3 – no errors
2 – one error
1 – Two or 3 errors
0 – More than 3 errors

9. Insight rating

3 – Awareness of (in)accuracy of performance (and of its severity and significance, if deficient)
2 – Awareness of errors but limited understanding of their severity or significance
1 – Only partial or occasional awareness of deficient performance
0 – Completely lacking insight into accuracy of performance

10. Mirroring Errors (even if self corrected)

3 – no errors
2 – one error
1 – two or 3 errors
0 – More than 3 errors

TOTAL SCORE – ADD ALL RAW SCORES FOR 1 – 10.

ENTER SCORE HERE _____

APPENDIX B

AUSTRALIAN NORMATIVE SAMPLE FOR AGES 14-16 YEARS

REY COMPLEX FIGURE, TOWER OF LONDON, VERBAL FLUENCY AND DIGIT SPAN

Test	Age					
	14 (N=26)		15 (N=18)		16 (N=14)	
	M	SD	M	SD	M	SD
Rey Complex Figure (RCF)						
Accuracy	34.0	2.6	34.1	3.0	33.9	2.6
Organisation	5.2	1.0	5.4	1.3	5.4	1.1
Tower Of London (TOL)						
Summary Score	98.4	16.8	99.9	18.2	102.9	18.3
Verbal Fluency Test (COWAT)						
Total Words	28.1	8.7	30.6	9.8	32.7	8.6
Number Errors	0.8	1.0	1.0	1.3	0.8	1.1
Digit Span Task						
Forwards	6.1	1.0	6.9	1.3	6.3	1.1

Source: Anderson, V., Anderson, P., Northam, E., Jacobs, R. & Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology, 20(1)*, 385-406.

APPENDIX C

CONTROLLED ANIMAL FLUENCY TEST
UNPUBLISHED AUSTRALIAN NORMATIVE SAMPLE

Age	Mean/SD	TEST		
		Animal Automatic	Animal Size	Animal Alphabet
6	M	10.1	5.3	3.9
	SD	4.2	3.1	3.0
7	M	11.6	6.6	5.3
	SD	3.7	3.0	2.9
8	M	13.2	8.0	6.8
	SD	4.2	3.1	3.0
9	M	14.7	9.3	8.2
	SD	4.7	3.2	3.1
10	M	15.6	9.5	9.0
	SD	4.4	3.2	3.5
11	M	16.5	9.6	9.8
	SD	4.0	3.2	3.9
12	M	17.1	10.4	9.9
	SD	4.6	3.0	3.7
13	M	17.6	11.1	10.0
	SD	5.1	2.8	3.5
14	M	18.3	11.3	10.5
	SD	5.3	3.3	4.5
15	M	18.9	11.5	10.9
	SD	5.4	3.8	5.5
16	M	19.9	11.9	11.8
	SD	5.8	3.9	4.9

Source: Tucker, A., Ewing, J. & Ross, N. (1996). Animal Fluency – A new test of executive functioning: Normative data and clinical experience with children and adolescents. Paper presented at the Second National Conference of the College of Clinical Neuropsychologists.

APPENDIX D

BASC SELF REPORT OF PERSONALITY (SRP) SCALE DEFINITIONS

Scale	*Definition*
CLINICAL	
Anxiety	Feelings of nervousness, worry, and fear; the tendency to be overwhelmed by problems
Attitude to School	Feelings of alienation, hostility, and dissatisfaction regarding school
Attitude to Teachers	Feelings of resentment and dislike of teachers; beliefs that teachers are unfair, uncaring, or overly demanding
Atypicality	The tendency towards gross mood swings, bizarre thoughts, subjective experiences, or obsessive-compulsive thoughts and behaviours often considered 'odd'
Depression	Feelings of unhappiness, sadness, and dejection; a belief that nothing goes right
Locus of Control	The belief that rewards and punishments are controlled by external events or other people
Sensation Seeking	The tendency to take risks, to like noise, and to seek excitement
Sense of Inadequacy	Perceptions of being unsuccessful in school, unable to achieve one's goals, and generally inadequate
Social Stress	Feelings of stress and tension in personal relationships; a feeling of being excluded from social activities
Somatisation	The tendency to be overly sensitive to, experience, or complain about relatively minor physical problems and discomforts
ADAPTIVE	
Relations with Parents	A positive regard towards parents and a feeling of being esteemed by them
Self-Esteem	Feelings of self-esteem, self-respect, and self-acceptance
Self-Reliance	Confidence in one's ability to solve problems; a belief in one's personal dependability and decisiveness
Interpersonal Relations	The perception of having good social relationships and friendships with peers
COMPOSITE	
School Maladjustment	Composition of Attitude to School, Attitude to Teachers and at an adolescent level, Sensation Seeking scales. It is a broad measure of adaptation to school.

Clinical Maladjustment	Consists of Anxiety, Atypicality, Locus of Control, Social Stress, and at an adolescent level, Somatisation scales. This composite may be characterised as a broad index of distress that reflects the clinical, internalizing problems a child may be experiencing.
Personal Adjustment	Consists of Relations with Parents, Interpersonal relations, Self-Reliance, and Self-Esteem scales. High scores reflect positive levels of adjustment. Low scores suggest problems with interpersonal relationships, self-acceptance, identity development, and ego strength
Emotional Symptoms Index (ESI)	Consists of Social Stress, Anxiety, Interpersonal Relations, Self-Esteem, Depression and Sense of Inadequacy. The ESI is the most global indicator of serious emotional disturbance, particularly internalized disorders.

Source: C. R. Reynolds and R.W. Kamphaus (1992). BASC Manual p. 58

APPENDIX E

BASC PARENT RATING SCALES (PRS) SCALE DEFINITIONS

Scale	*Definition*
CLINICAL	
Anxiety	The tendency to be nervous, fearful or worried about real or imagined problems
Aggression	The tendency to act in a hostile manner(either verbal or physical) that is threatening to others
Attention Problems	The tendency to be easily distracted and unable to concentrate more than momentarily
Atypicality	The tendency to behave in ways that are immature, considered 'odd' or commonly associated with psychosis (such as experiencing visual or auditory hallucinations
Conduct Problems	The tendency to engage in antisocial and rule-breaking behaviour, including destroying property
Depression	Feelings of unhappiness, sadness and stress that may result in an inability to carry out everyday activities (neurovegetative symptoms) or may bring on thoughts of suicide
Somatisation	The tendency to be overly sensitive to, experience, or complain about relatively minor physical problems and discomforts
Withdrawal	The tendency to evade others to avoid social contact
Hyperactivity	The tendency to overly active, rush through work or activities, and act without thinking
ADAPTIVE	
Adaptability	The ability to adapt readily to changes in the environment
Leadership	The skills associated with accomplishing academic, social or community goals, including, in particular, the ability to work well with others
Social Skills	The skills necessary for interacting successfully with peers and adults in home, school, and community settings
COMPOSITE	
Externalising Problems	Consists of Hyperactivity, Aggression and Conduct Problems scales. This composite is characterised by disruptive behaviour problems such as aggression, hyperactivity, and delinquency.
Internalising Problems	Consists of Anxiety, Depression and Somatisation scales. This composite includes scales that measure depression, anxiety, and similar difficulties that are not marked by acting-out behaviour.
Behavioural Symptoms Index	Consists of a combination of central scales from the clinical composites that reflect the overall level of problem behaviour.
Adaptive Skills	Consists of Adaptability, Social Skills, and Leadership. This composite summarises prosocial, organisational, study and other adaptive skills.

Source: C. R. Reynolds and R.W. Kamphaus (1992). BASC Manual p 48

APPENDIX F

SOCIAL COGNITION QUESTIONNAIRE

Name:_____

Date:_____

Questionnaire

Complete the following section by circling 0 if the statement is not at all true of your child, 1 if it is quite or sometimes true of your child, and 2 if it is very or often true of your child.

		Circle Number	
1. Lacking an awareness of other people's feelings.	0	1	2
2. Does not realise when others are upset or angry.	0	1	2
3. Is oblivious to the effect of his/her behaviour on other members of the family.	0	1	2
4. Behaviour often disrupts normal family life.	0	1	2
5. Very demanding of people's time.	0	1	2
6 Difficult to reason with when upset.	0	1	2
7. Does not seem to understand social skills e.g. interrupts conversation.	0	1	2
8. Does not pick up on by language	0	1	2
9. Unaware of acceptable social behaviour	0	1	2
10. Unknowingly offends people with behaviour.	0	1	2
11. Does not respond to commands.	0	1	2
12. Has difficulty following commands unless they are carefully worded	0	1	2

APPENDIX G

SPEARMAN RHO CORRELATION MATRIX: COGNITIVE, SCQ AND BASC

COGNITIVE VARIABLES	ATTENTION		HYPERACTIVITY		LEADERSHIP		ADAPTIVE SKILLS		ATYPICALITY		BEHAV. PROBS.		N	ADAPTABILITY		
	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)		Corr. Coefficient	Sig. (2-tailed)	N
DIGIT FWD	-0.359	0.025	-0.195	0.235	0.258	0.113	0.257	0.114	-0.273	0.092	-0.300	0.064	39	0.188	0.486	16
FIQ	-0.570	0.000	-0.298	0.059	0.588	0.000	0.499	0.001	-0.314	0.045	-0.385	0.013	41	0.408	0.093	18
VIQ	-0.656	0.000	-0.387	0.012	0.536	0.000	0.485	0.001	-0.406	0.008	-0.514	0.001	41	0.403	0.098	18
PIQ	-0.335	0.032	-0.047	0.772	0.465	0.002	0.321	0.041	-0.148	0.354	-0.116	0.469	41	0.313	0.206	18
VC	-0.586	0.000	-0.322	0.040	0.517	0.001	0.489	0.001	-0.313	0.046	-0.417	0.007	41	0.440	0.068	18
PO	-0.308	0.050	0.020	0.903	0.467	0.002	0.316	0.044	-0.134	0.403	-0.069	0.667	41	0.246	0.325	18
FD	-0.567	0.000	-0.407	0.008	0.319	0.042	0.241	0.129	-0.377	0.015	-0.483	0.001	41	0.052	0.838	18
ARITH.	-0.602	0.000	-0.356	0.022	0.340	0.030	0.291	0.065	-0.426	0.005	-0.543	0.000	41	0.086	0.735	18
REY COPY	-0.317	0.049	-0.037	0.825	0.466	0.003	0.406	0.010	-0.210	0.199	-0.251	0.124	39	0.458	0.074	16
REY 30'	-0.181	0.271	-0.004	0.980	0.367	0.022	0.276	0.089	0.123	0.456	-0.095	0.566	39	0.285	0.285	16
REY ORG.	0.365	0.181	-0.022	0.939	0.133	0.636	0.230	0.409	-0.245	0.378	-0.140	0.618	15	0.584	0.046	12
BDS-2	-0.509	0.001	-0.464	0.002	0.312	0.047	0.279	0.077	-0.355	0.023	-0.468	0.002	41	-0.046	0.856	18
COWAT	-0.441	0.005	-0.164	0.318	0.394	0.013	0.258	0.112	-0.365	0.022	-0.297	0.066	39	0.017	0.950	16
ANI SIZE	-0.367	0.018	0.020	0.902	0.378	0.015	0.290	0.066	-0.195	0.221	-0.197	0.216	41	0.483	0.042	18
ANI ALPHA	-0.282	0.074	-0.130	0.418	0.183	0.252	0.102	0.525	-0.304	0.054	-0.278	0.079	41	0.144	0.570	18
TOL	-0.243	0.136	0.041	0.805	0.272	0.094	0.212	0.194	0.019	0.906	-0.077	0.640	39	0.570	0.021	16
BLOCK SPAN	-0.330	0.040	-0.317	0.049	0.158	0.336	0.133	0.419	-0.258	0.112	-0.252	0.122	39	0.370	0.158	16
WCST PERS.	-0.164	0.306	-0.401	0.009	0.116	0.471	0.131	0.415	-0.258	0.104	-0.290	0.066	41	0.285	0.251	18
WCST NONP.	-0.265	0.094	-0.185	0.247	0.385	0.013	0.356	0.023	-0.114	0.476	-0.256	0.106	41	0.281	0.258	18
SCQ	0.667	0.000	0.660	0.000	-0.378	0.015	-0.355	0.023	0.532	0.000	0.814	0.000	41	-0.451	0.061	18

SPEARMAN RHO CORRELATION MATRIX: COGNITIVE, SCQ AND BASC

BASC PARENT RATING SCALE	ATTENTION		HYPERACTIVITY		LEADERSHIP		ADAPTIVE SKILLS		ATYPICALITY		BEHAV. PROBS.		N	ADAPTABILITY		
	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)		Corr. Coefficient	Sig. (2-tailed)	N
SOCIAL SKILLS	-0.311	0.048	-0.140	0.382	0.674	0.000	0.867	0.000	-0.117	0.467	-0.271	0.087	41	0.473	0.048	18
ANXIETY P	0.276	0.080	0.143	0.373	-0.081	0.617	0.019	0.908	0.329	0.035	0.458	0.003	41	-0.591	0.010	18
DEPRESSION P	0.442	0.004	0.590	0.000	-0.340	0.030	-0.407	0.008	0.590	0.000	0.813	0.000	41	-0.805	0.000	18
EXTERNALIZING	0.647	0.000	0.776	0.000	-0.313	0.046	-0.417	0.007	0.342	0.029	0.828	0.000	41	-0.586	0.011	18
AGGRESSION	0.520	0.000	0.569	0.000	-0.267	0.092	-0.371	0.017	0.257	0.105	0.739	0.000	41	-0.652	0.003	18
CONDUCT	0.517	0.001	0.367	0.018	-0.340	0.029	-0.464	0.002	0.221	0.164	0.533	0.000	41	-0.472	0.048	18
ADAPTABILITY	-0.458	0.056	-0.462	0.054	0.647	0.004	0.783	0.000	-0.389	0.110	-0.723	0.001	18	1.000	.	18
HYPERACTIVITY	0.586	0.000	1.000	.	-0.129	0.421	-0.174	0.278	0.345	0.027	0.761	0.000	41	-0.462	0.054	18
LEADERSHIP	-0.529	0.000	-0.129	0.421	1.000	.	0.908	0.000	-0.248	0.118	-0.409	0.008	41	0.647	0.004	18
ADAPTIVE SKILLS	-0.470	0.002	-0.174	0.278	0.908	0.000	1.000	.	-0.219	0.169	-0.421	0.006	41	0.783	0.000	18
ATYPICALITY P	0.448	0.003	0.345	0.027	-0.248	0.118	-0.219	0.169	1.000	.	0.674	0.000	41	-0.389	0.110	18
BEHAV. PROB.	0.772	0.000	0.761	0.000	-0.409	0.008	-0.421	0.006	0.674	0.000	1.000	.	41	-0.723	0.001	18

BASC SELF REPORT OF PERSONALITY	ATTENTION		HYPERACTIVITY		LEADERSHIP		ADAPTIVE SKILLS		ATYPICALITY		BEHAV. PROBS.		N	ADAPTABILITY		
	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)		Corr. Coefficient	Sig. (2-tailed)	N
ATT. TO SCHOOL	0.306	0.070	0.168	0.328	-0.513	0.001	-0.564	0.000	0.252	0.139	0.336	0.045	36	-0.734	0.004	13
ATT. TO TEACHER	-0.094	0.587	0.090	0.601	0.126	0.462	0.077	0.654	0.108	0.532	0.061	0.724	36	-0.377	0.204	13
LOCUS CONTROL	0.184	0.282	0.154	0.369	-0.178	0.298	-0.240	0.158	0.301	0.075	0.227	0.184	36	-0.386	0.193	13
SOCIAL STRESS	0.098	0.571	0.347	0.038	-0.022	0.897	-0.113	0.513	0.107	0.535	0.258	0.129	36	-0.356	0.233	13
RELN. PARENTS	0.153	0.374	-0.228	0.180	-0.101	0.557	0.077	0.657	-0.008	0.965	-0.088	0.608	36	0.234	0.443	13
SCHOOL MAL.	0.189	0.271	0.156	0.364	-0.319	0.058	-0.389	0.019	0.277	0.103	0.317	0.060	36	-0.730	0.005	13
CLINICAL MAL.	0.039	0.823	0.286	0.091	-0.041	0.813	-0.063	0.714	0.145	0.397	0.184	0.284	36	-0.384	0.195	13
EMOTIONAL SYM.	0.066	0.702	0.283	0.095	-0.062	0.720	-0.095	0.581	0.123	0.473	0.227	0.183	36	-0.423	0.149	13
SELF RELIANCE	0.170	0.322	-0.292	0.084	0.072	0.678	0.173	0.314	-0.076	0.661	-0.126	0.465	36	0.662	0.014	13
PERSONAL MAL.	0.098	0.570	-0.286	0.091	0.049	0.776	0.157	0.361	-0.066	0.702	-0.168	0.329	36	0.475	0.101	13
SELF ESTEEM	-0.044	0.800	-0.097	0.572	-0.009	0.958	-0.032	0.854	-0.003	0.987	-0.099	0.564	36	0.073	0.812	13
INTERPERSONAL	-0.001	0.997	-0.212	0.215	0.147	0.392	0.256	0.131	-0.013	0.938	-0.170	0.320	36	0.552	0.051	13
ATYPICALITY C	0.232	0.174	0.211	0.217	-0.248	0.145	-0.189	0.268	0.408	0.013	0.278	0.101	36	0.041	0.895	13
ANXIETY C	0.057	0.740	0.223	0.190	-0.045	0.794	-0.063	0.713	0.091	0.599	0.134	0.436	36	-0.338	0.258	13
DEPRESSION C	0.098	0.568	0.292	0.084	-0.022	0.898	-0.043	0.805	0.240	0.158	0.296	0.080	36	-0.297	0.324	13

SPEARMAN RHO CORRELATION MATRIX: COGNITIVE, SCQ AND BASC

COGNITIVE MEASURES	SELF ESTEEM		INTERPERSONAL		ATYPICALITY C		N
	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	
DIGIT FWD	-0.065	0.705	-0.010	0.953	-0.209	0.220	36
FIQ	0.066	0.703	-0.047	0.784	-0.459	0.005	36
VIQ	-0.051	0.766	-0.024	0.891	-0.497	0.002	36
PIQ	0.145	0.400	-0.127	0.460	-0.238	0.161	36
VC	-0.011	0.948	-0.001	0.996	-0.441	0.007	36
PO	0.196	0.251	-0.126	0.463	-0.269	0.113	36
FD	-0.065	0.708	-0.025	0.886	-0.389	0.019	36
ARITH.	0.027	0.877	-0.061	0.723	-0.362	0.030	36
REY COPY	0.088	0.608	0.143	0.405	-0.115	0.505	36
REY 30'	0.205	0.230	0.022	0.897	-0.074	0.669	36
REY ORG.	-0.185	0.586	0.148	0.663	-0.211	0.534	11
BDS-2	-0.140	0.416	0.208	0.223	-0.259	0.128	36
COWAT	-0.102	0.554	-0.151	0.380	-0.368	0.027	36
ANI SIZE	-0.276	0.104	-0.158	0.358	0.025	0.887	36
ANI ALPHA	-0.169	0.324	-0.053	0.757	-0.208	0.224	36
TOL	-0.337	0.044	-0.302	0.074	0.381	0.022	36
BLOCK SPAN	0.023	0.896	0.018	0.916	-0.123	0.473	36
WCST PERS.	-0.151	0.379	-0.089	0.606	0.186	0.278	36
WCST NONP.	-0.066	0.702	-0.239	0.161	-0.167	0.330	36
SCQ	0.011	0.950	-0.125	0.467	0.183	0.286	36

SPEARMAN RHO CORRELATION MATRIX: COGNITIVE, SCQ AND BASC

PARENTAL RATING SCALE	SELF ESTEEM		INTERPERSONAL		ATYPICALITY C		N
	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	
SOCIAL SKILLS	-0.040	0.816	0.279	0.100	-0.213	0.212	36
ANXIETY P	-0.466	0.004	-0.162	0.346	-0.044	0.797	36
DEPRESSION P	-0.202	0.238	-0.302	0.074	0.091	0.597	36
EXTERNALIZING	-0.008	0.964	-0.202	0.237	0.226	0.185	36
AGGRESSION	-0.008	0.961	-0.199	0.244	0.283	0.094	36
CONDUCT	0.097	0.573	-0.042	0.808	0.139	0.418	36
ADAPTABILITY	0.073	0.812	0.552	0.051	0.041	0.895	13
HYPERACTIVITY	-0.097	0.572	-0.212	0.215	0.211	0.217	36
LEADERSHIP	-0.009	0.958	0.147	0.392	-0.248	0.145	36
ADAPTIVE SKILLS	-0.032	0.854	0.256	0.131	-0.189	0.268	36
ATYPICALITY P	-0.003	0.987	-0.013	0.938	0.408	0.013	36
BEHAV. PROB.	-0.099	0.564	-0.170	0.320	0.278	0.101	36

SPEARMAN RHO CORRELATION MATRIX: COGNITIVE, SCQ AND BASC

BASC SELF REPORT OF PERSONALITY	ADAPTABILITY			SELF ESTEEM		INTERPERSONAL		ATYPICALITY C		N
	Corr. Coefficient	Sig. (2-tailed)	N	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	Corr. Coefficient	Sig. (2-tailed)	
ATT. TO SCHOOL	-0.734	0.004	13	-0.234	0.169	-0.445	0.006	0.393	0.018	36
ATT. TO TEACHER	-0.377	0.204	13	-0.557	0.000	-0.503	0.002	0.240	0.158	36
LOCUS CONTROL	-0.386	0.193	13	-0.478	0.003	-0.525	0.001	0.494	0.002	36
SOCIAL STRESS	-0.356	0.233	13	-0.613	0.000	-0.734	0.000	0.476	0.003	36
RELN. PARENTS	0.234	0.443	13	0.439	0.007	0.747	0.000	-0.142	0.409	36
SCHOOL MAL.	-0.730	0.005	13	-0.431	0.009	-0.579	0.000	0.418	0.011	36
CLINICAL MAL.	-0.384	0.195	13	-0.587	0.000	-0.638	0.000	0.603	0.000	36
EMOTIONAL SYM.	-0.423	0.149	13	-0.732	0.000	-0.804	0.000	0.467	0.004	36
SELF RELIANCE	0.662	0.014	13	0.414	0.012	0.565	0.000	-0.139	0.419	36
PERSONAL MAL.	0.475	0.101	13	0.689	0.000	0.846	0.000	-0.305	0.070	36
SELF ESTEEM	0.073	0.812	13	1.000	.	0.507	0.002	-0.276	0.103	36
INTERPERSONAL	0.552	0.051	13	0.507	0.002	1.000	.	-0.200	0.243	36
ATYPICALITY C	0.041	0.895	13	-0.276	0.103	-0.200	0.243	1.000	.	36
ANXIETY C	-0.338	0.258	13	-0.609	0.000	-0.614	0.000	0.427	0.009	36
DEPRESSION C	-0.297	0.324	13	-0.591	0.000	0.260	0.126	0.520	0.001	36