Face Processing in Turner syndrome

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Abstract

This thesis explored the influence of X-linked genes on the development of face-processing abilities. It assessed face-processing abilities in women with Turner syndrome (TS) who have just one, instead of two, X-chromosomes. Study One assessed the nature and severity of face processing deficits by applying a diverse battery of neuropsychological tests to 45,X<sup>m</sup> and control females. Women with TS performed at below average levels in terms of face and emotion recognition (particularly fearful faces) despite processing faces in a typical configural manner. Study Two found equivalent deficits in 45,X<sup>p</sup> women. Using Voxel Based Morphometry, Study Three found evidence for increased volume of the amygdalae and orbito-frontal cortices in women with TS. Because males, like 45,X females, have a single X-chromosome, Study Four sought to identify whether there was any sexual dimorphism in face processing abilities – there was not. However, differences were found between normal males and females in terms of correlations between face and emotion recognition task performance. These differences were similar to those seen in 45,X<sup>m</sup> compared with 45,X<sup>p</sup> females and are consistent with the hypothesis that imprinted X-linked genes influence functional mechanisms that are relevant to social cognition. Together, the results of these studies suggest a role for X-linked genes in the typical development of face processing abilities. This role might involve the development of structures involved in social and emotional processing, including the amygdala and orbito-frontal cortices. It is suggested that affective responses to faces may have an important role in our subsequent memory for them. Ways in which issues raised by these studies could be explored further are discussed.
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1 Chapter One – Introduction

1.1 Studying Genetic Influences on Cognitive Development

There has been a genetics of behaviour since 1909 when anthropologist Francis Galton, the cousin of Charles Darwin, wrote at length about his conviction that intelligence, and in particular pre-eminence in various fields, was almost entirely due to genetic factors (Darwin, 1968). However, the study of genetics in relation to behaviour became politically tainted from 1925 to 1990 with the emergence of eugenics, first because of fascism in Europe and then due to Soviet State socialism.

Even as genetics came to be better understood in the twentieth century it was still believed that, “Genes...could set up the scaffold of the brain, but would have a limited influence on the mind” (Flint, 1999). In recent years, however, it has become widely accepted that the actions of genes influence the development and operations of the brain and consequently behaviour. In fact, it is estimated that at least half of the human genome is expressed in the brain although we still know relatively little about how these influences operate. The proteins that genes produce are important determinants of the pattern and nature of interconnections between neurons but behaviours are not written indelibly in our genes. They are not immutably pre-determined but rather can exist only in the context of environmental influences.
Various different approaches can be taken to study genetic influences on the brain and cognitive development, that is the links between *genotype* (the actual genetic makeup of an individual) and behavioural *phenotype* (the observable behaviour characteristics). The approaches can be broadly categorised into those whose focus is on behavioural genetics and those where the focus is on molecular genetics.

Traditionally, behavioural genetics has studied individual differences within a population for traits that are normally distributed. Familial and inheritance patterns of this trait are studied to establish the proportion of the trait that is thought to be due to heritability (genetic influences). The ultimate aim would be to identify the gene(s) responsible for this heritability by the use of linkage studies. This could be seen as a bottom-up approach – trying to work one’s way from a complex behaviour back to the genes that may be influencing it.

Molecular genetics conversely adopts a top-down approach, working its way from an identified gene to the behaviour that may be associated with it. There is a vast amount of overlap in the two approaches and both molecular and behavioural studies are critical to the advancement of any work trying to identify gene influences on the brain and cognitive development. Behavioural neuroscience is concerned with "the neural and endocrine basis of behaviour and their genetic substrates" (Skuse, 2000) and this terminology could be seen to better conceptualise modern approaches to understanding the genetic underpinnings of the brain and mind that combine both behavioural and molecular genetics at some level.
This study could therefore be seen to adopt a behavioural neuroscience approach, exploring the neuropsychological phenotype in individuals with Turner syndrome. These individuals are lacking either all or part of their second X-chromosome; meaning that they have an insufficient dose of X-linked genes for which there would be two expressed copies in typically developing females. Therefore the starting point of the study is individuals who are lacking numerous X-chromosome genes, from this, the behavioural characteristics (phenotype) associated with the genetic deletion will be considered. Taking this one step further, the studies in this thesis will attempt to define an endophenotype, which will be a trait (or traits) that are much closer to the underlying genetic defect than the original behavioural characteristics that were described. Studying such a syndrome allows us not only to gain an understanding of the implications of missing genes on the X-chromosome for development but it can also inform our understanding of the importance of these genes in typical development.

1.2 TURNER SYNDROME – OUTLINE

Turner syndrome (TS) is a sex-chromosome disorder occurring in 1 in 2,500 live female births. Normal males and females have 23 pairs of chromosomes, with one chromosome in each pair being inherited from the mother and one from the father. Males possess an X and a Y sex-chromosome, while females have two X-chromosomes. In Turner syndrome, all or part of the second sex-chromosome is missing due to a problem in sex-chromosome segregation in early development. Consequently, women with Turner syndrome have just
one intact X-chromosome with the second X-chromosome being either entirely deleted or structurally abnormal. Where the entire second sex-chromosome is deleted the condition is karyotypically defined as X monosomy or 45, X and is the sole example of a human disorder in which an entire chromosome can be missing without lethal consequences. However, the incidence of TS is markedly higher at conception with as few as 1% of all conceived cases surviving to birth (Hook & Warburton, 1983). In fact, of all the chromosomal abnormalities that result in spontaneous abortion or miscarriage, Turner syndrome is the most common, accounting for as many as 20% of all miscarriages (White, 1994).

1.2.1 Historical Perspective

The clinical symptoms of Turner syndrome were first noted many years before the underlying genetic aetiology was discovered. In 1805, Dr Charles Pears described a patient who had short stature alongside ovarian deficiency and a lack of secondary sexual characteristics (Pears, 1805). A more systematic description came from Otto Ullrich (Ullrich, 1930) who published an account of an 8 year old girl with a variety of physical anomalies that seemed to indicate a possible underlying syndrome. The phenotypic anomalies included short stature, lymphedema of the neck, hands and feet, and an increased carrying angle of the elbow (cubitus valgus).
It was not until the late 1930’s that a professor of medicine at the University of Oklahoma, Henry Turner, described a series of seven young women who had the features that we now associate with the syndrome which bears his name (Turner, 1938). He noted the unusual co-occurrence of a triad of features in these women, namely infantilism (stunted growth and sexual immaturity), webbing of the skin of the neck and cubitus valgus.

The first suggestion that an X-chromosome deletion may underlie the phenotype described by Turner came from Polani et al (Polani, Lessof, & Bishop, 1956) who noticed that the incidence of colour-blindness was as common in women with Turner syndrome as it was in males. They postulated that since males possess only one X-chromosome, women with Turner syndrome too might just have a single X-chromosome. Charles Ford and his colleagues (Ford, Jones, Polani, De Al-Meida, & Briggs, 1959) cytogenetically confirmed that a female with Turner syndrome had the karyotype X0 (now known as 45,X or X monosomy), and 45 rather than the normal 46 chromosomes. Since this date many different types of cytogenetic anomaly of the X-chromosome have been identified and Turner syndrome is used to refer to any of a number of different karyotypes that result in the triad of features identified by Turner.
1.2.2 Diagnosis

The diagnosis of Turner syndrome is first made at different stages of development. The criteria that draw attention to the diagnosis at each age are associated, broadly speaking, with different presenting symptoms. Although there are many physical manifestations of X-monosomy, the diagnosis can be established only by chromosome analysis, which reveals that either all or part of one X-chromosome is missing in a proportion of cells analysed. Turner syndrome can be detected prenatally by amniocentesis, although false positive diagnoses have been made (Fejgin, Arbel-DeRowe, Shul, & Amiel, 1997; Griffiths, Miller, & Stibbe, 1996). A significant proportion of cases are detected at birth or in early infancy, usually due to an investigation precipitated by the occurrence of lymphedema of hands and feet, small size and excessive skin at the nape of the neck (Hall & Gilchrist, 1990). Cases that are diagnosed in later life will frequently have had defining physical features of the syndrome present at birth, such as lymphedema of the extremities (Savendahl & Davenport, 2000) that were not further investigated at the time. In childhood and adolescence, short stature is the primary reason that girls with the syndrome are picked up (Savendahl et al., 2000) although a failure to enter spontaneous puberty can also be an alerting factor. Finally, diagnosis has been known to occur in adulthood when females may be investigated after difficulties conceiving. Diagnosis has even been known to be made in elderly patients (Toth & Jogerst, 1996).
1.2.3  Cytogenetic variants

Advances in DNA technology have facilitated the analysis of sex chromosomal anomalies at the molecular level (Connor & Loughlin, 1989). A number of different karyotypes, all involving X-chromosome anomalies, can result in the phenotype of Turner syndrome. The most common karyotype is X monosomy, which is found in approximately 50% of all cases with Turner syndrome (Pearce, 1992). This is where there is a complete absence of the second sex-chromosome, so affected individuals will have 45, as opposed to the normal 46 chromosomes. An isochromosome X occurs where one arm of the second X-chromosome is missing and the other arm is duplicated and this can occur in approximately 20% of cases (Pearce, 1992). In the case of a ring chromosome, which is present in about 15% of diagnosed cases (Jacobs et al., 1997) the second X loops round to form a ring shape with varying sized portions from both arms of the chromosome missing. In a minority of cases (approximately 6%), the single X may occur together with a fragment of Y chromosome. Individuals may also be missing just a portion of their second X-chromosome in the form of a straightforward deletion. In these cases, a segment of X-chromosome, which may be tiny or substantial, is missing from one arm of the X-chromosome.

Many studies that consider both the physical and psychological aspects of TS treat the condition as homogeneous, considering all these different karyotypes as being equal. Such methodology cannot aid the quest to identify the genetic factors that may contribute to the phenotypic expression of the syndrome. In
any group of heterogeneous karyotypes, some women will possess genes, in multiple copies, that the others are missing.

1.2.4 Life expectancy

In a prospective study of 156 female patients with Turner syndrome, that had survived infancy and been followed up for an average of 17 years, there were 15 deaths (Price, Clayton, Collyer, De Mey, & Wilson, 1986). The reduction in life expectation was 12.5 years at age 1 year, 11 years at age 20, and 10 years at age 40. In this study, deaths were due to a broad spectrum of diseases although women with Turner syndrome have a reduced life expectancy primarily because of cardiovascular disease (Elsheikh, Conway, & Wass, 1999). An increased risk of death from diseases of the nervous, respiratory, digestive and genitourinary systems (Swerdlow et al., 2001) may also affect mortality rates.

1.2.5 Physical abnormalities

Since Henry Turner first described the triad of features that gave rise to the definition of the syndrome, our knowledge has advanced to provide a fuller understanding of the physical features associated with the syndrome.
1.2.5.1 Short stature

The cardinal physical feature of Turner syndrome is short stature with a mean adult height of approximately 20-cm less than peers (Sylven, Magnusson, Hagenfeldt, & von Schoultz, 1993). Women with Turner syndrome are on average around 2 standard deviations shorter than their peers, which in real terms translates to an adult height of approximately 140cm (4 feet 7 inches). Short stature is not due to growth hormone deficiency per se. It is associated with the deletion of one copy of the SHOX (short stature homeobox-containing) gene on the distal (pseudo-autosomal) portion of the short arm of the X-chromosome, which is important for normal growth in stature. This gene is needed in two copies for normal growth in stature (Rao et al., 1997b). The importance of this gene to the short stature outcome in this condition has been supported by more recent studies (Ogata et al., 2001).

Short stature in Turner syndrome does not simply reflect the absence of a pubertal growth spurt. Rather it results from a generalised growth defect that is first manifest in utero and then continues with postnatal growth failure which is most marked after the second year of life (Ranke et al., 1983). In order to enhance growth potential most children are now treated with synthetic growth hormone. Accurate estimates of the potential growth increase afforded by growth hormone treatment are not readily available. However most studies suggest an average gain of approximately 5cm (Bramswig, 2001). The dose of growth hormone and the age at which treatment commences may be critical mediating factors (Sas et al., 1999).
1.2.5.2 Ovarian Dysgenesis

Individuals with TS have abnormal ovarian development whereby the ovaries appear to degenerate prematurely. In the first 12 weeks of intrauterine life the ovaries appear to have a normal complement of oocytes (Pearce, 1992). However, past this period of pre-natal development, oocyte degeneration is rapid and the ovaries soon become fibrous streaks. The ovaries are incapable of producing normal levels of oestrogen, resulting in depleted levels of endogenous oestrogen. Women with Turner syndrome are also infertile, although with ovum donation and intrauterine embryo transfer, becoming pregnant is now possible (Gutierrez Gutierrez, Grimalt, Remohi, & Pellicer, 1994).

The majority of adolescents with Turner syndrome do not spontaneously enter puberty although exceptions do exist (Paoloni-Giacobino et al., 2000). Therefore, to mimic sexual maturation, hormone replacement therapy is administered. The doses given and age of administration can vary widely, but treatment often begins with oestrogen being given alone before progressing on to an oestrogen/progesterone combination such as the contraceptive pill.

Administration of exogenous oestrogen can cause the growing points at the end of bones (the epiphyses) to fuse and this may cause a slow down or ultimately a halt in growth in terms of height. Therefore the trade off between eliciting early secondary sexual characteristics and achieving a maximum adult height must be carefully considered by clinicians when deciding the
timing of oestrogen therapy commencement (Chernausek, Attie, Cara, Rosenfeld, & Frane, 2000).

1.2.5.3 Other physical characteristics

Short stature and ovarian Dysgenesis are almost invariably seen in individuals with Turner syndrome. Other congenital malformations associated with the syndrome are not present in all cases. In any sample of individuals with the condition, some may not possess any obvious malformations while others may have one or two, with others still being affected by a large number of these sequelae.

The skeletal dysmorphisms associated with Turner syndrome are thought, along with short stature, to be linked to haploinsufficiency of the SHOX gene (Clement-Jones et al., 2000). Individuals with TS may have any of the following: a short neck, short metacarpals, Madelung deformity, Scoliosis, Genu valgus, Micrognathia and a high arched palate. Cubitus valgus (a wide carrying angle of the elbow) may be linked to SHOX deficiency but may also be linked to oedema.

Approximately one third of individuals with TS are thought to have cardiovascular anomalies, most commonly coarctation of the aorta, where the primary blood vessel carrying blood away from the heart is narrowed.
A number of the physical features that may be present seem to be associated with lymphatic obstruction. These include, webbing of the neck, a low posterior hairline, rotated ears, oedema of the hands and feet, nail dysplasia, ptosis and a shield chest.

In addition to these physical manifestations, renal abnormalities, including horseshoe kidneys, multiple pigmented nevi and stabismus may occur (Lippe, 1989).

1.2.6 Turner syndrome – psychological characteristics

Since the syndrome was first described on the basis of a cluster of physical anomalies, many observations have been made regarding particular behavioural or psychological traits that may be associated with the syndrome.

1.2.6.1 Cognitive functioning

Despite early reports suggesting that Turner syndrome was associated with pervasive learning difficulties (Haddad & Wilkins, 1959) and mental retardation (Polani, 1960), it is now widely thought that verbal abilities are within the normal range. However, specific cognitive difficulties may exist, particularly with regard to visuo-spatial functioning (Pennington et al., 1985; Ross, Reiss, Freund, Roeltgen, & Cutler, Jr., 1993; Silbert, Wolff, & Lilienthal,
1977a; Temple & Carney, 1995). Schaffer (Schaffer, 1962) was the first to suggest that a particular profile of cognitive deficits may exist in Turner syndrome. Verbal comprehension was found to be at normal levels, being significantly higher than performance on tasks that required perceptual organisation or freedom from distractibility.

Money and Alexander (Money & Alexander, 1966), describe what they term 'space-form blindness' as being characteristic of the condition. A wide body of research supports their claims for a number of related deficits in visuo-spatial functioning. These deficits include difficulty identifying positions in space (Money et al., 1966), mental rotation of geometric shapes (Rovet & Netley, 1980) and visual memory (Ross, Stefanatos, Roeltgen, Kushner, & Cutler, Jr., 1995).

Motor function is often described as being sub-optimal in individuals with Turner syndrome. Difficulties have been noted in the drawing of human figures and copying shapes and designs (Silbert, Wolff, & Lilienthal, 1977b; Waber, 1979), visual-motor integration (Lewandowski, Costenbader, & Richman, 1985), handwriting (Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982), construction (Murphy et al., 1994), and a recent study describes a general motor impairment (Nijhuis-van der Sanden RW, Smits-Engelsman, & Eling, 2000).
Alongside these difficulties, arithmetic is frequently reported as an additional area of difficulty (Rovet, Szekely, & Hockenberry, 1994), with problems being manifest at both school age and beyond.

1.2.6.2 Behavioural and Psycho-social characteristics

Among the early descriptions of an adult behavioural phenotype in Turner syndrome, Money and Mittenthal (Money & Mittenthal, 1970) suggested that individuals with the syndrome are likely to have low initiative, inertia of arousal and high acceptance and tolerance of personal adversity. These claims have been supported and expanded upon by subsequent studies that have also demonstrated psychosocial deficits primarily involving immaturity and problems with social relations (McCauley, Ito, & Kay, 1986). Individuals with the syndrome are consistently reported to have difficulties forming and maintaining friendships (Swillen et al., 1993), a limited number of friends, social isolation and a poor self concept (Ross et al., 1996; Sylven et al., 1993). Girls have significant problems in terms of social relationships and are reported to have fewer friends and spend less time with friends (McCauley, Feuillan, Kushner, & Ross, 2001). In adulthood, too, women with TS experience difficulties with social and partner relationships (Wide Boman, Bryman, Halling, & Moller, 2002).

Despite the lack of normal female hormones, it would appear that female gender identity and gender role behaviour develop normally during childhood (Ehrhardt, Greenberg, & Money, 1970; Shaffer, 1963); with normal levels of
heterosexual sexual orientation in adulthood (Hettmer, Hoepffner, Keller, & Brahler, 1995). However, despite this, it is consistently found that a high proportion of adult women with TS never marry or co-habit and many never have sexual intercourse (McCauley, Sybert, & Ehrhardt, 1986; Nielsen, Nyborg, & Dahl, 1977; Toublanc, Thibaud, & Lecointre, 1997).

1.2.6.3 Psychopathology

Early studies reported no increase in incidence of psychopathology amongst women with TS. For example, (Money et al., 1970) reviewed interviews with 68 TS patients, finding only three with severe psychopathology and six more with mild psychopathology. Furthermore, (Nielsen, Nyborg, & Dahl, 1977) report only four out of 45 patients as having significant psychopathology. Both studies sought to explain psychopathology in terms of stressful or dysfunctional family environments. None of the 103 cases reviewed by (Nielsen & Sillesen, 1981) had any history of psychiatric treatment.

However, more recent studies identify inflated levels of psychiatric disturbance in childhood. In a parental questionnaire study by Skuse et al (Skuse, Percy, & Stevenson, 1994), 23% of the girls with TS (but only 4% of the short-stature controls) had a probable psychiatric disorder. More specifically, despite reports of inertia of emotional arousal and low spontaneity, at least a subgroup of children with Turner syndrome have increased behaviour problems. These include poor attention skills and
hyperactivity (Reiss et al., 1993; Rovet, 1993) although the difficulties tend to decrease with age. An increased incidence of autism has also been noted in females with Turner syndrome (Creswell & Skuse, 2000; Donnelly et al., 2000). Even those cases who do not meet the full diagnostic criteria have been noted to have autistic like behaviours including social difficulties and obsessive compulsive behaviours (el Abd, Patton, Turk, Hoey, & Howlin, 1999). In addition, a number of case reports have described anorexia nervosa, depression and schizophrenia in TS women (Darby, Garfinkel, Vale, Kirwan, & Brown, 1981; Halmi & DeBault, 1974; McCauley, 1990; Raft, Spencer, & Toomey, 1976; Sabbath, Morris, Menzer-Benaron, & Sturgus, 1961).

1.2.6.4 Social dysfunction

Among the behavioural and cognitive traits that have been associated with Turner syndrome, difficulties with social functioning and development have frequently been reported. These psychosocial difficulties were initially reported to primarily relate to immaturity and problems with social relations (McCauley et al., 1986), with difficulties forming and maintaining friendships (Swillen et al., 1993). Girls and women with the condition may have a limited number of friends, social isolation and a poor self-concept (Ross et al., 1996; Sylven et al., 1993). In adulthood there is a reduced likelihood that the women will cohabit or develop a lasting intimate relationship (Boman, Bryman, Halling, & Moller, 2001). Skuse and colleagues (Skuse et al., 1997) have suggested
that difficulties in social adjustment may stem from difficulties in social
cognition. Parents of children and adolescents with TS frequently reported
that their children had difficulties understanding social cues. For example,
questionnaire items such as 'lacking an awareness of other people’s feelings’
and 'unaware of appropriate social behaviour' were consistently endorsed.

Where appropriate control groups have been used, it becomes clear that
social difficulties in TS are not related to short stature, lack of sexual
development, physical anomalies or environmental factors. It is necessary to
postulate alternative mechanisms that may give rise to these difficulties.

1.2.7 Turner syndrome - Neuropsychology

1.2.7.1 Right hemisphere dysfunction

It has been noted by many researchers that the profile of cognitive strengths
and weaknesses in Turner syndrome is suggestive of right hemisphere
dysfunction (Rovet, 1990). Dichotic listening tasks designed to elucidate
hemispheric specialisation, have also revealed anomalous hemispheric
involvement in typically lateralised tasks. For example, TS individuals
demonstrate weaker left hemisphere involvement, sometimes accompanied
by increased right hemisphere involvement, during verbal information
processing (Gordon & Galatzer, 1980; Lewandowski et al., 1985).
Examination of brain activation patterns in TS supports the suggestion of anomalous hemispheric specialisation. Individuals with TS produce electroencephalogram maps that show greater right hemisphere activation for reading and greater left hemisphere activation for arithmetic than controls (Portellano-Perez, Bouthelier, & Monge, 1996). In addition, where structural anomalies are identified, these are typically more evident within the right hemisphere (Reiss, Eliez, Schmitt, Patwardhan, & Haberecht, 2000).

### 1.2.7.2 Occipital/Parietal dysfunction

Based on the cognitive profile observed in TS, researchers have also sought to identify particular cerebral regions that may be affected. Money concluded that space form dysgnosia, directional sense dysgnosia and impaired numerical ability implicated right parietal involvement (Money, 1973). The right temporo-parietal-occipital junction was suggested as a possible region for impairment by (Christensen & Nielsen, 1981) who noted difficulty on tasks requiring sequencing and on complex motor tasks. However, others suggest that women with TS have a range of perceptual and motor difficulties that cannot easily be localised to a particular region of one cerebral hemisphere (Lewandowski et al., 1985). In addition, Pennington et al. (1985), who have conducted one of the few studies that have attempted to control for karyotype heterogeneity, found no evidence of anomalous lateralisation in a group of 10 participants with the 45,X karyotype. Other cortical regions suggested as being possibly defective using similar methods are the right postcentral and
adjacent parietal cortex (McGione, 1985), right cerebral cortex (Silbert et al., 1977b), and the right and left parietal and frontal cortex (Waber, 1979).

### 1.2.7.3 Neuropathology and neuroimaging

A neuropathological study of a young TS woman (Reske-Nielsen, Christensen, & Nielsen, 1982) revealed abnormally small gyri at the junction of the right temporo-parietal and occipital lobes. More recent Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) techniques have also identified abnormalities in these neural regions. For example, PET studies report a bilateral reduction of glucose uptake in parietal and occipital lobes (Clark, Klonoff, & Hayden, 1990). While MRI studies report reductions in grey and white matter in right temporal and parietal lobe and left parietal perisylvian regions (Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995). Reductions are also reported in the cerebellum and pons (Reiss et al., 1993), hippocampus, lenticular nucleus and thalamus (Murphy et al., 1993). The most consistent finding are anomalies in (usually right-sided) occipital-parietal regions, which would seem to fit with the visuo-spatial deficits that are a key feature of the psychological phenotype of this condition.
1.2.7.4 Neural correlates of social adjustment difficulties?

Although the consistent findings of occipital-parietal anomalies would seem to provide a logical explanation for the pattern of visual-spatial deficits in TS, they do not seem a good explanation for the social difficulties experienced by many individuals with the syndrome. With respect to the neuropsychology of social cognition, it has been proposed that there is functional neural circuitry which subserves the process of evaluating mood, beliefs and desires in others and even in oneself (Brothers, 1990; Brothers, 1992). This system, including the amygdala, superior temporal sulcus and orbito-frontal cortex, is also believed to mediate some aspects of face and emotion recognition that are considered to be essential for successful social interaction (Broks et al., 1998). However, there is no hint in the literature that these brain systems are structurally or functionally anomalous in TS.

We know little, even at the descriptive level, of the nature and severity of the social difficulties experienced by this population. This is despite the fact that at a clinical level these difficulties are a major concern for parents of children with the condition (McCauley et al., 2001). Might social difficulties be related to cognitive deficits, and might these cognitive deficits in turn reflect dysfunction of specific neuro-cognitive systems? This is the central question addressed by this thesis. By continuing this chapter with a focused investigation into particular aspects of social cognition, the scene is set for the reasoning behind the way in which I chose to investigate the question.
Social cognition relates to the mechanisms by which we gauge the beliefs, intentions and internal state of those around us. Recent developments in this field allow us to explore this aspect of the syndrome more fully. In the first instance, the social cognitive profile of women with TS was explored with view to understanding more about the nature and severity of social difficulties in this syndrome.

1.2.8 Insights into social cognitive impairments

From the literature on TS, it can be seen that children, adolescents and adult women with TS experience a range of social adjustment difficulties. These would appear NOT to be attributable to their short stature, odd physical appearance or infertility (McCauley, Kay, Ito, & Treder, 1987; Skuse et al., 1994). However, more needs to be understood about the nature of these difficulties. Reviewing the data from the pre-existing TS study database at the Institute of Child Health (see below) gave some valuable insights into the ways in which the social difficulties are manifest.

1.2.8.1 Autistic symptomatology

The Turner syndrome database at the Institute of Child Health, London is a nationwide record of children and adults with TS. It has been running since 1994 (Skuse et al., 1994) and now has data on almost 1,000 individuals with the syndrome. In the first piece of analysis reported in this thesis, adult
women with monosomic TS (45,X) were compared to age and Verbal IQ matched control women on the Autism Quotient Self-report Questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001).

The Autism Quotient Self-report Questionnaire assesses the extent to which adults of normal intelligence possess traits that are characteristic of autism. Its validity in discriminating individuals with autism from non-autistic individuals has been established (Baron-Cohen et al., 2001). Sixty-one women with TS and twenty-six control females were assessed. Figure 1.1 shows that women with TS display significantly more autistic-like traits than a control group of women, having elevated total scores ($t (1, 85) = -3.17, p=.002$).
Figure 1.1: Mean total scores for control (XX) and Turner syndrome (XO) individuals on the Autism Quotient Self-report Questionnaire. Bars show mean. Error bars show standard error.

The clinical cut-off for this scale is 32+, with three (5%) of the women with TS obtaining scores above this criterion. None of the control females or the females in the original standardisation study obtained scores above the clinical cut-off (Baron-Cohen et al., 2001). Women with TS generally displayed more autistic-like traits. Thirty three percent of the TS women endorsed twenty or more of the fifty items compared to twelve percent of the females without TS.

Analysis of the separate subscales revealed that these differences reached significance in two domains; namely social skill (F (1,85) = 13.05, p< .001) and imagination (F (1, 85) = 8.61, p<.004). The scale on which the TS group was
most severely affected was in the domain of social skills. TS women endorsed an average of nearly three out of ten items while control women endorsed less than one.

The individual items comprising the social skills subscale were analysed using Chi-square statistics, revealing that half of the items were more significantly endorsed (indicating an autistic-like trait) by the women with TS than by the control group (see table 1.1). Of these, the proportion of each group agreeing with the items remained significantly different (after Bonferroni corrections for multiple comparisons) for two of the items. Forty two percent of the women with TS indicated that they found it hard to make new friends compared to just 8 percent of the control group. A further item may provide an insight into the precise nature of the social difficulties of the TS women. Nearly all (96%) of the control women indicated that they found it easy to work out what someone was thinking or feeling just by looking at their face compared to just 65% of the TS women.
Table 1.1: Autism self-report questionnaire – response rates for items comprising the 'social' subscale.

<table>
<thead>
<tr>
<th>Item</th>
<th>Control females</th>
<th>Turner syndrome</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I prefer to do things with others rather than on my own.</td>
<td>80.0</td>
<td>81.0</td>
<td>n/s</td>
</tr>
<tr>
<td>11. I find social situations easy.</td>
<td>88.0</td>
<td>58.7</td>
<td>P=.008</td>
</tr>
<tr>
<td>13. I would rather go to a library than a party.</td>
<td>4.0</td>
<td>12.7</td>
<td>n/s</td>
</tr>
<tr>
<td>15. I find myself more strongly drawn to people than to things.</td>
<td>96.0</td>
<td>81.0</td>
<td>n/s</td>
</tr>
<tr>
<td>22. I find it hard to make new friends.</td>
<td>8.0</td>
<td>42.9</td>
<td>P=.002*</td>
</tr>
<tr>
<td>36. I find it easy to work out what someone is thinking or feeling just by looking at their face.</td>
<td>96.0</td>
<td>65.1</td>
<td>P=.003*</td>
</tr>
<tr>
<td>44. I enjoy social occasions.</td>
<td>92.0</td>
<td>87.3</td>
<td>n/s</td>
</tr>
<tr>
<td>45. I find it difficult to work out people's intentions.</td>
<td>20.0</td>
<td>47.6</td>
<td>P=.017</td>
</tr>
<tr>
<td>47. I enjoy meeting new people.</td>
<td>96.0</td>
<td>84.1</td>
<td>n/s</td>
</tr>
<tr>
<td>48. I am a good diplomat.</td>
<td>96.0</td>
<td>76.2</td>
<td>P=.03</td>
</tr>
</tbody>
</table>

*Significant at p<.05 after bonferroni corrections for multiple comparisons.

^For these items, agreement is indicative of an autistic-like trait. On all other items in the table, disagreement is indicative of such traits.
Women with TS report that they do not find it easy to work out what someone is thinking or feeling just by looking at their face. In clinical populations other than Turner syndrome face and emotion recognition deficits have been known to co-occur with difficulties in social functioning (Calder et al., 1996; Langdell, 1978; McConachie, 1976). Might there be something critical about the link between understanding and interpreting faces and facial expressions and typical social adjustment (Elgar & Campbell, 2001)? One of the hypotheses derived from this literature review will be that face and emotion recognition will be associated with poor social adjustment in women with TS.

Is there any evidence in the existing cognitive literature that women with Turner syndrome may have difficulties in processing faces, particularly concerning the emotional content of these facial displays?

1.2.9 Face Processing in Turner syndrome

There are several reports of defective face recognition in girls and women with Turner syndrome. These reports have generally considered difficulties with face processing to be a component of the generalised visuo-spatial deficits that are frequently associated with Turner syndrome. However, I will now consider these studies with respect to the notion that a deficit in face processing may indicate dysfunction in a partially distinct area of functioning. Skills in this domain are related not only to visuo-spatial processing (broadly
speaking a parietal lobe function), but also to object recognition (a largely
temporal lobe mediated skill). In addition, social cognition (mediated by
network of interconnected cortical and subcortical structures including the
orbito-frontal cortex, superior temporal sulcus and amygdala) may play a role.

### 1.2.9.1 Face perception and face matching

Reiss and colleagues (Reiss et al., 1993) used the Facial Recognition Test
(Benton & van Allen, 1973a), to compare performance of a monozygotic twin
with TS with that of her unaffected co-twin. This task requires the participant
to match concurrently presented face images based on identity. In the early
trials, the pictures shown are identical but as the test progresses, the same
identity has to be matched across different viewing angles and under different
lighting conditions. Despite just a three-point difference in Verbal IQ between
the twins, the girl with TS performed significantly worse on this test, having
difficulties matching faces. The Benton task (Benton et al., 1973a) has also
been used to compare the performance of groups of girls with TS to that of
typically developing girls. Ross and colleagues (Ross, Kushner, & Zinn, 1997;
Ross et al., 1995) found that girls with TS were significantly impaired at
discriminating faces compared to control participants who had been matched
in terms of age and Verbal IQ. This result has subsequently been replicated
(Romans, Stefanatos, Roeltgen, Kushner, & Ross, 1998). One study (Murphy
et al., 1994) failed to find a significant difference between groups on this task.
However, they did observe a deficit of similar magnitude to those reported in
other TS studies. The statistical analysis of the small sample size of this study (18 women with TS compared to the 56 in Ross’s study and 99 in the study by Romans) may not have had sufficient power to detect statistically significant differences. Murphy did however find that women with TS performed worse at a delayed face-matching test than did controls. Deficits at delayed face matching have since been replicated, again in adults with TS, using a slightly different methodology (Buchanan, Pavlovic, & Rovet, 1998).

1.2.9.2 Interpreting social information from faces

With respect to using facial information to make socially relevant judgements, (McCauley et al., 1987) compared the performance of seventeen girls with TS and seventeen control girls on a task of affective discrimination. Forty videotaped facial expressions were presented and the task was to determine whether the facial message was to come closer (positive affective intent) or go away (negative affective intent). Girls with TS were significantly less accurate at reading facial affect. Performance on this task correlated with parent ratings of social skills, but not with visuo-spatial abilities. This would suggest that problems with face processing may not simply be secondary to weak perceptual visuo-spatial skills but might represent a partially separable area of diminished functioning that may be related to social dysfunction.

To sum up, face recognition deficits have been reported in most studies of TS where this has been tested. However, the size of the effect was small and its consistency variable. This might have been due to variation in genetic
karyotype and possibly to the age-range and size of the samples tested. The understanding of the nature of the deficit or factors that may underlie it is minimal. In this thesis, this research is extended in order to explore the nature and severity of face processing deficits in Turner syndrome.

1.3 FROM GENES TO BEHAVIOUR...

At least three different mechanisms exist that may mediate the link between genes and development in Turner syndrome (see figure 1.2 for a schematic representation). These mechanisms are in no way mutually exclusive and indeed may all exert an influence independently or interactively on the psychological phenotype we see in TS. The following experiments will employ techniques to help to unravel which of these mechanisms may be exerting an influence on the development of face processing abilities in Turner syndrome.
Normal females have two X-chromosomes whereas females with TS have just a single intact X-chromosome. Since in normal females one of the X-chromosomes is inactivated early in embryonic development, it is perhaps surprising that having just one X-chromosome, as opposed to two, should have any neurodevelopmental consequences. If the second X-chromosome is inactivated then genes on this chromosome will not be expressed. Therefore,
typically developing women, like women with TS, express genes from just one X-chromosome. However, according to the haploinsufficiency hypothesis, some genes on the X-chromosome escape X inactivation. This means that despite the X-chromosome being inactivated, certain genes are still able to express themselves. Therefore, phenotypic abnormalities would be the result of deficient gene product from these genes on the X-chromosome that escape X inactivation (Zinn & Ross, 1998). These genes would usually be expressed in two copies in typically developing females but would only have a single dosage in individuals with TS.

At least some aspects of the TS phenotype may be a direct result of insufficient dosage of such gene products. At the level of the physical phenotype, it has been noted that cases who have monosomic TS (missing an X in all their cell lines) may display nearly twice as many physical stigmata as those women who have a proportion of cells that contain two normal X-chromosomes (mosaicism) (Skuse et al., 1994). Therefore, the severity of the physical phenotype may be mediated in part by the proportion of cells in which an X is missing or anomalous.

At a cognitive level, this group also found that TS girls with mosaicism displayed less marked symptomatology (Skuse et al., 1994). Girls with 45,X TS scored at a higher level (indicating greater pathology) on the total problem scale of the Child Behaviour Checklist than did TS girls with mosaicism. Similarly, Murphy and colleagues (Murphy et al., 1994) found that within their mosaic group, a negative relationship was observed between the percentage
of lymphocytes with the 45,X karyotype and results on tests of spatial processing. The greater number of cells containing the 45,X karyotype, the greater the degree of impairment. In a follow-up study, this group (Murphy et al., 1997) reports that the level of neuro-metabolic abnormalities in TS women with a mosaic karyotype is intermediate between controls and TS women with a 45,X karyotype. Taken together, these results are suggestive that the phenotypic consequences of missing an X-chromosome may be somewhat diluted in those women with the condition who possess some normal cell lines.

1.3.2 Genomic imprinting

It is also possible that imprinted genes may play a role in determining the TS phenotype. Genomic imprinting inactivates one member of a pair of alleles, according to the parental origin of the chromosome. An increasing number of mammalian genes are known to be subject to this phenomenon (Barlow, 1995). Genomic imprinting has been described in a number of conditions including Prader-Willi and Agelman’s syndrome.

Let us consider how this process would operate in relation to the sex-chromosomes. Normal females possess both a maternally and a paternally derived X-chromosome, one of which is randomly inactivated in any given somatic cell line (Lyon, 1971). Therefore, on average, a typical female would have 50% of her active X-chromosomes maternally derived and 50%
paternally derived. If genes are expressed differentially depending on whether they are inherited from the mother or from the father, women with Turner syndrome who have just a single X-chromosome may differ according to whether their single X originates from their mother or father.

The evidence for genomic imprinting in TS is less clear. Although a gene on the mouse X-chromosome has been demonstrated to be subject to imprinting (Zuccotti & Monk, 1995), none on the human X-chromosome have yet been identified.

The genetic anomaly in Turner syndrome is thought to occur after the zygote has formed or just after the fusion of the gametes (Chu & Connor, 1995). One would therefore expect an equal chance of the X-chromosome from either parent being retained. However, in practice 70-80% of cases have a single maternal X-chromosome (Lorda-Sanchez, Binkert, Maechler, & Schinzel, 1992). This observation has led to speculation that genes on the X-chromosome may be subject to imprinting. One study has demonstrated that the morphological appearance of foetuses retaining a paternal X differed from those retaining a maternal X in TS (Hassold, Benham, & Leppert, 1988). This could be indicative that the maternal sex-chromosome might be more critical to intrauterine survival. However, the same amount of aborted foetuses retain the maternal X-chromosome as liveborns (Jacobs et al., 1990). This suggests that the difference in prevalence of a single maternal X and a single paternal X in TS individuals is not in fact mediated by some factor that predisposes
those with a maternal X-chromosome to greater survival and may be quite complex (Naumova, Greenwood, & Morgan, 2001).

At a psychological level, earlier work from this lab has reported that social difficulties may be more pronounced in TS women who have inherited their single X from their mother \((45,X^m)\) than in those whose single X comes from their father \((45,X^p)\). Skuse et al. (1997) devised a parental report questionnaire to assess social cognition in children and adolescents with TS. Parents were asked to respond to statements such as, 'lacking an awareness of other people's feelings' and 'unaware of acceptable social behaviour', indicating whether these statements applied to their child. It emerged that those women who had inherited their single X from their mother had significantly greater social dysfunction than those who had their father's X-chromosome. This is suggestive of an imprinted locus on the X-chromosome that influences social cognitive development. This gene would seem only to be expressed when it is on a paternally inherited chromosome and silenced when on a maternally inherited chromosome. In this way, normal females will have one expressed copy, as will individuals with TS who have inherited their X from their father. However, those women with TS that have an X-chromosome that has been maternally inherited will not be expressing this locus.
1.3.3 Oestrogen

A complicating factor in understanding the influence of the absence of an X-chromosome on development is that, by the very nature of the disorder, women with Turner syndrome are also oestrogen deficient. Oestrogen therapy is administered and it is not known whether this may have a beneficial affect in terms of the cognitive or psychological characteristics associated with the condition.

A growing body of research suggests that female sex hormones are able to influence brain function and cognition. In humans, for example, cyclical changes in oestrogen across the menstrual cycle have been linked to fluctuations in performance on various tasks. High levels of oestrogen have been associated with decreased mental rotation and implicit memory skills, alongside improved motor skills and verbal fluency (Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Gunturkun, 2000; Maki, Rich, & Rosenbaum, 2002). Animal models have demonstrated that oestrogen may be directly involved in the development and maturation of many brain regions including the amygdala (Nishizuka & Arai, 1981; Zhou, Cohen, & Pandey, 2001).

Although some endogenous oestrogen may be circulating throughout infancy and early childhood, the major surge in this hormone in typical females comes at puberty. Maturational brain changes as assessed by event-related brain potentials (ERP’s) have been noted over this period. Johnson Jr. and colleagues (Johnson, Jr., Rohrbaugh, & Ross, 1993) recorded ERP
responses to auditory stimuli in both young (ages 9-14) and old (ages 15-20) individuals with TS and controls. None of the TS individuals had been given oestrogen replacement. For the young TS group, the ERP responses were identical to those of the control group. However, in the older TS girls the ERP’s elicited were more similar to those in both of the young groups than to those found in their age-matched controls. These results are consistent with a maturational rather than a congenital defect but may or may not be related to oestrogen deficiency.

It has been hypothesised that a subset of the neuro-cognitive TS deficits (visual-spatial, perceptual and social-cognitive) are genetically determined and result from abnormal expression of one or more X-chromosome genes. However, a different subset of deficits (namely reaction time and speeded motor function) may result from oestrogen deficiency and could be at least somewhat reversible with oestrogen treatment (Ross, Roeltgen, Feuillan, Kushner, & Cutler, Jr., 2000). Positive oestrogen treatment effects on motor and memory function have been demonstrated in girls and women with TS (Romans et al., 1998; Ross, Roeltgen, Feuillan, Kushner, & Cutler, Jr., 1998). However, these studies are cross-sectional rather than longitudinal and it is impossible to know whether some other maturational factor might be able to account for the group differences. A separate body of evidence that may add weight to these claims is the suggestion that memory function may also be enhanced in postmenopausal women who are given oestrogen supplementation (Resnick & Maki, 2001). However, research in this area is still controversial and many contradictory results exist.
The cognitive phenotype of adults with TS, with or without ovarian failure, are similar (Ross et al., 2002), indicating that oestrogen deficiency can not provide a full explanation for the deficits we see in this syndrome. In theory it would be possible to compare the development of the small number of TS females who have a spontaneous puberty with the remainder. This would enable you to test whether oestrogen deficiency in and of itself may be contributing to the TS phenotype.

1.4 CHAPTER SUMMARY

I began this chapter by considering the ways in which we can study the influence of genes on brain development and behaviour, outlining that this study would adopt a behavioural neuroscience approach. The study will focus on individuals with Turner syndrome who are missing an entire X-chromosome and therefore have just 45 as opposed to 46 chromosomes. Studying this population affords us with the opportunity to understand more about the difficulties that may be manifest in this clinical syndrome. It also enables inferences to be drawn about the importance of genes on the X-chromosome in typical development.

Turner syndrome has a number of physical manifestations but can also affect cognitive development and behaviour. Visuo-spatial difficulties have been widely reported and studied, with plausible neuroanatomical anomalies detected in occipital-parietal brain regions. However, not all psychological aspects of the condition have been so fully explored or understood. Notably,
social dysfunction is frequently reported but with little understanding of the exact nature of these difficulties, how they are manifest and what may underlie them. In an attempt to form some ideas about what aspects of social cognition would be important to study in this group, questionnaire data was reviewed. This further supported the notion that social dysfunction was evident in many individuals with Turner syndrome but also hinted at a potentially interesting area to study.

It appeared that social difficulties were most pronounced in the domain of interpreting non-verbal behaviour, including knowing what someone was feeling just by looking at their face. Since the face is the most communicative of all channels of non-verbal communication, it became the focus of this thesis. In other clinical populations, face-processing difficulties have been noted to co-occur with difficulties in social functioning. There are some hints from the literature that face processing may be anomalous in Turner syndrome but little is known about the nature or severity of the deficit. The experiments in this thesis will aim to enrich our understanding of these possible difficulties.

Finally, this chapter outlined the mechanisms by which the absence of an X-chromosome could affect cognitive development. Three primary mechanisms by which genetic factors may influence brain structure or function and ultimately cognition and behaviour were considered. This thesis will attempt to help clarify which of these mechanisms may be playing a role in the development of face processing anomalies in Turner syndrome. It will select

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karyotypically distinct groups of women with Turner syndrome and obtain information regarding oestrogen supplementation. In this thesis, I will investigate face-processing abilities in Turner syndrome with the hypothesis that they will be sub-optimal in this group.
2 CHAPTER TWO – FACE PROCESSING SYSTEMS

2.1 OVERVIEW

This chapter considers the cognitive neuroscience of face processing, looking at what is known about the way in which faces are processed in the typically developing brain. It takes as its starting point a review published in 2001 (Elgar et al., 2001), but extends beyond that to address a number of issues that continue to attract researchers' efforts. Much of the current interest in face processing brain systems arose from the discovery that certain aspects of face processing can be selectively impaired consequent to brain damage.

Face recognition is often considered to be a modular function. Modularity can be considered as the brain being composed of discrete domain-specific modules that are innately pre-programmed and insensitive to environmental influence (Fodor, 1983). I present evidence here to suggest that while faces are 'special' in a number of respects, the recognition of them and interpretation of them also makes use of general-purpose cortical systems that are involved in high level vision, memory, learning and emotion more generally. These neural systems can be conceived as distinct but overlapping cortical streams: a medial stream (for learning and social salience of faces)
and a lateral stream (for distributed representations of visual properties and facial identities). The areas discussed are represented diagrammatically in figure 2.1.

This conceptualisation differs from other models (Bruce & Young, 1986). Although it distinguishes between different elements of face processing it considers them to be inter-related. It seeks to present two partially distinct but highly interconnected cortical streams that may be differentially recruited to best serve the different computations involved in many different types of processing necessary in dealing with faces.
Figure 2.1: Lateral (A) and medial (B) diagrammatic views of the human brain to show the lateral and medial flows of face-identity information. Largely the temporal order of information processing is shown, although there is a degree of information transfer in both directions.
2.2 HISTORICAL PERSPECTIVE

Modern neuropsychological interest in face perception and recognition arose from the observation that brain damage could produce selective impairments in this skill while leaving other aspects of visual recognition intact (Bodamer, 1947). The selective inability to recognise faces known to the patient premorbidly is referred to as prosopagnosia, meaning 'face-blindness'. The selectivity of this deficit is strengthened by the opposing observation that individuals can have impairments in object or word recognition but have intact face recognition abilities (Farah, 1991). This double dissociation, alongside the astonishing human ability to recognise and discriminate between an infinite number of faces, led to theorising about special processing mechanisms that operated for faces (Bruce et al., 1986). Throughout the last decades of the twentieth century issues of modularity dominated research into face processing. The paramount question was 'Is face processing special, compared with the processing of other visual objects?'

Recent developments in neuroimaging have shifted the focus towards consideration of the cortical and sub-cortical substrates of face processing. This has recontextualised research towards understanding the networks of interconnected neural systems that together support the perception, memory and interpretation of faces.

This review will take a look at some of the neural regions believed to be involved in face processing, considering both the role of these regions in
typical face recognition and incidences where the functional integrity of these systems have been compromised. The focus will also be on whether these neural regions implicated in face processing are known to play a role in social cognitive functioning more generally. Firstly, however, it will consider the special type of processing that is implicated in face recognition.

2.3 CONFIGURAL PROCESSING IN FACE RECOGNITION

At a processing level it has been argued that the fusiform gyri (in particular of the right hemisphere) are critical for face recognition because they afford the capacity to analyse visual patterns in a holistic or configural manner (Tanaka & Farah, 1993). The terms ‘holistic processing’ and ‘configural processing’ are often used interchangeably, but are not synonymous. Even within the domain of configural processing ambiguities exist. As Maurer and colleagues point out (Maurer et al., 2002), ‘there is no consensus about terminology’. In a recent review they suggest that configural processing is best conceptualised by being broken down into three sub-components, which are defined in table 2.1 and form the basis for the subsequent consideration of evidence for this type of processing.
<table>
<thead>
<tr>
<th>Configural processing type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to first order relations</td>
<td>Seeing a stimulus as a face because its features are arranged with two eyes above a nose, above a mouth</td>
</tr>
<tr>
<td>Holistic processing</td>
<td>Gluing together the face features into a gestalt</td>
</tr>
<tr>
<td>Sensitivity to second order relations</td>
<td>Perceiving the distances between face features</td>
</tr>
</tbody>
</table>

Table 2.1: Three types of configural processing as conceptualised by Maurer and colleagues (Maurer et al., 2002). They are thought to have different developmental trajectories with sensitivity to first order relations emerging early on in development, followed by holistic processing competence and finally adult sensitivity to second order relations.

### 2.3.1 Sensitivity to first order relations

First order relations are those aspects of a face that are shared by all faces, namely the fact that they contain two eyes, symmetrically positioned above a nose, which in turn is positioned centrally above a mouth. This arrangement is one to which human infants would appear to be sensitive from very early on in development. Neonates orient to faces in preference to other objects and within the first hours of life can discriminate between face-like patterns and patterns with the same features arranged in a different configuration (Johnson, Dziurawiec, Ellis, & Morton, 1991). One method of assessing sensitivity to first-order relations would be to present stimuli such as the Mooney faces (Mooney, 1957). Despite being little more than patterns of light
and dark, these images appear face-like. This is because the features are arranged in such a way as to form the first-order relations of a face although no face details are present.

Figure 2.2: An example of a Mooney face, where a face-like image can be detected in the absence of face detail due to the presence of intact first-order face relations.

It would appear that the fusiform gyri respond to first-order face relations, since Mooney faces are found to activate this region in functional imaging studies (Kanwisher, Tong, & Nakayama, 1998).

2.3.2 Holistic processing

In contrast to sensitivity to first-order features, holistic processing involves the gluing together of the face features into a 'whole'. Evidence for the existence of this type of processing is provided by a number of experimental paradigms. For example, the composite face effect where face images are split in half and
then joined with a half from another face. If the two different halves are laterally offset, so as to prevent them being perceived as a whole, recognition of the parts is superior (see figure 2.3) than when they form a whole (Hole, 1994; Young, Hellawell, & Hay, 1987). This phenomenon is interpreted as demonstrating that internal features are automatically integrated making it difficult to parse the face into its isolated features (Maurer et al., 2002).

Figure 2.3: An example of the 'chimeric' face effect demonstrated by Young and colleagues (Young et al., 1987). Shown here using the faces of Robbie Williams (top) and Tony Blair (bottom). When the top and bottom halves of the different identities are aligned to form a whole, the faces are typically more difficult to identify than when misaligned.

A similar observation holds for the perception of emotional expressions. Where the top half of a face showing one expression is fused with the bottom half of a face showing a different expression, recognition of the composite parts is slowed compared to when the face halves are misaligned (Calder,
Young, Keane, & Dean, 2000). This suggests that our ability to recognise facial expressions of emotion also depends, in part, on holistic processing.

The part-whole recognition effect as studied by Tanaka and colleagues (Tanaka et al., 1993), also provides evidence for the importance of holistic processing in face recognition. For example, individual face features (e.g. a nose) are recognised better when they are presented in the context of the original face configuration than in isolation (Tanaka & Sengco, 1997). This advantage was not found for any of the control stimuli they examined, including scrambled faces, inverted faces and houses. Similarly, individuals are better at matching whole faces than individual parts of faces (Rossoin et al., 2000).

2.3.3 Sensitivity to second order relations

Unlike first-order relations, not all faces share the same second-order relations (distances between the face features). They help us to individuate faces and recognise particular faces. In support of the notion that the processing of second-order relations is particularly important for face recognition, it has been shown that changes in visual properties of faces that disproportionately affect their second-order relations impair recognition.

Blurring faces obscures fine-detailed information about facial features and forces recognition to be achieved by sensitivity to second order relations.
(Hayes, Morrone, & Burr, 1986). This is generally quite easy for normal adults (see figure 2.4c) but can be very difficult for patients with face recognition difficulties (Bliem, 1998). This suggests that insensitivity to second-order relations may underlie face recognition difficulties in some patients.

Finally, possibly the most studied paradigm within experimental research into face processing, is the inversion effect. Face recognition is disproportionately impaired by inverting the orientation of the image (Eimer, 2000; Valentine, 1991; Yin, 1969). Upside-down faces are more difficult to recognise than upright faces (see figure 2.4 a&b).

It is not just that faces are more difficult to recognise inverted than upright but that inversion may produce a greater recognition decrement for faces than for other classes of objects. When face recognition has been tested alongside the recognition of photographs of other objects (such as houses and aeroplanes), recognition for faces is typically better than for other classes of objects (Yin, 1969). However, when the stimuli are inverted, faces typically become the most difficult stimuli to recognise (Yin, 1969) with the effect intensifying with increasing degree of rotation away from the upright (Collishaw & Hole, 2002). Inversion disrupts the discrimination of faces that differ in terms of second-order relations much more than it disrupts discrimination of faces that differ in terms of featural information (Leder, Candrian, Huber, & Bruce, 2001). Maurer (Maurer et al., 2002) suggests that the facial inversion effect is likely to occur at the level of perceptual encoding rather than storage or retrieval.
Figure 2.4: Examples of the influence of manipulations of second-order relation image characteristics on face recognition, demonstrated here with the face of actress, Julia Roberts.

Firstly as a normal image (a) then showing the detrimental affect of inversion on face recognition (b). In (c) we see that blurring a face fails to severely disrupt our recognition ability.
This is because the effect is found to be of a similar magnitude when the faces are presented simultaneously to when they have to be remembered for up to 10 seconds (Freire, Lee, & Symons, 2000).

In terms of developmental trajectory, sensitivity to first-order face relations is present very early in development. However, sensitivity to second-order relations develops at a slower rate and over a much longer period than featural face processing (Mondloch, Le Grand, & Maurer, 2002). It has been argued that young children are not able to make appropriate use of this type of processing in face recognition (Carey, Diamond, & Woods, 1980) and can be fooled by manipulations of featural aspects of the face more than adults. The inversion effect for faces, though present in young children (Brooks & Goldstein, 1963), becomes more pronounced with age (see Chung & Thomson, 1995), for a review), which is often taken as a sign of increasing configural competence in processing faces in the developing child.

Feature based processing is also important for normal face recognition (Cabeza & Kato, 2000) and typically operates in tandem with configural analysis of a face image. However, individual and developmental differences may exist in the extent to which each is relied upon. Even within individuals, face recognition can be more or less configural or feature based depending on manipulations of the processing environment. For example, face recognition can be disrupted by engagement in concurrent tasks (such as letter identification) that activate a featural processing strategy (Macrae & Lewis, 2002).
In development, it is possible that configurational aspects of face recognition will be more susceptible to disruption since they develop over a longer period. In addition, experiments with individuals who were born with cataracts in both eyes demonstrate that early visual experience is critical for the normal development of configurational face processing in later years. It was found that children with congenital cataracts that had been operated on in early infancy had poorer configurational face processing than normal children when assessed in later childhood (Le Grand, Mondloch, Maurer, & Brent, 2001). This is suggestive of a sensitive or critical period in early infancy for the development of optimal configurational face processing skills.

2.4 FACE PERCEPTION

The recognition of faces, like the recognition of any other visual object begins in the ganglion cells of the human retina. These cells project through the optic nerve to the lateral geniculate nucleus (LGN) of the thalamus. Beyond these primary perception sites, visual association cortex comprises two streams, with functional specialisation. The ventral visual stream projects forwards within the temporal lobe. This is involved in recognising 'what' an object is. The dorsal visual stream projects upward to the posterior parietal lobe and, on one formulation at least, processes information concerned with 'where' something happens (Mishkin & Ungerleider, 1983). The ventral visual stream that projects through the temporal lobes is primarily concerned with all kinds of visual object (including face) recognition (see back to figure 2.1).
2.4.1 The fusiform face area

Prosopagnosia (the failure to recognise previously familiar faces) can occur subsequent to a number of types and extents of brain injury. However, common to the majority of patients is damage to one particular region of inferior temporal cortex, dubbed the fusiform face area. A landmark post-mortem study by Meadows delimited the anatomically critical regions for acquired prosopagnosia to include the fusiform gyrus and possibly the lingual gyrus of the right temporal lobe (Meadows, 1974). It was further believed that the presence of other posterior lesions might contribute to the syndrome. Brain imaging techniques in typically developing adults have confirmed the role of the fusiform gyrus and inferior temporal lobes in face processing.

Studies using event-related potentials (Bentin, Allison, Puce, Perez, & et al, 1996), positron emission tomography (Sergent, Ohta, & MacDonald, 1992), and functional magnetic resonance imaging (Clark et al., 1996; Clark, Maisog, & Haxby, 1998; Kanwisher, McDermott, & Chun, 1997; Puce, Allison, Gore, & McCarthy, 1995; Puce, Allison, Asgari, Gore, & McCarthy, 1996) have unambiguously supported Meadows’ clinical neuroanatomical observations. Viewing faces is associated with increased activity in the fusiform gyrus. Where hemispheric asymmetry occurs, as is found in most patient studies (De Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994), the right rather than the left hemisphere is implicated. The middle part of the right fusiform gyrus shows activation in most reported studies and has been named the ‘Face Fusiform Area (FFA)’ (Kanwisher et al., 1997). Earlier behavioural studies using
unilateral presentation of face images also generally demonstrated right-hemisphere (left visual field) superiority in face recognition (Sergent & Bindra, 1981).

However, despite demonstrations that the fusiform gyri clearly play an important role in face recognition, many argue that the role of this region is not specific to faces. Rather it may specialised for the type of configural processing that the recognition of faces recruits. Does the recognition of any other classes of stimuli involve this type of visual processing mediated by the fusiform gyri?

2.4.1.1 Intra-class discrimination

The idea that face recognition was only unique in so far as it required subtle intra-class discriminations was first championed by Damasio and colleagues (Damasio, Tranel, & Damasio, 1990). Inter-class discrimination can be considered as discriminating between different object categories e.g. a shoe, a table, and a football. Intra-class discrimination, on the other hand would require us to discriminate between different types of the same class of object, for example discriminating between different pairs of shoes. While recognising faces frequently involves subtle intra-class discriminations between many similar exemplars, this is not so for most other visual identification tasks. You need to be able to discriminate the face of your mother from that of a stranger.
but with objects it is often adequate to simply recognise the object class e.g. a shoe, or a table.

Damasio and his colleagues have argued extensively that prosopagnosia is (only) a form of visual object agnosia, selective for intra-class discrimination. When intra-class discrimination of non-face objects is assessed, prosopagnosia is frequently accompanied by other selective agnosias at this level (Damasio, Damasio, & Van Hoesen, 1982; Damasio et al., 1990; Henke, Schweinberger, Grigo, Klos, & Sommer, 1998). Prosopagnosics can have difficulty discriminating between different makes of car, just as they have difficulty discriminating between different faces. Gauthier and colleagues compared brain activation for discrimination of objects at an inter-class level (e.g. car or bird) or intra-class level (e.g. Honda or Ferrari) (Gauthier et al., 2000). Intra-class level decisions activated the fusiform gyrus. This property, rather than any intrinsically face-like 'pre-wiring' may account for the role of the fusiform gyrus in face processing. A similar conclusion may be drawn from studies on visual expertise.

2.4.1.2 Expertise

Experience is required to make fine-category discriminations within a homogenous class of stimuli. The typical decrement in recognising objects when inverted as opposed to upright is magnified for faces, for which inversion severely disrupts recognition. Dog and bird experts show similar
inversion decrements for images within their expert category as do typical individuals when shown faces (Diamond & Carey, 1986; Rhodes, Tan, Brake, & Taylor, 1989). In one experimental study, participants were trained to become experts at recognising “greebles”. Greebles are visual patterns that are not faces but are of a similar level of complexity, with a high degree of visual similarity between exemplars. Participants that had been trained to recognise these patterns were faster and more accurate at recognising greebles than non-trained participants (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997). However, this advantage disappeared when images were inverted. This suggests that the experience served to enhance upright recognition by way of enabling configural processing. Since inversion disrupts configural processing, no advantage could be seen for the stimuli when in this orientation. Moreover, it has been found that activation of the fusiform gyrus increases with expertise at discriminating greebles (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999). This perhaps implies that the configural processing learning in these participants was mediated in part by this neural region.

The ability to recognise faces can also be predictive of the ability to become expert at making other visual discriminations. Berbaum and Platz report that pathologists who are good at discriminating visually similar pathological specimens are also more accurate at recognising faces, suggesting a common neural substrate involved in both tasks (Berbaum & Platz, 1988). Considering such findings, Tarr and Gauthier suggest that the fusiform face area should more appropriately be renamed a ‘flexible fusiform area’ (for subordinate-level visual processing) (Tarr & Gauthier, 2000).
The finding that the cortical substrates and (configural) processing characteristics for faces need not be confined to such images suggests that faces may be special in degree rather than in kind. However, for most of us, faces constitute a domain that is emotionally salient, contains very many exemplars that require individual recognition, and is structurally (visually) homogeneous. The unique combination of these factors leads to a (relatively) unique mode of processing for faces compared to other sorts of visual stimuli. This type of processing would appear to be heavily dependent on the normal functioning of the fusiform gyri.

2.4.1.3 Damage to the fusiform

What happens when the functional integrity of the fusiform gyrus is impaired? The way in which damage to this region can result in prosopagnosia has already been considered. However, for many prosopagnosic patients, the exact extent of the brain damage is often not known. It is important not to equate prosopagnosia with fusiform damage. Many patients with prosopagnosia are thought to have specific difficulty with configural aspects of face processing — they see the face as individual parts rather than an integrated whole with spatial relationships between the independent elements (Levine, 1989).

Patients may be able to extract other information from the face such as gender or emotional expression (Sacks, 1985), which in some cases can be less reliant on configural processing. Such patients can be as good (or better!)
at recognising faces when they are presented inverted as they are when they are presented upright. Patient LH (whose brain damage may include but is by no means confined to the fusiform gyri) showed this pattern (de Gelder & Rouw, 2000). One could argue that he could not discriminate faces that were upright because of poor configural processing, but inverted faces do not invoke configural processing and therefore could be processed by an intact piecemeal processing system. This would suggest that his part-based recognition system is functioning but in some way, this is prevented from being used to recognise upright faces for which configural processing is typically recruited. LH would seem to be using a faulty configural processing to analyse upright faces although an intact piecemeal system would be more effective. Do upright faces, either innately or through experience, so strongly recruit configural processing that we can not override the recruitment of this type of processing even when the system is faulty?

Prosopagnosic patients are typically not reported to have social difficulties except for those directly resulting from their ability to recognise faces.

2.4.1.4 Developmental prosopagnosia

In a handful of individuals with prosopagnosia the deficit is thought to be congenital in origin and there is no known acquired neurological insult (Bentin, Deouell, & Soroker, 1999; de Haan & Campbell, 1991; Duchaine, 2000; Nunn, Postma, & Pearson, 2001). In several of these patients, the face recognition
deficit would appear to be qualitatively different to that experienced by patients with acquired lesions. Some developmental prosopagnosic patients are able to match concurrently presented faces, with difficulties appearing to be more concerned with memory for faces (Bentin et al., 1999; Kracke, 1994). Furthermore, while patients with acquired prosopagnosia often show covert recognition for faces that they explicitly claim not to recognise, this would not appear to be the case for patients with developmental prosopagnosia. Three patients with developmental prosopagnosia failed to show any covert recognition of faces. This could be linked to a failure to establish a store of accurate facial memories, which would have been possible for patients with acquired prosopagnosia pre-lesion (Barton, Cherkasova, & O'Connor, 2001). However, some covert recognition has been detected in one child with developmental prosopagnosia (Jones & Tranel, 2001).

In addition, where other aspects of face processing have been assessed, the difficulties seem to be wider reaching in developmental cases. Face recognition difficulties are often accompanied by problems with facial emotion recognition (Ariel & Sadeh, 1996; Kracke, 1994) (but see (Jones et al., 2001)) and difficulties with lip-reading and judging direction of eye gaze (de Haan et al., 1991). In addition, a number of these patients have been reported to experience social adjustment difficulties, for example patients AB and HD (Kracke, 1994; McConachie, 1995).

Therefore, patients with developmental prosopagnosia would appear to have, at least in some ways, qualitatively different impairment to those with acquired
prosopagnosia. Furthermore, one study has assessed configural processing abilities of an individual with developmental prosopagnosia and found them to be intact (Duchaine, 2000). None of these developmental patients are known to have neurological abnormalities so the findings provide no clear indication of the neural regions involved in their anomalous abilities. However, it is interesting to note that in these congenital cases, where other face processing abilities have been examined, no face identity recognition specific impairment like those found in acquired prosopagnosia, has been reported. Perhaps whatever the cause of face recognition difficulties congenitally or in early development, there will be many knock on affects to other elements of face processing systems? This is an important consideration, and caution needs to be drawn in modelling developmental profiles on acquired disorders (Karmiloff-Smith, 1997; Karmiloff-Smith, 1998).

As is pointed out by de Haan et al (de Haan, Humphreys, & Johnson, 2002), the fact that early neural damage often fails to have a significant impact on face recognition abilities is suggestive of a system that is either plastic following disruption or relatively widely distributed. For example, it has been found that less than 50% of children experiencing perinatal unilateral lesions to either hemisphere have any detectable face recognition impairments (Mancini, de Schonen, Deruelle, & Massoulier, 1994). In a similar study, it has been reported that face recognition impairments are more likely to result from early damage to the parietal lobes than to the temporal lobes (Ballantyne & Trauner, 1999).
2.4.1.5 Face processing in developmental disorders

In individuals with both autism and William's syndrome, anomalies in the configural processing of faces (thought to be mediated by the fusiform gyri) have been noted.

Youngsters with autism tend to perform at the level of much younger children on tasks that require them to match face features both within and without a supporting face context. They resemble mental-age matched controls when matching isolated face features, but fail to show any facilitation when the features are embedded in a whole face (Teunisse & de Gelder, 1994).

People with autism can also be less sensitive than controls to face inversion (Hobson, Ouston, & Lee, 1988; Langdell, 1978). Davies et al (Davies, Bishop, Manstead, & Tantam, 1994) found that high-functioning youngsters with autism and Asperger syndrome were impaired on a task that required the detection of configural similarity within an array of dots as well as detecting the configural similarity of faces. This suggests that a 'configural processing anomaly' might be a general feature of autistic processing style. This is consistent with the notion that individuals with autism rely on a (default) cognitive style that uses local detail rather than global pattern (Happe, 1999).

Functional brain imaging indicates that faces may not engage a special circuit in people with autism. People with autism have been found to show relatively reduced activation of fusiform regions by faces compared with objects (Pierce,
Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000). Similarly, individuals with autism fail to show normal ERP amplitude differences to familiar, as opposed to unfamiliar faces while they do show differential amplitudes for familiar versus unfamiliar objects (Dawson et al., 2002).

Despite having relatively spared face recognition abilities, individuals with William's syndrome also demonstrate anomalous configural face processing. They perform poorly on tasks that require configural face processing (Karmiloff-Smith, 1997) tending to rely on featural processing. Further evidence of anomalous configural face processing has been reported, where individuals with Williams syndrome are found to show a reduced face-inversion effect (Deruelle, Mancini, Livet, Cassse-Perrot, & de Schonen, 1999).

Atypical cognitive processes may be mediating face processing in this syndrome. Individuals with Williams Syndrome have been found not to show the typical gamma burst in EEG activity associated with viewing faces (Grice et al., 2001). This activity has been linked to the perceptual integration of features and its absence in WS may suggest that such processing is not critical to face recognition in this syndrome.
2.4.1.6 Beyond the Fusiform face area...

While all and any face processing task appears to enhance activation in the face-fusiform regions, the processing of facial identity – both the learning of new faces and the recall or recognition of learned ones – along with understanding social characteristics of the face, requires activation of more extensive networks. Here too, right rather than left-sided structures are critical. What is less clear is exactly which structures are implicated in which aspects of face processing.

2.4.2 Face Perception (continued)

2.4.2.1 Parietal lobe

Although it is the temporal lobe that is primarily concerned with identifying and recognising objects and faces, it would seem that the parietal lobe possibly has a role to play given the complex visuo-spatial nature of faces. This role may be more important in the establishment of face expertise than in adult skilled face recognition. Prenatal and peri-natal lesions to the parietal lobes (of either hemisphere) are known to result in residual deficits in face recognition, being suggestive of the importance of the parietal lobes in the development of face recognition (Ballantyne et al., 1999). One of the functions of the parietal lobes is to perform mental rotation type manipulations with stimuli so that they
can be represented from differing viewpoints (Vanrie, Beatse, Wagemans, Sunaert, & Van Hecke, 2002). Our initial experience with a new face is typically from a particular viewpoint. Perhaps, as children, our inferences about what a face looks like from different angles are partly based on mentally rotating the face. This processing may then influence the development of object (or face) recognition, which is represented more in temporal areas. Additionally, Adolphs and colleagues (1996) using lesion analysis, report that damage to the right inferior parietal cortex correlated with recognition of facial expressions of emotion.

2.5 FACE RECOGNITION AND FACE MEMORY

2.5.1 Fusiform Gyrus

The fusiform gyrus may be involved in simple perceptual memory for faces. Repetition priming effects have been observed in right fusiform for famous faces and in the left inferior occipital region for both familiar and unfamiliar faces (Henson, Shallice, Gorno-Tempini, & Dolan, 2002). The inference is that the fusiform gyrus has two-way connections to other cortical and sub-cortical regions. The fusiform response is unlikely to be specific to faces, since it also exhibits an attenuated response to repeated exposure of familiar non-face stimuli (Henson, Shallice, & Dolan, 2000).
2.5.2 Hippocampus

In PET studies, activity in the right parahippocampal gyrus has been generated by face recognition tasks (Sergent et al., 1992). This structure, rostral and medial to the fusiform gyrus, projects to hippocampal regions. The role of the hippocampus and neighbouring regions, including the amygdalae, in all aspects of learning is well known, and has been confirmed in imaging studies (Haxby et al., 1996). The process of forming new face-name associations is supported by hippocampus, in addition to the fusiform and dorso-lateral prefrontal regions (Sperling et al., 2001). These changes in hippocampal activity may form part of a consolidation process for face learning that lasts for a few years (Haist, Bowden, & Mao, 2001).

In patients with acquired hippocampal lesions, faces are one of many classes of material that are poorly learned and remembered. However, as with other material tested in such populations, faces learned a long time before damage can be relatively spared. This suggests that some aspects of established face knowledge are represented in, and accessed through, other cortical systems. The lateralisation that is seen in the fusiform gyrus, with right hemisphere lesions being particularly implicated in producing prosopagnosia, is also seen in the hippocampus where right hemisphere lesions may be particularly critical to face memory abilities (Baxendale, 1997). Suggesting differential roles for the hemispheres, Seidenberg et al (Seidenberg et al., 2002), found that patients with left hippocampal damage had a selective impairment in naming famous faces, while those with right hippocampal damage were impaired.
across all components of face memory, face recognition, semantic
identification and face naming.

2.5.3 Amygdala

As a central operator in the limbic system, the amygdala is important in
learning and memory for events or stimuli that have emotional or social
valence. The amygdala is thought to enhance memory for arousing material
(Phelps et al., 1998) possibly by modulating other regions that are involved
with brain storage. Activity of the amygdala while participants view emotionally
provocative stimuli correlates with the degree to which the stimuli are retained
in long term memory (Cahill, 1996; Cahill et al., 2001b; Canli, Zhao, Brewer,
Gabrieli, & Cahill, 2000). Since faces are emotionally arousing stimuli it is
suggested here that the amygdala would also be involved in remembering
faces.

One study suggests how this might be so. When faces were encoded with a
‘deep’ strategy (making judgements of pleasantness) they were remembered
better in a recognition test. Additionally, activity was found to be enhanced in
the amygdala relative to a shallow encoding condition (judging right/left
orientation (Bernstein, Beig, Siegenthaler, & Grady, 2002). This suggests that
our emotional reactions to faces may also modulate our subsequent ability to
remember them.
In what ways could activity of the amygdala enhance memory for faces? With regard to emotionally charged events more generally, evidence suggests that the amygdala interacts with endogenous stress hormones released during these events to modulate memory storage in other brain regions (Cahill, 2000; Cahill & McGaugh, 1996). During the perception of faces showing a fearful expression, the amygdala may influence the activity of the fusiform gyrus and other regions involved in face processing (Morris et al., 1998) possibly enhancing our perception of these stimuli. However ‘modular’ face processing may be, it is still susceptible to influences from other processing systems.

Activity of the amygdala when viewing faces is also modulated by familiarity of the faces. Less activity is elicited by faces of people with whom we are familiar than by faces that are unknown to us (Gobbini, Leibenluft, Santiago, & Haxby, 2002). Haxby, Hoffman, & Gobbini (2002) suggest that this reduction in activity may be associated with feeling more at ease and less guarded when one is with close acquaintances as opposed to strangers – the amygdala responds to threat (Isenberg et al., 1999).

In a study addressing the relationship between face memory and medial temporal lobe structures, an intriguing association was noted between amygdala volume and scores on a face recognition memory task (Mackay et al., 1998). The males who attained the highest scores on this task had significantly smaller right amygdala volumes than the males who attained the lowest scores. This is perhaps suggestive of the importance of structural elements of amygdala development in face recognition memory.
2.5.3.1 **Damage to the amygdala**

Patients who have bilateral amygdala damage, as a consequence of surgery or neural disease have been found to exhibit a number of difficulties in the processing of faces. Most notably, individuals can develop post lesion difficulties in recognising facial expressions of emotion; in particular those emotions with negative valence (this evidence is considered later in this chapter). In addition to these emotion recognition difficulties, problems with recognising faces can also exist; whereby the ability to learn new faces encountered post-lesion is severely affected (Calder et al., 1996). Sometimes this is detectable in laboratory tests of face learning and memory (Calder et al., 1996; Tranel & Hyman, 1990a) but this isn't always the case (Adolphs, Tranel, Damasio, & Damasio, 1995a).

Difficulties can present irrespective of whether the damage to the amygdalae occurs in adulthood or childhood. For example, patient SM had a congenital disease (Urbach-Wiethe) which produced bilateral calcification of her amygdala in early childhood if not before (Adolphs et al., 1995a). Therefore much of her development would have been experienced without normal amygdala function. However, like patients with acquired damage in adulthood, SM had difficulties with unfamiliar face memory (Tranel & Hyman, 1990b), suggesting that there is limited neural plasticity for these aspects of face memory.
When face recognition difficulties are present in either congenital or acquired cases with bilateral amygdala lesions, they are usually less severe and probably of a different nature to those experienced by prosopagnosic patients. An inability to adequately match concurrently presented faces has also been noted in some (Jacobson, 1986) but not all individuals with this neurological insult (Tranel et al., 1990a). Poor face memory may be part of a wider impairment in declarative memory for any emotional material. Since amygdala activation is associated with enhanced memory for emotionally salient stimuli, it is not surprising that damage to this region can result in impaired memory for emotionally arousing material (Adolphs, Cahill, Schul, & Babinsky, 1997).

Do patients with amygdala damage have difficulties with social functioning? Patient S.M., with developmental damage, is described as being 'somewhat coquettish & disinhibited...(she) often makes mildly inappropriate sexual remarks' (Tranel et al., 1990a). This same patient is also described as having a 'history of inadequate social decision making, somewhat inappropriate social behaviour' (Adolphs et al., 1995a). The first case with acquired amygdala damage to be described was a female adult patient referred to as DR. Jacobson notes a number of unusual social characteristics about this patient including; marked placidity, blunting of affect, social anxiety and absence of anger (Jacobson, 1986). She was also reported to be somewhat apathetic and failed to make any new friendships or attachments post operatively.
Although both of these patients have difficulties in social adjustment, they may be conceived to be qualitatively slightly different in nature, which perhaps relates to the age at which amygdala damage occurred. More evidence that this might be the case emerges from animal literature on the subject.

Since the observations made by Heinrich Kluver, bilateral amygdala lesions have long been known to impact on social interactions for Rhesus monkeys (see (Nahm, 1997) for a review). Amygdalectomised monkeys are known to demonstrate increased social affiliation and decreased anxiety during social encounters, in particular with unfamiliar monkeys (Emery et al., 2001). Neurons within the medial amygdala respond selectively to features of the social environment in this species (Brothers, Ring, & Kling, 1990). In macaques it is also possible to study the affect of lesions at different ages and assess the developmental consequences. Selective amygdala lesions have been produced in two week old monkeys, leading to somewhat different affects on social behaviour to those found in adult lesioned monkeys (Prather et al., 2001). In contrast to adult monkeys, who have been found to show decreased fear of inanimate objects and increased social affiliation, these monkeys demonstrated LESS fear of inanimate objects but MORE fear during dyadic social interactions. Therefore, it is of critical import to consider the impact of damage to the developing human brain separately (but alongside) to damage to the more developed adult brain. The consequences may be different.
2.5.3.2 The amygdala and autism

Individuals with autism, who by definition have difficulties in social functioning, have also been reported to have anomalous amygdala function (Howard et al., 2000). Decrements have been reported on tests of incidental face learning (Boucher & Lewis, 1992), memory for recently presented faces (Ellis, Ellis, Fraser, & Deb, 1994), and recognition of familiar faces (Boucher, Lewis, & Collis, 1998). Memory for other (non-social) objects appears to be at an appropriate level. It has been reported that control children remembered faces better than objects, while children with autism show no such distinction (Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998). This possibly reflects the enhanced emotional significance of faces for typically developing children but not for children with autism.

2.5.4 Orbito-frontal cortex

Just as the amygdala receives both efferent and afferent projections from the fusiform gyri, the orbito-frontal cortex is anatomically connected to the amygdala (Amaral & et al., 1992; Rolls, 2000). Within the macaque orbito-frontal cortices there are cells that appear to respond selectively to faces (Thorpe, Rolls, & Maddison, 1983). Different face recognition tasks may make differential demands on the face recognition system. Recognising newly learned faces may cause relatively more medial frontal activation, in particular the right medial orbito-frontal region, whereas recalling well-remembered faces may depend more on the posterior visual areas (Wiser et al., 2000). The
frontal lobes may also be recruited under restricted viewing conditions. Increased degradation of the face image is also reported to be coupled with increased activation of medial frontal regions (Grady, McIntosh, Horwitz, & Rapoport, 2000).

The orbito-frontal cortices additionally would appear to be involved in the processing of other information relevant to social functioning. For example, in normal individuals, judging expressions from another person's eyes produces activation of the amygdala, STS, and regions of prefrontal cortex (Baron-Cohen et al., 1999). Some cortical imaging studies also suggest that OFC is selectively involved in the performance of Theory of Mind tasks (Gallagher et al., 2000; Goel, Grafman, Sadato, & Hallett, 1995; Stone, Baron-Cohen, & Knight, 1998).

Damasio and his co-workers have discussed the role of the orbito-frontal cortex in social functioning (Damasio, 1996; Damasio, 1999). One of their key claims is that ventromedial parts of the inferior frontal cortex have a critical role in moderating activity flowing to the cortex from subcortical structures, including the amygdala and parts of the thalamus. One role of the orbito-frontal regions appears to be in modulating social interactions. It has been noted since the classic study of Phineas Gage (see (Damasio, Grabowski, Frank, Galaburda, & Damsio, 1994)) that lesions of prefrontal cortex affect social behaviour. Abnormalities in behaviour consequent to lesions to this area could reflect an underlying difficulty in altering behavioural
responses when the emotional significance of stimuli changes (Dias, Robbins, & Roberts, 1996).

2.5.4.1 The orbito-frontal cortex and autism

Based on behavioural tests (including social orientation), it has been suggested that children with autism have pathologies of orbito-frontal regions (Dawson, Meltzoff, Osterling, & Rinaldi, 1998). And individuals with autism fail (in a selective fashion) tasks that have been shown to activate this region in typically developing individuals such as reading the language of the eyes and theory of mind tasks (Baron-Cohen, Leslie, & Frith, 1985).

2.5.5 Anterior middle temporal gyrus & other regions

Functional imaging studies consistently reveal that the recognition of known famous or familiar faces, compared to unknown faces, activates the anterior temporal regions, in particular the middle temporal gyrus (Gorno-Tempini et al., 1998; Leveroni et al., 2000; Nakamura et al., 2000; Sergent et al., 1992).

Involvement of these regions would not seem unique to the processing of famous faces. PET technology has been used to investigate the processing of famous faces and famous buildings (Gorno-Tempini & Price, 2001). Activation of the left middle temporal gyrus was common to both famous (versus non-famous) faces and buildings, suggesting that this region might be critical in
storing unique semantic associations that are not shared by other perceptually similar category members, rather than having a specific role in famous face recognition. This is supported by the fact that this area is also found to be activated by the perception of familiar outdoor scenes (Nakamura et al., 2000). A recent study by Shah and colleagues indicates that person familiarity in general, accessed by either face or voice information, is associated with increased neural activity in the posterior cingulate cortex (Shah et al., 2001). This again points to the involvement of multi-purpose systems in the higher level processing of faces. However, it could be that the involvement of the posterior cingulate was more related to task demands than to the face recognition aspect of the study. Subjects were required to attend to faces but at the same time press a button to indicate the appearance of a random stimulus. It is possible that such attentional demands make the task more effortful, and therefore require recruitment of the posterior cingulate.

2.6 FACIAL EXPRESSIONS OF EMOTION

Neural regions beyond the fusiform gyrus are involved with the processing of affect in faces and are additionally implicated in the personal experience of affect.
2.6.1 The amygdala

The role of the amygdala in the recognition of fearful facial expressions in typically developing individuals was first reported by Morris and colleagues, who noted increased activation in the amygdala when participants viewed fearful as opposed to happy faces (Morris et al., 1996). Numerous studies using a variety of imaging techniques have since confirmed these findings. When activation elicited by viewing fearful faces is contrasted against activation associated with viewing other facial expressions, the amygdala is consistently found to be differentially activated by fearful faces (Breiter et al., 1996; Phillips et al., 1998). However, not all studies have replicated these findings (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998) although this may be in part due to the rapid habituation of the amygdala response to fearful faces shown in the course of an experiment (Breiter et al., 1996).

It would seem that rather than responding selectively to fear the amygdala responds to stimuli that pose an immediate threat, of which a fearful facial expression is an obvious example. Angry faces would also seem to signal threat, this time from the person displaying the expression rather than from some other aspect of the environment. It is therefore interesting to note a number of studies that have also found amygdala activation in response to facial expressions of anger (Hariri, Bookheimer, & Mazziotta, 2000) and there is a suggestion that this region also responds to sad facial expressions (Blair, Morris, Frith, Perrett, & Dolan, 1999).
From a developmental perspective, it has been argued that emotional facial expressions are first perceived in terms of pleasure and arousal (Bullock & Russell, 1984). They suggest that fear and anger would initially both be assigned the meaning of unpleasant/high arousal and the ability to discriminate between these two expressions relies on close attention to specific facial features. In this way it might be hypothesised that the amygdala is involved in the unpleasant or high arousal aspect of recognising fearful and angry faces but that what ultimately allows us to distinguish between them is high-level visual processes elsewhere in the brain and their interaction with the amygdala.

The amygdala is also thought to be involved in the processing of more complex facial displays. Baron-Cohen et al. (2000) found that interpreting higher level mental states from pictures of people’s eyes also gave rise to amygdala activation in healthy control participants.

Amygdala lesions in humans can lead to impaired formation of conditioned autonomic responses to aversive stimuli (Desmedt, Garcia, & Jaffard, 1998). LeDoux (1995) suggests that involuntary and voluntary responses to fear are mediated by different neural networks emanating from the amygdala. This region would seem to be critical to personal experience and appropriate reaction to fear inducing stimuli. However, interest in this region with regard to facial expressions of emotion arose from the discovery that subsequent to bilateral lesioning, difficulties in recognising facial expressions of emotion conveying negative valence, in particular those displaying fear, were evident.
(Adolphs, Tranel, Damasio, & Damasio, 1995b; Young et al., 1995). Fear is the most commonly affected emotion, although difficulties with the identification of anger and sadness are also common (Adolphs et al., 1999; Adolphs, Tranel, Damasio, & Damasio, 1994; Calder et al., 1996) although less so in patients with isolated lesions. See Chapter Six for a full consideration.

Where other aspects of reading social information from the face have been studied, for example assessing direction of eye gaze (Calder et al., 1996) or judging trustworthiness and approachability (Adolphs, Tranel, & Damasio, 1998), these aspects also appear to be affected by amygdala lesions.

Damage to amygdala can result in a multitude of difficulties in interpreting the face as a social cue. Difficulties may vary between individuals, possibly in part due to differences in extent of damage or the amount of connective tissue involved in the lesion. However, it is clear that the amygdalae are structures that are of critical import in enabling us to understand and interpret faces in a normal way. As was reviewed in the previous section of this chapter, individuals with amygdala lesions can also have difficulties with recognising faces and face memory and may have anomalous social behaviour. An isolated case in the literature (SM) is described who had congenital amygdala mineralisation, bilaterally due to Urbach-Wiethe disease (Adolphs & Tranel, 1999; Tranel et al., 1990a). This is perhaps the only pure case that allows us to evaluate the developmental consequences of damage to this region. In this
case difficulties in emotion recognition (for fear, surprise and anger),
alongside difficulties in face recognition memory and social adjustment exist.

2.6.1.1 The amygdala and autism

Concerning the involvement of the amygdala in face processing and social
adjustment there are indications that the functional integrity of this region may
be impaired in autism. In normal individuals, judging expressions from another
person's eyes produces activation of the amygdala, STS, and regions of
prefrontal cortex. This, however, is not the case for individuals with autism
(Baron-Cohen et al., 1999; Baron-Cohen et al., 2000) who fail to activate the
amygdala. In addition facial emotional expressions would appear not to
activate this region in individuals with autism as is found in typically
developing individuals. Critchley et al. (2000) found that individuals with
autism did not activate a cortical 'face area' when explicitly judging emotional
expressions and also failed to activate the left amygdala when processing was
implicit.

At a structural level, researchers have reported both increased (Abell et al.,
1999) and decreased (Aylward et al., 1999) amygdala grey matter volumes in
individuals with autism. Relative size is possibly influenced by whether the
individuals are high or low functioning. Individuals with Asperger's syndrome
have been found to have significantly greater left amygdala volume than
individuals with classic autism (Haznedar et al., 2000).
Dysfunction of the amygdala may be one causal factor underlying face recognition difficulties in individuals with autism (Baron-Cohen et al., 2000; Howard et al., 2000). The amygdala has also been implicated in psychopathy, where children with such tendencies are found to have difficulties recognising fearful and sad facial expressions (Blair, Colledge, Murray, & Mitchell, 2001).

2.6.2 The insula and basal ganglia

The basal ganglia have been widely implicated in the recognition of facial expressions of disgust. The basal ganglia are a group of sub-cortical nuclei in the telencephalon, and include the caudate nucleus, the globus pallidus, and the putamen, which are important parts of the motor system. Distinct neural substrates for fear and disgust have been identified (Phillips et al., 1997). Viewing facial expressions of disgust was found to produce activation of the right anterior insula.

Similar results were found in an fMRI study looking at emotion recognition in faces (Sprengelmeyer, Rausch et al, 1998) which identified differential neural substrates for the recognition of fear, anger and disgust. Disgusted faces activated the right putamen and thalamus and the left insula cortex whilst also increasing activation in medial frontal cortex.
In primates, the anterior insula is connected to the ventro posterior medial thalamic nucleus, which is thought to contain neurons which respond to pleasant and unpleasant tastes (Yaxley, Rolls, & Sienkiewicz, 1988). Furthermore, the anterior insula contains neurons that respond selectively to taste (Plata Salaman, Smith Swintosky, & Scott, 1996). It has also been found, in human PET studies, that the anterior insula is activated while tasting salt (Kinomura et al., 1994). It is suggested that activation of the anterior insula, during perception of facial expressions of disgust, implies that appreciation of visual stimuli depicting other’s disgust is closely linked to the perception of unpleasant tastes and smells (Kinomura et al., 1994). As with the multiple functions of the amygdala, the neural areas concerned with the perception of facial expressions of disgust appear also to be implicated in the subjective experience of this emotion. In fact the insula may be key in the conscious experience of emotion more generally (Morris, 2002).

Initial interest in the neural substrate of disgust also arose from the identification of selective impairments in a patient group. Sprengelmeyer and colleagues reported that patients with Huntington’s disease had particularly severe difficulty recognising facial expressions of disgust, although the recognition of other emotions was also affected to some extent (Sprengelmeyer, Young, Calder, Karnat, & et al, 1996). Less severe impairment of the other emotions may reflect a general deterioration in Huntington’s disease, in which there seems to be a progression from specific impairments to more general impairments of all cognitive functions as the disease progresses.
One group (Gray, Young, Barker, Curtis, & Gibson, 1997) have looked at
disgust recognition in the earliest stages of Huntington's disease, in patients
who were gene carriers but who were either asymptomatic or showed only
minor symptoms of the disease. People symptomatic with Huntington's
disease have often suffered some degeneration of many regions of the brain.
In the early stages it seems to be the basal ganglia which show the most
degeneration, so testing patients in the early stages of the disease was used
as a way of tapping the importance of these structures in the recognition of
disgust. It was found that Huntington's gene carriers showed a highly selective
deficit in the recognition of disgust alongside intact intellectual functioning and
normal ability on other tasks of face processing, including recognition of the
other basic emotions from facial expressions. It is likely that the putamen and
insula can respond to multiple social signals of disgust and not just those
conveyed by facial expressions. Damage to these regions has been linked
both to impairments in recognising vocal expressions of disgust and in the
personal experience of feelings of disgust (Calder, Keane, Manes, Antoun, &
Young, 2000).

Individuals with Obsessive Compulsive Disorder (OCD) have been shown to
have impaired recognition of facial expressions of disgust (Sprengelmeyer et
al., 1997). This may well be linked to their abnormal experience of disgust in
relation to the false contamination alarm that such patients can experience
(Stein, Liu, Shapira, & Goodman, 2001). One possibility is that in a dynamic
way, the excessive and abnormal experience of a particular emotion is linked
to difficulties in recognising the emotion in the facial displays of others. The emotion of disgust may be experienced more frequently and intensely in some patients with OCD and as a response to stimuli that would perhaps not ordinarily evoke this emotion. This experience could in turn be linked with some dysregulation of the system involved in recognising this emotion in others.

2.6.3 Orbito-frontal cortex

Functional imaging studies have revealed activation in the orbito-frontal cortices when typically developing adults view emotionally expressive faces (George et al., 1993; Phillips et al., 1997; Sprengelmeyer et al., 1998). There would appear to be less specificity in response to different facial expressions than in the amygdala or insular cortices, with studies reporting activation linked with a variety of different emotions, including those conveying both positive and negative affect.

The orbito-frontal cortex may have a specialised role in the perception of angry facial expressions. Increasing intensity of angry facial expression has been found to be associated with enhanced activity in the orbito-frontal cortex and the anterior cingulate cortex (Blair et al., 1999). The authors suggest that when a facial expression of anger activates the orbito-frontal cortex, the activation may serve to suppress current behaviour through either inhibition or activation of alternative behaviours.
Even relatively small lesions of orbito-frontal regions may result in impairments in the ability to identify affect from facial and vocal expressions of emotion (Hornak, Rolls, & Wade, 1996). Temporary pharmaceutical disruption of the function of the orbito-frontal cortices using diazepam has also been found to selectively impair the recognition of angry facial expressions (Blair & Curran, 1999). Furthermore, as was reviewed in the previous section, damage to this region can result in anomalous social behaviour. Additionally, anomalous function of the area has been suggested in individuals with autism.

2.7 INTERPRETING SOCIAL INFORMATION OTHER THAN EXPRESSION FROM THE FACE

2.7.1 Superior Temporal Sulcus

One region that may serve to connect the lateral and medial systems involved in face processing (that are schematically represented in figure 6.1) is the superior temporal sulcus (STS). This is a lateral temporal structure with projections to medial structures including the amygdala and orbito-frontal cortex. This region receives inputs from both the dorsal visual stream of the parietal cortex and the ventral stream of the temporal cortex, affording it a role in the integration of form and movement information. STS is activated during viewing of biological motion (Grossman et al., 2000) and would seem to be particularly responsive to facial movement including movement of the lips and
movement of the eyes. However, the posterior superior temporal sulcus is also activated during the perception of static pictures of faces (Chao, Martin, & Haxby, 1999; Hoffman & Haxby, 2000). Haxby and colleagues suggest that this activity may reflect the involvement of this area in evaluating potential movement or the aspects of the face that change with movement (Haxby et al., 2002). STS has back-projections to inferotemporal face processing regions and may be involved, not only in integrating facial form with more dynamic facial information, but also in moderating the development of inferotemporal regions and their function.

2.7.1.1 Mouth movements

In humans, viewing mouth movements is found to elicit activity within the STS (Puce, Allison, Bentin, Gore, & McCarthy, 1998). Typically developing individuals, even those with no hearing difficulties, will make use of movements of the lips, jaw and tongue in understanding spoken language — a process that is normally referred to as lip-reading. Lip-reading may be more important in situations where sound quality is reduced for example in a noisy room but is used continuously and often unconsciously, allowing us to disambiguate spoken sounds. Lip movements that are inconsistent with auditory speech are confusing to us and frequently produce hearing errors, such that a sound intermediate to the one presented auditorily and the one presented visually is perceived (McGurk & MacDonald, 1976).
The superior temporal sulcus has also been found to be involved in the perception of lip-reading in functional imaging studies (Calvert, Bullmore, Brammer, Campbell, & et al, 1997). STS is known to be activated by watching stilled images of speaking faces (Calvert & Campbell, 2002; Sams et al., 1991) although the lateralsation of STS activation to speech and non-speech gestures can differ (Campbell et al., 2001).

2.7.1.2 Eye gaze

Perceiving direction of gaze is important to humans as a social species. It provides us with important social information, such as the location or object another is interested in. It can also be used to express intimacy and social control (Kleinke, 1986; Kleinke & Pohlen, 1971). A number of neural regions are implicated in gaze processing. Perrett and his colleagues (Perrett, Hietanen, Oram, & Benson, 1992; Perrett, Rolls, & Caan, 1982) have identified cells within primate STS that are responsive to whether head and eyes are facing or averted from the viewer. These cells are thought to be important in signalling the direction of another individual's attention.

In a positron emission tomography study (PET) of human volunteers, parieto-temporal regions including the STS were activated during perception of gaze (Wicker, Michel, Henaff, & Decety, 1998). The STS showed significantly more activation when participants were monitoring eye gaze (either mutual or averted gaze) than for a condition in which the actor looked down such that
the eyes appeared closed. Similar results have been found using MRI technology (Puce et al., 1998). Here participants viewed a face in which the eyes were averted to the left or to the right. Eye movement was found to activate several focal regions of visual cortex including bilateral STS. More recently, direct gaze has been found to activate STS to a greater degree than averted gaze (Calder et al., 2002). Lesions to the STS region in monkeys have been found to impair judgements of eye gaze direction (Campbell, Heywood, Cowey, Regard, & Landis, 1990; Heywood & Cowey, 1992).

If the ways in which gaze is used in social interactions are considered, there are essentially two separate functions that it performs, the meaning of which is influenced by other contextual factors. We use gaze to decide where a person is looking or directing his or her attention in the external world and we also use gaze to decide if someone is looking at us. In the first instance we might want to follow their gaze in order to ascertain what is of interest to the other person, and in the second situation we would need to assess why the person was looking at us in order to know how to respond to them. It would seem that these two functions of gaze, although much overlapping and used together in everyday situations, would seem to rely on at least partially separate neural substrates both of which have anatomical connections with the STS (Seltzer & Pandya, 1994; Stefanacci & Amaral, 2000).
2.7.2 Intra-parietal sulcus

Gaze directed away from the viewer has been found to activate regions of the brain that deal with spatial attention. Laterally averted gaze produces increased activity in the intra-parietal sulcus (George, Driver, & Dolan, 2001). Haxby and colleagues (Haxby, Hoffman, & Gobbini, 2000), and Wicker et al (Wicker et al., 1998) also report activation of this parietal region when viewers discriminate line of sight from a face image, perceiving where an actor is looking. This region is involved in spatial attention and given that humans shift their attention reflexively to the direction of gaze of another (Driver et al., 1999) it is easy to conceive how this area is functionally important to our reaction to seen gaze.

2.7.3 Orbito-frontal cortex

Activation in response to averted gaze has also been reported to occur within the orbito-frontal cortex (Calder et al., 2002). This region has also been associated with theory of mind performance. The authors propose that the reason why averted gaze may differentially activate this region is that more computation is involved to work out the goals and intentions of a person with averted gaze relative to a person with direct gaze.
2.7.4 Amygdala

Several independent neuroimaging studies report distinct patterns of cortical activation depending on whether eye gaze is directed at the viewer or averted. A gaze monitoring study has reported that the right amygdala is specifically engaged when viewers watch a face making direct eye contact with them (Kawashima et al., 1999). Exploring passive face processing, it has been reported that engaged gaze activates the amygdala bilaterally (George et al., 2001). This activity was also found to enhance activity in the fusiform regions, again exemplifying the cross talk in the complex system. Direct gaze is a socially salient cue to which we must respond rapidly as it can signal both threat and affiliative approach and the amygdala would seem to be a key structure in signalling this.

In one patient with amygdala damage (DR), ability to judge direct gaze has been assessed and was found to be suboptimal (Young et al., 1995). Furthermore, individuals with autism, where anomalous amygdala function has been proposed are impaired both at laboratory tests of eye gaze (Howard et al., 2000) and at making appropriate eye contact and joint attention behaviours in everyday functioning (Charman et al., 1997).

2.8 A DISTRIBUTED FACE PROCESSING NETWORK

The middle parts of the fusiform gyri (the ‘face fusiform’ area) appear to be the critical ‘gateway’ to the face-processing circuitry - but thereafter many cortical
sites are recruited, depending on task, stimulus properties and individual differences. We should not expect less. Faces are probably the most visually complex, intrinsically meaningful visual stimuli with which we interact. They form part of a cognitive, an affective, and a social nexus within which we function. At least two interconnected right-dominant systems suggest themselves in face processing - a medial system (hippocampus, orbito-frontal cortex, amygdala) related to learning, social and affective value and salience of faces, and a lateral system (fusiform gyrus, superior temporal sulcus and middle lateral temporal gyri) that may be implicated in long-term face-knowledge and the perception and production of a range of face acts. Different face processing tasks make differentially weighted demands on the same systems.

2.9 PREDICTIONS ABOUT FACE PROCESSING IN TURNER SYNDROME

In Chapter One, evidence for face processing deficits in TS was reviewed as a possible explanation for the social difficulties experienced by women with the syndrome. In most studies that had assessed this ability, face matching was found to be sub-optimal in both children and adults with the syndrome. In the current chapter, various additional aspects of face processing have been considered, including face recognition memory, famous face recognition and the recognition of facial expressions of emotion. The type of processing thought to be important for optimal face processing was also considered, with
an exploration of three partially distinct types of configural processing. None of
these other types of face processing have been studied in Turner syndrome
although all would seem to play an important role in normal social interaction.

If face-processing difficulties are related to social functioning difficulties in
Turner syndrome, it is important to understand the nature of these difficulties
more fully. In considering the exploration, in Chapter One, of the ways in
which gene/behaviour relationships can be studied, could face processing
difficulties be an endophenotypic marker for the anomalous social function
experienced by women with Turner syndrome?

2.9.1 HYPOTHESES

1 TS women will have impaired face processing skills in the domains of...
   a. face matching
   b. face recognition memory
   c. familiar face recognition
   d. all aspects of facial emotion recognition
   e. configural face processing

2 Face processing abilities will correlate with visuo-spatial abilities in
   women with TS

3 Face processing abilities will correlate with social adjustment abilities in
   women with TS

4 Face processing abilities will correlate with age at which oestrogen
   supplementation commences for women with TS
CHAPTER SUMMARY

This chapter began by considering why there is such great interest in what to all intents and purposes would seem like a non-specific skill – our immense ability to recognise a limitless amount of faces. The fact that this ability could be selectively impaired following brain damage led to experimental techniques being applied which in turn led to notions of ‘special’ mechanisms that are important for face recognition. The right hemisphere typically would seem to play a greater role in face processing then left hemisphere. But moving away from the modularity research that dominated the 1980s and 90's this chapter considered the many different cortical structures that contribute to a wide number of different aspects of face recognition.

Firstly, it considered evidence for the importance of configural visual processing in face recognition and the ways in which this type of processing has been measured. The proportion of this chapter dedicated to considering the role of the fusiform gyrus in face recognition goes just a small way towards reflecting the amount of journal coverage that this tiny brain region has been given over the past decade or so. This region of the inferior temporal lobe really does seem to have a unique ability to analyse visual stimuli to the level that is necessary to discriminate between the vast number of faces that we encounter. However, while the adequate function of this cortical structure may be ‘necessary’ for normal face recognition, it is by no means ‘sufficient’ and the remainder of this chapter focused upon the neural systems connected to the fusiform gyri that are also important to face processing.
A number of regions outside the fusiform gyri are recruited by different face processing tasks. Face perception may additionally involve parietal lobe regions. Face recognition memory would appear to make use of medial brain structures involved in memory and affective learning more generally including the hippocampus, amygdala and orbito-frontal cortex. The processing of facial expressions of emotion is also found to call on these sites and additionally places demands on the insula and basal ganglia. Other information from the face that is of social relevance includes eye gaze and lip movements and for these tasks the superior temporal sulcus would appear to have a particularly important role.

In considering the different elements of the face processing networks, I have highlighted the involvement of a number of these regions in other aspects of social functioning. It has been demonstrated that damage to various components of these neural circuits often results in difficulties with face processing and frequently in more wide-reaching difficulties in social functioning. The co-morbidity of these impairments demonstrates the interdependency of the functional mechanisms involved in face perception and social behaviour.

The neural circuits involved in the processing of faces are all highly interconnected and undoubtedly rely on much feedback and cross talk, particularly in the development and setting up of these specialised systems.
Finally, it was considered how our knowledge of face processing could inform our investigations of face processing in Turner syndrome. Many different aspects of face processing, in addition to face matching will be assessed in women with TS with the hypothesis being that impairments will be seen in all these domains. In Chapter Three, the mechanisms and neural regions involved in face processing will be used to inform a study of face processing in Turner syndrome.
3  CHAPTER THREE - METHODOLOGY

3.1  GROUP SELECTION CONSIDERATIONS AND CHARACTERISTICS

Standardised IQ assessments of girls and women with Turner syndrome frequently reveal depressed Performance IQ's where Verbal IQ is within the normal range, reflecting their difficulties in visuo-spatial functioning. Since women with TS have an unusual profile of cognitive abilities, it would be difficult to match groups in terms of both Verbal and Performance IQ without having a control group that was not representative of the general population.

In the experiments reported in this thesis, participants were matched on a group basis in terms of Verbal IQ, as assessed by the Weschler Adult Intelligence Scale (WAIS). Performance IQ was then entered as a covariate in the group comparisons, using parametric statistics.

3.2  KARYOTYPE SPECIFICITY

Karyotypic differences within the TS population have not been satisfactorily dealt with in many previous studies with women with TS. As the studies reviewed in Chapter One demonstrate, different karyotypes, and ultimately the
presence or absence of different genes on the X-chromosome can have an impact on the phenotypic expression of Turner syndrome. In order to make conclusions about the importance of any genetic mechanisms to the resultant phenotype it is necessary to consider different karyotypes individually. The first study includes only those women who have been identified to have monosomic (45,X) Turner syndrome. None of the cases were found to have any evidence of mosaicism in the cell lines analysed.

As was also highlighted in Chapter One, the parental origin of the single remaining X-chromosome in monosomic TS has been reported to affect phenotypic expression, specifically concerning socio-cognitive abilities. Study One focused on individuals who have inherited their single X from their mother (45,X<sup>+</sup>). Since girls with this karyotype have been found to have greater social adjustment difficulties (Skuse et al., 1997), it was hypothesised that face processing difficulties would be most readily detectable in this sub-group.

3.3 SAMPLE RECRUITMENT

Twenty three individuals with Turner syndrome (45,X<sup>+</sup>) were recruited from a National survey of Turner syndrome, through the Child Growth Foundation and through a specialist clinic at the Middlesex Hospital. Formal written consent was obtained. Participants were invited to take part in this further phase of the research. An outline of the type of tasks to be administered was given, along with an estimate of the duration of the test session. Participants
then returned a slip, in a pre-paid envelope, indicating whether or not they were interested in taking part and furthermore the times of day and days of the week that would most convenient for them to be tested. Positive responses were followed up by a telephone call to arrange a test session and answer any questions that the subject may have about the study. For a small number of participants, testing arrangements were made through the participants' parents.

Control participants were recruited by means of posters that were placed within Great Ormond Street Hospital, The Institute of Child Health and University College London. The posters advertised the study as involving taking part in some ‘fun psychological tests’ and informed participants that they would be paid £15 for their participation. Participants were invited to take part if they were female, between 18 and 36 years of age and had been resident in the UK for more than three years.

3.3.1 Response rates

Thirty 45,X<sup>m</sup> women were approached to participate in the study. Twenty-five women consented to take part in the study, three declined and a further two failed to respond. Two of the participants were later excluded from analyses for reasons detailed below.

Forty-five women responded to the advertisement for control participants. A screening interview on the telephone enabled the exclusion of individuals who
had known psychiatric or neurological disease (past or present), and of those who had not been resident in the UK for at least the past three years. Of the remainder of volunteers, participants were chosen for participation according to availability.

3.4 GROUP CHARACTERISTICS

3.4.1 Age

The women in both the TS and control groups were young adults, all between the ages of 18 – 36 years and groups were matched for age (t (44) = .27, p=.79). Age characteristics are shown in table 3.1.

Table 3.1: Age in years of study participants.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XX (females)</td>
<td>23</td>
<td>25.30</td>
<td>4.53</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>45,X0 (Turner syndrome)</td>
<td>23</td>
<td>24.91</td>
<td>5.28</td>
<td>18</td>
<td>36</td>
</tr>
</tbody>
</table>

3.4.2 Ethnicity

Participants were asked to indicate their ethnicity as being one of the following White, Indian/Pakistani, Asian, African/Caribbean or other. All women in the TS group were of Caucasian ethnicity as were the majority of control
participants, except one who was African/Caribbean and another who was Indian/Pakistani.

3.4.3 Educational level

Participants indicated the highest educational level that they had attained out of the following options: No exam qualifications, GCSE/O-Level, Secretarial or technical, A-Level, Professional qualification without University degree (e.g. SRN, teaching diploma, HNC, TEC), University degree (or equivalent).

Proportions for each educational level can be seen in table 3.2. The control females on average attained a higher level of educational qualification, with a mean rank that was significantly higher than that for the TS women according to Mann-Whitney test statistics (46,XX females =27.76, 45,Xm TS = 19.24, U=166.5, p=.03).
Table 3.2: Maximum level of educational qualification achieved

<table>
<thead>
<tr>
<th>Educational qualifications</th>
<th>46,XX females</th>
<th>45,Xm (Turner syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GCSE/O-Level</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>Secretarial/Technical</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A-Level</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>Professional qualification</td>
<td>5</td>
<td>21.7</td>
</tr>
<tr>
<td>University degree</td>
<td>12</td>
<td>52.2</td>
</tr>
</tbody>
</table>

3.4.4 Social class

Participants occupations were classified according to the Standard Occupational Classification 2000 (Office of National Statistics, 2000). Thirty percent of the TS women were in the two highest groups (managers/senior officials, and professional occupations), 26% were in the following two groups (associate professional and technical occupations, and administrative and technical occupations), and 44% in the lower groups. For the control group, the respective percentages were 21%, 75% and 4%. Proportions for each level can be seen in table 3.3. The mean rank of the women in both groups was highly similar according to Mann-Whitney test statistics (46,XX females =22.13, 45,Xm TS = 24.87, U=233.00, p=.48).
Table 3.3: Social group classification

<table>
<thead>
<tr>
<th>Occupation</th>
<th>46,XX (females)</th>
<th>45,Xm (Turner syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Unemployed (not classified)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1. Managers/Senior officials</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Professional occupations</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>3. Associate professional &amp; technical</td>
<td>10</td>
<td>43.5</td>
</tr>
<tr>
<td>4. Administrative &amp; secretarial</td>
<td>8</td>
<td>34.8</td>
</tr>
<tr>
<td>5. Skilled trades</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6. Personal Service</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>7. Sales/Customer service</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8. Elementary</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
3.4.5 IQ

Participants were excluded if their Verbal IQ was below 70. This led to the exclusion of one individual with TS but none of the control volunteers.

Controls were matched to the TS group for Verbal IQ. The IQ distributions of the groups can be seen in table 3.4. The women with 45,X(m) (TS) had a significantly lower mean Performance IQ as is typically reported. However, groups were matched for Verbal IQ.

Table 3.4: Mean WAIS IQ scores

<table>
<thead>
<tr>
<th></th>
<th>46,XX (females)</th>
<th>45,X(m) (TS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>sd</td>
<td>mean</td>
<td>sd</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>99.57</td>
<td>11.64</td>
<td>98.30</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>105.70</td>
<td>11.44</td>
<td>94.52</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>102.30</td>
<td>11.58</td>
<td>96.30</td>
</tr>
</tbody>
</table>
3.5 MEASURES OF GENERAL FUNCTIONING

3.5.1 Performance IQ (PIQ)

The Picture Completion, Block Design and Digit Symbol sub-tests of the WAIS-R (Wechsler, 1981) were administered and scores pro-rated to provide an estimate of Performance IQ (Ward & Ryan, 1996). A short version was used due to time constraints and the sub-tests chosen because they correlate strongly with full Performance IQ.

3.5.2 Verbal IQ (VIQ)

To give an estimate of Verbal IQ, four sub-tests of the WAIS were used: Information, Digit Span (which is also related to verbal memory), Arithmetic and Similarities. These sub-test scores were then pro-rated. A short version was used due to time constraints and the sub-tests chosen because they correlate strongly with full Verbal IQ (Ward et al., 1996).

3.5.3 Verbal memory

The word subtest of the Recognition Memory Test (RMT, (Warrington, 1984)) was administered. In this test, 50 printed words were shown individually to participants, to rate as pleasant or unpleasant. Before being shown the words, participants were told that it was a 'test of memory for words'.
Immediately after presentation, the words were presented one at a time, each one accompanied by a new foil. A forced choice procedure required the participant to choose the one that had been presented previously. The dependent variable was choice accuracy (/50).

3.6 TESTS OF FACE RECOGNITION

3.6.1 The Benton Test of Facial Recognition - short form (Benton, Hamsher, Varney, & Speen, 1983)

This test provides a standardised procedure for assessing discrimination of face images presented as halftone images. It is a graded test. The first part requires matches of identical face images, where one image is presented on one sheet and the recognition set on the sheet below. In the harder parts of the test, a front view image of a face has to be matched for identity to three faces from a set seen from different viewing angles (3/4 or full face), and under different lighting conditions (from above, left or right). Raw scores were adjusted to give estimated long form scores (Benton et al., 1983).

3.6.2 Warrington face recognition task

This was a forced choice recognition test for halftone images of male faces that used an identical presentation procedure as the word recognition test.
above (Warrington, 1984). This recognition task was administered directly after the word sub-test of the Warrington recognition memory test.

3.6.3 Familiar face recognition

This test was computer administered. First, a set of photographs of 50 famous people was chosen, all of which were named accurately on presentation by at least 17 out of 20 women (age range 18-36 years) who did not take part in the experiment proper. The face-images were downloaded from copyright-free sites on the worldwide web and digitally manipulated to generate halftone images of similar size and general appearance. The identities of the famous individuals in each group (cropped and uncropped) are shown in table 3.5 with identification rates (out of twenty) for the initial standardisation study.

In the experiment itself, participants were asked to name the individual within 20 seconds of display onset. There were two presentation conditions, one for each half-set of 25 faces. In the cropped condition, the facial features were close-cropped using a rectangular frame to remove facial outline and hairstyle, but leaving eyes, nose and mouth fully visible. Under these conditions, only facial features, and their configuration (i.e. relative distances between features and overall disposition with respect to each other) could be used to identify the face. In the other condition, the whole head condition, faces were presented whole, including hairstyle and general contour. Examples of cropped and uncropped images are shown in figure 3.1.
Table 3.5: Identification rates of the famous people from the initial standardisation experiment.

<table>
<thead>
<tr>
<th>Name</th>
<th>Correct id /20</th>
<th>Name</th>
<th>Correct id /20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold Schwarzenegar</td>
<td>20</td>
<td>Michael Jackson</td>
<td>20</td>
</tr>
<tr>
<td>Charlie Chaplin</td>
<td>20</td>
<td>Adolph Hitler</td>
<td>20</td>
</tr>
<tr>
<td>Princess Diana</td>
<td>20</td>
<td>Sarah Ferguson</td>
<td>20</td>
</tr>
<tr>
<td>Elvis</td>
<td>20</td>
<td>Marilyn Monroe</td>
<td>20</td>
</tr>
<tr>
<td>Queen Mother</td>
<td>20</td>
<td>Queen Elizabeth II</td>
<td>20</td>
</tr>
<tr>
<td>Richard Branson</td>
<td>20</td>
<td>Prince Charles</td>
<td>20</td>
</tr>
<tr>
<td>Tony Blair</td>
<td>20</td>
<td>Margaret Thatcher</td>
<td>20</td>
</tr>
<tr>
<td>Cherie Booth/Blair</td>
<td>20</td>
<td>John Major</td>
<td>19</td>
</tr>
<tr>
<td>William Hague</td>
<td>19</td>
<td>Bill Clinton</td>
<td>19</td>
</tr>
<tr>
<td>Hugh Grant</td>
<td>19</td>
<td>George Clooney</td>
<td>19</td>
</tr>
<tr>
<td>Leonardo DiCaprio</td>
<td>19</td>
<td>Brad Pitt</td>
<td>19</td>
</tr>
<tr>
<td>Madonna</td>
<td>19</td>
<td>Julia Roberts</td>
<td>19</td>
</tr>
<tr>
<td>Tom Cruise</td>
<td>19</td>
<td>Oprah Whinfrey</td>
<td>19</td>
</tr>
<tr>
<td>Richard Gere</td>
<td>19</td>
<td>Sean Connery</td>
<td>19</td>
</tr>
<tr>
<td>Joan Collins</td>
<td>18</td>
<td>Chris Evans</td>
<td>19</td>
</tr>
<tr>
<td>Andre Agassi</td>
<td>18</td>
<td>Pierce Brosnan</td>
<td>18</td>
</tr>
<tr>
<td>Einstein</td>
<td>18</td>
<td>Rowan Atkinson</td>
<td>18</td>
</tr>
<tr>
<td>Elton John</td>
<td>18</td>
<td>Mick Jagger</td>
<td>18</td>
</tr>
<tr>
<td>Harrison Ford</td>
<td>18</td>
<td>Michael Caine</td>
<td>18</td>
</tr>
<tr>
<td>Terry Wogan</td>
<td>18</td>
<td>Noel Edmonds</td>
<td>18</td>
</tr>
<tr>
<td>Carol Vorderman</td>
<td>18</td>
<td>Jonathan Ross</td>
<td>18</td>
</tr>
<tr>
<td>Catherine Zeta-Jones</td>
<td>17</td>
<td>Elizabeth Hurley</td>
<td>17</td>
</tr>
<tr>
<td>Paddy Ashdown</td>
<td>17</td>
<td>Michael Douglas</td>
<td>17</td>
</tr>
<tr>
<td>Michelle Pfieffer</td>
<td>17</td>
<td>Cindy Crawford</td>
<td>17</td>
</tr>
<tr>
<td>Prince William</td>
<td>17</td>
<td>Prince Phillip</td>
<td>17</td>
</tr>
</tbody>
</table>
Figure 3.1: Examples of uncropped (George Clooney) and cropped (Paddy Ashdown) faces used in the famous face recognition test.

Scoring took account of distinguishing information given by the respondent when they were unable to name the face. Responses were scored correct when distinctive semantic information (i.e. a specific role played by a TV actor) was given. These scores were further corrected for knowledge of the individual. Following presentation of the faces, participants were given the names of the individuals seen and asked what they knew about them. Recognition scores were calculated based on only those individuals for whom they demonstrated adequate individual knowledge (Corrected score).
3.6.4 Incidental face recognition

In this computer-based test, unfamiliar face images that had been seen earlier in the test session (part/whole and face inversion – for details, see next section) were presented for recognition. The target set comprised 22 grey-scale face images and 22 distracter faces chosen to be similar in general appearance to the target faces. The new and old faces appeared one at a time in a randomised order in the centre of the computer screen for old/new decision. The dependent variable was accuracy of recognition, measured using a sensitivity measure, $Pr'$, which takes account of both hits and correct rejections (Snodgrass & Corwin, 1988).

3.7 TESTS OF CONFIGURAL FACE PROCESSING

These tests were designed to probe face-processing style, without implicating memory for known faces directly. They assess three partially distinct areas of configural processing.
3.7.1 Mooney Face recognition (Sensitivity to first-order relations)

Mooney faces are hand-painted images of human faces rendered in photographic half tone (Mooney, 1957). It has been suggested (de Haan & Campbell, 1991) that the perception of these patterns as faces may require the ability to detect (facial) shape from shading. It is also thought to require gestalt-closure abilities (holistic processing). According to Maurer’s definitions of configural processing discussed in Chapter Two (Maurer, Le Grand, & Mondloch, 2002), detecting the presence of a face in these stimuli requires sensitivity to first-order relations. Foils were also constructed from parts of Mooney images in which no face was present (see figure 3.2).

Figure 3.2: A Mooney face (on the left) and a foil (on the right).

Images were presented on a computer screen. In the practice series, 3 faces and one foil were seen. In the main experiment, there were 25 faces and 5 foils – these appeared in a randomised order in each block. There were two blocks giving 60 trials in total. Participants pressed a key to indicate whether a face was present. If they indicated the presence of a face, they then pressed a
key to indicate ‘yes’ or ‘no’ to the following questions: ‘Is it male?’ & ‘Is it young (under 50)?’ The dependent variable was the Pr’ prime score based on ‘correct’ and ‘incorrect’ responses.

3.7.2 Whole and part-face matching. (Holistic processing)

According to Maurer (Maurer et al., 2002), the reason that we are better at matching whole faces than individual parts of faces is that we process faces in a holistic way that ‘glues together’ the features. If individuals’ process faces in this manner then they should demonstrate an advantage for matching whole faces compared to just the eyes or just the mouths. In addition, different face parts are of different emotional significance with the upper face (eyes) generally conveying more information about feelings, thought and intentions (Baron-Cohen, Wheelwright, & Joliffe, 1997). Perhaps then, accuracy for matching upper and lower face stimuli may differ according to the social and emotional competencies of the individual. Indeed, children with autism have been found to be selectively impaired at using the eye region to identify faces (Langdell, 1978).

This task examined accuracy at matching whole full-face images compared with matching just the upper face or just the lower face. A similar procedure was used to that outlined above (X-AB recognition paradigm, using similar presentation schedules). Twelve matched pairs of faces were seen under three presentation conditions (96 trials). A pair of items presented for
recognition followed the target image, which was presented first. The stimuli could be whole face, upper-face or lower-face (represented in figure 3.3). Condition (whole/upper/lower) was unpredictable from trial to trial. Participants again chose the left or right image in the recognition array by pressing the left or right marked key of the computer keyboard. The dependent variables were the percentage of correct responses for each of the three conditions.

Figure 3.3: Examples of a whole, lower and upper face stimulus set.

### 3.7.3 Upright and inverted face matching (Sensitivity to second-order relations)

What Daphne Maurer (Maurer et al., 2002) describes as sensitivity to second-order relations can be assessed using a facial inversion task. Sensitivity to second-order relations involves representing the distances between face features. This ability is thought to underlie skilled adult face recognition but is disrupted when faces are inverted and the distance relations between the parts altered. If individuals are processing faces in a configural manner,
sensitive to the second-order relations, they should be more accurate at matching faces when presented in an upright orientation rather than when they are inverted.

In this task, a face image appeared on the computer screen for matching to an immediately aftercoming target. The orientation of the image varied unpredictably. It could be upright in both presentation and recognition phase – or it could be upside-down in both phases.

Each trial proceeded as follows: Following practice (24 trials – of which 12 were upright and 12 inverted, where no feedback was given) a fixation cross appeared for 250 msecs followed by a face image for 250 msecs. This was followed by a laterally arranged pair of face images, one of which was the previously seen face. Participants were instructed to press the key on the side at which the target appeared. The process is represented diagrammatically in figure 3.4. The only feedback given during the experiment was non-specific praise. The 32 grey-scale images (16 pairs) were matched in terms of sex, age, luminance, contrast and general appearance. Each pair appeared 4 times in the upright condition and 4 times in the inverted condition, giving 128 trials. Image size was approximately 8cm by 6cm on the computer monitor used in testing. The dependent variables were the percentage of correct choices for the upright and the inverted face conditions, for each participant.
Both faces presented simultaneously until response is made.

Figure 3.4: Example of a trial from inversion experiment.
3.8 FACIAL EXPRESSION CATEGORISATION

3.8.1 The Ekman-Friesen Test of Affect Recognition

Participants were shown 60 photographic half-tone face images derived from the Ekman set (Ekman & Friesen, 1976). In these, 10 different individuals posed the six basic emotions: happiness, surprise, fear, sadness, disgust and anger, using the FACS posing method (Ekman et al., 1976) (examples are shown in figure 3.5). These were shown as single, card-mounted (15cm x 10cm) images to participants. The six emotion labels were also provided. Participants selected one of six emotion labels to match to the face. The dependent variable was the number of correct responses (/10) for each expression.
Figure 3.5: Examples of the six 'basic' facial expressions of emotion used in the Ekman-Friesen task.
3.9 OVERALL PROCEDURE

All participants were tested individually in a quiet room either within their own home or at the Institute of Child Health. Tests were administered in a single session lasting approximately 2 ½ hours, with appropriate breaks given as necessary to minimise fatigue. The order of administration of the tasks was identical for all participants. The session commenced with tests of face processing style: inverted face matching, part-whole face matching and Mooney faces, followed by tests of face recognition: Famous face recognition, Benton face recognition, the emotion recognition task and the Warrington memory task. The WAIS was administered at the end of the test session with the final task being the incidental face memory task. It was not possible for the experimenter to be blind to the group membership of the participants.
4 CHAPTER FOUR – RESULTS – STUDY ONE

4.1 STATISTICAL PROCEDURES

For all variables (separately for each group), the assumption of normality of distributions was tested using one-sample Kolmogorov-Smirnov tests. Normality was found for all tests reported here except for the Benton task for control participants and the Warrington word recognition memory task for both groups. Data for these variables were transformed using appropriate manipulations but it was not possible to achieve normal distributions. Because of this, non-parametric analyses were applied. In the reported analyses, PIQ, which was the single background variable that differed systematically between the groups, was entered as a covariate.

4.2 IQ RESULTS

Groups were matched in terms of Verbal IQ. Group means for full-scale IQ did not differ but, as is typically reported, women with Turner syndrome had significantly lower Performance IQ’s according to Independent Samples T-Test ($t(44) = 2.61, p= 0.01$). Mean results are displayed in table 4.1.
## Table 4.1: IQ results

<table>
<thead>
<tr>
<th></th>
<th>46,XX (females)</th>
<th>45,X(^n) (TS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>mean</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>sd</td>
<td>sd</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>99.57 11.64</td>
<td>98.30 13.63</td>
<td>.74</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>105.70 11.44</td>
<td>94.52 17.08</td>
<td>.01</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>102.30 11.58</td>
<td>96.30 14.75</td>
<td>.13</td>
</tr>
</tbody>
</table>

### 4.3 TESTS OF FACE RECOGNITION

#### 4.3.1 Benton test of face recognition

Figure 4.1 suggests a marked group difference in performance. Test scores (long-form) were entered into analysis (SPSS GLM factorial) in which the dependent variable was test score, the fixed factor was group (control vs. TS), and the covariate was PIQ. The main effect of group was significant (F (2,43) = 11.19, p= 0.002). The distribution of results for the control females on this task was found to be skewed according to one-sample Kolmogorov-Smirnov tests. The distributions could not be normalised using appropriate manipulations, so a non-parametric test was applied. A Mann-Whitney U test also revealed significant group differences in their mean rank for this task (TS rank 15.87, controls rank 31.13, U=599.5, p<.001).
Figure 4.1: Distribution of Benton long-form face recognition scores for women with Turner syndrome and control females.

Although a group difference was detected on this task, the group mean for the women with Turner syndrome was within the normal range and would not be classified as being clinically significant according to test criteria. A score below 39 is classified as a clinically significant score – just 3 of the 23 TS women scored within this range. None of the control participants were clinically impaired on this task.
4.3.2 Warrington test of recognition memory for words and faces

An SPSS ANOVA (GLM multivariate) procedure was used to test the prediction of a group difference in recognition memory. The dependent variables were raw scores for word accuracy and for face accuracy. The fixed factor was group and PIQ was again entered as a covariate. Scores for faces in TS were significantly depressed compared to those for controls (F (2,43) = 12.10, p = .001). This was not the case for word recognition (F (2,43) = 0.04, NS) (see figure 4.2).

![Figure 4.2: Warrington recognition memory task for words and faces. Bars show mean. Error bars show standard error.](image)

The distributions of results for the word recognition aspect of this task were found to be skewed for both groups according to one-sample Kolmogorov-Smirnov tests. The distributions could not be normalised using appropriate
manipulations, so a non-parametric test was applied to the word recognition scores. A Mann-Whitney U test failed to reveal a significant group difference on this task (XX rank = 24.76, X0 rank = 22.24, U = 235.5, p = .50).

The mean score of 36/50 obtained for face recognition by the women with TS is lower than any of the means for the brain lesion groups reported in the original test standardisation (Warrington, 1984) and demonstrates clinically significant impairment.

### 4.3.3 Test of familiar face recognition

Naming accuracy scores were entered into analysis (SPSS repeated measures ANOVA) with group as the between-participants variable and condition (whole vs. cropped faces) as the within-participants variable. There was a significant main effect of both group (F (1,44) = 8.86, p = .005) and condition (F (1,44) = 4.94, p = .03). Post hoc T-tests confirmed that the TS group performed more poorly on both the whole face (t (25.49) = 2.73, p = .01) and cropped face (t (24.95) = 2.90, p = .008) conditions. The TS group performed relatively more poorly than the controls on the cropped than the uncropped faces, an interaction term indicating a statistically significant difference in this difference score (F (1,44) = 4.94, p = .03). While the women with TS recognised fewer of the cropped and uncropped faces than did the control women the deficit was statistically more significant for the cropped than uncropped faces. Data are presented in figure 4.3. This, however, could
be a function of near ceiling levels of recognition in the uncropped face condition.

Figure 4.3: Famous face recognition naming accuracy for cropped and uncropped faces. Bars show mean. Error bars show standard error.

4.3.4 Incidental face recognition test

Recognition prime (Pr') scores (Snodgrass et al., 1988) were calculated and entered into analysis (SPSS GLM factorial) with PIQ as a covariate. Pr' scores take into account both hit rate (HR) and false accuracy rate (FAR) with a score of 1 indicating total accuracy at correctly recognising face stimuli and correctly rejecting non-face stimuli. A Pr' score of 0 would indicate no correct judgements.
\[ Pr' = HR \times FAR \]

where \( HR = (\#\text{hits} + 0.5) / (\#\text{olds} + 1) \) and \( FAR = (\#\text{FAs} + 0.5) / (\#\text{news} + 1) \)

A main effect of group, with no effect of the covariate PIQ, was found with women with TS having depressed scores (F (2,42) = 8.00, p = .007). Data are presented in figure 4.4.

![Figure 4.4: Incidental face recognition Pr' scores for accuracy and false hits. Bars show mean. Error bars show standard error.](image)

### 4.3.5 Face recognition tests summary

As predicted in hypotheses 1a, b and c, all tests of face recognition showed depressed scores in women with TS compared with controls, as can been
seen in table 4.2. Covarying for PIQ did not eliminate these differences, suggesting that visuo-spatial (dis)abilities can not solely account for the main group effects. Furthermore, PIQ (when entered as a covariate) failed to account for a significant proportion of the variance in any of the face recognition scores. With regard to Hypothesis One, individuals with TS are impaired at face matching, face recognition memory and famous face recognition. Applying Bonferroni corrections for multiple comparisons, all differences remain significant except for the famous faces task, where cropped, uncropped and total recognition scores fail to reach significance.
Table 4.2: Group comparisons for tests of face recognition accuracy, showing ANCOVA results.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Mean</th>
<th>SD</th>
<th>ANCOVA (df=1,42)</th>
<th>F</th>
<th>P</th>
<th>Effect size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton face recognition</td>
<td>46.54</td>
<td>3.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrington recognition memory (faces)</td>
<td>42.46</td>
<td>4.54</td>
<td></td>
<td>10.28</td>
<td>.003^</td>
<td>1.02</td>
</tr>
<tr>
<td>Warrington recognition memory (words)</td>
<td>48.36</td>
<td>2.39</td>
<td></td>
<td>12.72</td>
<td>.001^</td>
<td>1.15</td>
</tr>
<tr>
<td>Famous faces (cropped)</td>
<td>94.54</td>
<td>3.77</td>
<td></td>
<td>.084</td>
<td>.774</td>
<td>-0.09</td>
</tr>
<tr>
<td>Famous faces (uncropped)</td>
<td>97.80</td>
<td>2.15</td>
<td></td>
<td>5.924</td>
<td>.019</td>
<td>0.92</td>
</tr>
<tr>
<td>Famous faces (total)</td>
<td>96.17</td>
<td>2.56</td>
<td></td>
<td>4.08</td>
<td>.050</td>
<td>0.48</td>
</tr>
<tr>
<td>Incidental face recognition (Pr' score)</td>
<td>.82</td>
<td>.10</td>
<td></td>
<td>8.00</td>
<td>.007^</td>
<td>0.92</td>
</tr>
</tbody>
</table>

* Estimated marginal means produced using SPSS General Linear Model.

^ These effects remain significant after applying Bonferroni corrections for multiple comparisons

\[
\text{Effect size}^* = \frac{\text{mean } XX - \text{mean } X0}{\sqrt{\frac{\sigma XX + \sigma X0}{2}}}
\]
4.4 TESTS OF CONFIGURAL FACE PROCESSING

4.4.1 Mooney faces test (Sensitivity to first-order relations)

Univariate analysis (SPSS GLM factorial) tested the effect of group (controls vs. TS) on adjusted $Pr'$ scores (Snodgrass et al., 1988) derived from performance on this task, with PIQ as a covariate (see figure 4.5).

$$Pr' = \frac{HR - FAR}{HR + FAR}$$

Where $HR = \frac{(#\text{hits} + 0.5)}{(#\text{olds} + 1)}$ and $FAR = \frac{(#\text{FAs} + 0.5)}{(#\text{news} + 1)}$

Figure 4.5: Recognition Prime scores for Mooney face recognition accuracy and false hits. Bars show mean. Error bars show standard error.
There were no significant group differences, and PIQ did not account for any significant variance in the scores. As a further test of their ability to identify such patterns as faces, the ascription of gender and age given to the patterns judged to be faces were recorded. Gender classification of the face did not differ with group (F (2,42) = 0.90, N/S). A similar pattern was obtained for age judgements (F (2,42) = 1.65, N/S).

4.4.2 Whole/part face matching (Holistic processing)

Accuracy measures for whole face matching, upper face matching and lower face matching were entered into ANOVA (SPSS GLM repeated measures) as 3 levels of a single dependent variable (part-of-face) with PIQ as a covariate. Performance IQ failed to account for a significant proportion of the variance. The group factor was presence or absence of TS. There was a main effect of part-of-face: whole faces were more accurately discriminated (F (2,42) = 3.76, p = .03) as shown in figure 4.6. There was also a main effect of group. TS women matched less accurately (F (2,43) = 4.51, p = .04). However, this main effect of group failed to interact with condition (F (2,43) = 0.03, p=n/s). Whole faces were more accurately matched than face parts in controls and in TS.
Figure 4.6: Whole, upper and lower face matching accuracy. Bars show mean. Error bars show standard error.

4.4.3 Facial inversion test (Sensitivity to second-order relations)

Accuracy in matching upright and inverted faces is shown in figure 4.7. The data were examined by SPSS GLM procedures (repeated-measures analysis of variance). The dependent variable was orientation (upright or inverted), the group factor was presence or absence of TS. PIQ was again entered as a covariate. There was a main effect of orientation, in favour of upright faces ($F (1,43) = 4.19, p<.05$). There was also a significant effect of group ($F (1,43) = 7.27, p = .01$) with individuals with Turner syndrome being less accurate. There was no interaction between group and condition. Upright faces were matched more accurately by control women and women with TS.
4.4.4 Configural face processing summary

On all the tasks designed to assess sensitivity to configural aspects of faces, women with TS showed typical interaction effects. They were able to process faces in a configural manner. It did not appear that they were over-reliant on featural aspects of faces. Hypothesis 1e was not supported; no impairment in configural face processing skills was detected in women with TS.

Figure 4.7: Recognition accuracy for upright and inverted faces. Bars show mean. Error bars show standard error.
4.5 FACIAL EXPRESSION RECOGNITION

Figure 4.8 shows the pattern of the distribution of raw accuracy scores for each facial expression category. Accuracy (raw scores) for each facial expression category were entered into a MANOVA (SPSS GLM multivariate) with PIQ entered as a covariate. Bonferroni corrections were applied to the data to control for multiple comparisons, revealing that the facial expressions of fear ($F(2,43)=17.07, p<.001$, effect size $=1.5^1$) and, to a less marked extent, anger ($F(2,43)=7.43, p=.05$, effect size $=1.1$) were significantly less accurately recognised in TS than controls. By contrast, other expressions showed no group-specific decrement. The total score for emotion recognition was also significantly lower in the women with Turner syndrome (XX mean 52.30 (sd 2.8), XO mean 45.66 (sd 6.6)), $F(2,43)=12.15, p=.007$).

Figure 4.8: Emotion recognition accuracy for the six 'basic' emotions. Bars show mean. Error bars show standard error.

$^1$ Effect size $= \frac{\text{mean XX} - \text{mean XO}}{\text{sd XX} + \text{sd XO}} / 2$
The decrement for fear recognition was particularly severe. Paired sample T-tests for the TS group showed it was significantly less well recognised than any of the other emotions, including anger (t=2.63, p=.01). The hypothesis (1d) that women with TS would be impaired at all aspects of facial emotion recognition was not supported. Rather, difficulties appeared to relate to the expressions of fear and anger alone.

4.6 CORRELATIONAL ANALYSES

4.6.1 Face processing and IQ

Correlations were also performed for all the face recognition variables and Verbal and Performance IQ scores, separately for both groups. For both groups, the two IQ measures were significantly correlated with each other. The correlation coefficients were similar, which is remarkable given the discrepancy between PIQ and VIQ in the TS females (Pearson correlation - controls: .576, p=.004; TS: .571, p=.004). Performance IQ correlated with no other measures in either group. Verbal IQ correlated only with Warrington word recognition task performance in the TS group (Pearson correlation .422, p=.045), but with none of the face recognition variables. Full-scale IQ was correlated with surprise for both the TS (Pearson correlation .425, p=.043) and control females (Pearson correlation .440, p=.036). However, the correlations between Verbal IQ and Warrington word recognition and surprise...
2 CHAPTER TWO – FACE PROCESSING SYSTEMS

2.1 OVERVIEW

This chapter considers the cognitive neuroscience of face processing, looking at what is known about the way in which faces are processed in the typically developing brain. It takes as its starting point a review published in 2001 (Elgar et al., 2001), but extends beyond that to address a number of issues that continue to attract researchers' efforts. Much of the current interest in face processing brain systems arose from the discovery that certain aspects of face processing can be selectively impaired consequent to brain damage.

Face recognition is often considered to be a modular function. Modularity can be considered as the brain being composed of discrete domain-specific modules that are innately pre-programmed and insensitive to environmental influence (Fodor, 1983). I present evidence here to suggest that while faces are 'special' in a number of respects, the recognition of them and interpretation of them also makes use of general-purpose cortical systems that are involved in high level vision, memory, learning and emotion more generally. These neural systems can be conceived as distinct but overlapping cortical streams: a medial stream (for learning and social salience of faces)
and a lateral stream (for distributed representations of visual properties and facial identities). The areas discussed are represented diagrammatically in figure 2.1.

This conceptualisation differs from other models (Bruce & Young, 1986). Although it distinguishes between different elements of face processing it considers them to be inter-related. It seeks to present two partially distinct but highly interconnected cortical streams that may be differentially recruited to best serve the different computations involved in many different types of processing necessary in dealing with faces.
Figure 2.1: Lateral (A) and medial (B) diagrammatic views of the human brain to show the lateral and medial flows of face-identity information. Largely the temporal order of information processing is shown, although there is a degree of information transfer in both directions.
2.2 HISTORICAL PERSPECTIVE

Modern neuropsychological interest in face perception and recognition arose from the observation that brain damage could produce selective impairments in this skill while leaving other aspects of visual recognition intact (Bodamer, 1947). The selective inability to recognise faces known to the patient premorbidly is referred to as prosopagnosia, meaning ‘face-blindness’. The selectivity of this deficit is strengthened by the opposing observation that individuals can have impairments in object or word recognition but have intact face recognition abilities (Farah, 1991). This double dissociation, alongside the astonishing human ability to recognise and discriminate between an infinite number of faces, led to theorising about special processing mechanisms that operated for faces (Bruce et al., 1986). Throughout the last decades of the twentieth century issues of modularity dominated research into face processing. The paramount question was ‘Is face processing special, compared with the processing of other visual objects?’

Recent developments in neuroimaging have shifted the focus towards consideration of the cortical and sub-cortical substrates of face processing. This has recontextualised research towards understanding the networks of interconnected neural systems that together support the perception, memory and interpretation of faces.

This review will take a look at some of the neural regions believed to be involved in face processing, considering both the role of these regions in
typical face recognition and incidences where the functional integrity of these systems have been compromised. The focus will also be on whether these neural regions implicated in face processing are known to play a role in social cognitive functioning more generally. Firstly, however, it will consider the special type of processing that is implicated in face recognition.

2.3 CONFIGURAL PROCESSING IN FACE RECOGNITION

At a processing level it has been argued that the fusiform gyri (in particular of the right hemisphere) are critical for face recognition because they afford the capacity to analyse visual patterns in a holistic or configural manner (Tanaka & Farah, 1993). The terms 'holistic processing' and 'configural processing' are often used interchangeably, but are not synonymous. Even within the domain of configural processing ambiguities exist. As Maurer and colleagues point out (Maurer et al., 2002), 'there is no consensus about terminology'. In a recent review they suggest that configural processing is best conceptualised by being broken down into three sub-components, which are defined in table 2.1 and form the basis for the subsequent consideration of evidence for this type of processing.
<table>
<thead>
<tr>
<th>Configural processing type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to first order relations</td>
<td>Seeing a stimulus as a face because its features are arranged with two eyes above a nose, above a mouth</td>
</tr>
<tr>
<td>Holistic processing</td>
<td>Gluing together the face features into a gestalt</td>
</tr>
<tr>
<td>Sensitivity to second order relations</td>
<td>Perceiving the distances between face features</td>
</tr>
</tbody>
</table>

Table 2.1: Three types of configural processing as conceptualised by Maurer and colleagues (Maurer et al., 2002). They are thought to have different developmental trajectories with sensitivity to first order relations emerging early on in development, followed by holistic processing competence and finally adult sensitivity to second order relations.

2.3.1 Sensitivity to first order relations

First order relations are those aspects of a face that are shared by all faces, namely the fact that they contain two eyes, symmetrically positioned above a nose, which in turn is positioned centrally above a mouth. This arrangement is one to which human infants would appear to be sensitive from very early on in development. Neonates orient to faces in preference to other objects and within the first hours of life can discriminate between face-like patterns and patterns with the same features arranged in a different configuration (Johnson, Dziurawiec, Ellis, & Morton, 1991). One method of assessing sensitivity to first-order relations would be to present stimuli such as the Mooney faces (Mooney, 1957). Despite being little more than patterns of light...
and dark, these images appear face-like. This is because the features are arranged in such a way as to form the first-order relations of a face although no face details are present.

Figure 2.2: An example of a Mooney face, where a face-like image can be detected in the absence of face detail due to the presence of intact first-order face relations.

It would appear that the fusiform gyri respond to first-order face relations, since Mooney faces are found to activate this region in functional imaging studies (Kanwisher, Tong, & Nakayama, 1998).

2.3.2 Holistic processing

In contrast to sensitivity to first-order features, holistic processing involves the gluing together of the face features into a 'whole'. Evidence for the existence of this type of processing is provided by a number of experimental paradigms. For example, the composite face effect where face images are split in half and
then joined with a half from another face. If the two different halves are laterally offset, so as to prevent them being perceived as a whole, recognition of the parts is superior (see figure 2.3) than when they form a whole (Hole, 1994; Young, Hellawell, & Hay, 1987). This phenomenon is interpreted as demonstrating that internal features are automatically integrated making it difficult to parse the face into its isolated features (Maurer et al., 2002).

Figure 2.3: An example of the ‘chimeric’ face effect demonstrated by Young and colleagues (Young et al., 1987), Shown here using the faces of Robbie Williams (top) and Tony Blair (bottom). When the top and bottom halves of the different identities are aligned to form a whole, the faces are typically more difficult to identify than when misaligned.

A similar observation holds for the perception of emotional expressions. Where the top half of a face showing one expression is fused with the bottom half of a face showing a different expression, recognition of the composite parts is slowed compared to when the face halves are misaligned (Calder,
Young, Keane, & Dean, 2000). This suggests that our ability to recognise facial expressions of emotion also depends, in part, on holistic processing.

The part-whole recognition effect as studied by Tanaka and colleagues (Tanaka et al., 1993), also provides evidence for the importance of holistic processing in face recognition. For example, individual face features (e.g. a nose) are recognised better when they are presented in the context of the original face configuration than in isolation (Tanaka & Sengco, 1997). This advantage was not found for any of the control stimuli they examined, including scrambled faces, inverted faces and houses. Similarly, individuals are better at matching whole faces than individual parts of faces (Rossoin et al., 2000).

2.3.3 Sensitivity to second order relations

Unlike first-order relations, not all faces share the same second-order relations (distances between the face features). They help us to individuate faces and recognise particular faces. In support of the notion that the processing of second-order relations is particularly important for face recognition, it has been shown that changes in visual properties of faces that disproportionately affect their second-order relations impair recognition.

Blurring faces obscures fine-detailed information about facial features and forces recognition to be achieved by sensitivity to second order relations.
(Hayes, Morrone, & Burr, 1986). This is generally quite easy for normal adults (see figure 2.4c) but can be very difficult for patients with face recognition difficulties (Bliem, 1998). This suggests that insensitivity to second-order relations may underlie face recognition difficulties in some patients.

Finally, possibly the most studied paradigm within experimental research into face processing, is the inversion effect. Face recognition is disproportionately impaired by inverting the orientation of the image (Eimer, 2000; Valentine, 1991; Yin, 1969). Upside-down faces are more difficult to recognise than upright faces (see figure 2.4 a&b).

It is not just that faces are more difficult to recognise inverted than upright but that inversion may produce a greater recognition decrement for faces than for other classes of objects. When face recognition has been tested alongside the recognition of photographs of other objects (such as houses and aeroplanes), recognition for faces is typically better than for other classes of objects (Yin, 1969). However, when the stimuli are inverted, faces typically become the most difficult stimuli to recognise (Yin, 1969) with the effect intensifying with increasing degree of rotation away from the upright (Collishaw & Hole, 2002). Inversion disrupts the discrimination of faces that differ in terms of second-order relations much more than it disrupts discrimination of faces that differ in terms of featural information (Leder, Candrian, Huber, & Bruce, 2001). Maurer (Maurer et al., 2002) suggests that the facial inversion effect is likely to occur at the level of perceptual encoding rather than storage or retrieval.
Figure 2.4: Examples of the influence of manipulations of second-order relation image characteristics on face recognition, demonstrated here with the face of actress, Julia Roberts. Firstly as a normal image (a) then showing the detrimental affect of inversion on face recognition (b). In (c) we see that blurring a face fails to severely disrupt our recognition ability.
This is because the effect is found to be of a similar magnitude when the faces are presented simultaneously to when they have to be remembered for up to 10 seconds (Freire, Lee, & Symons, 2000).

In terms of developmental trajectory, sensitivity to first-order face relations is present very early in development. However, sensitivity to second-order relations develops at a slower rate and over a much longer period than featural face processing (Mondloch, Le Grand, & Maurer, 2002). It has been argued that young children are not able to make appropriate use of this type of processing in face recognition (Carey, Diamond, & Woods, 1980) and can be fooled by manipulations of featural aspects of the face more than adults. The inversion effect for faces, though present in young children (Brooks & Goldstein, 1963), becomes more pronounced with age (see Chung & Thomson, 1995), for a review), which is often taken as a sign of increasing configural competence in processing faces in the developing child.

Feature based processing is also important for normal face recognition (Cabeza & Kato, 2000) and typically operates in tandem with configural analysis of a face image. However, individual and developmental differences may exist in the extent to which each is relied upon. Even within individuals, face recognition can be more or less configural or feature based depending on manipulations of the processing environment. For example, face recognition can be disrupted by engagement in concurrent tasks (such as letter identification) that activate a featural processing strategy (Macrae & Lewis, 2002).
In development, it is possible that configural aspects of face recognition will be more susceptible to disruption since they develop over a longer period. In addition, experiments with individuals who were born with cataracts in both eyes demonstrate that early visual experience is critical for the normal development of configural face processing in later years. It was found that children with congenital cataracts that had been operated on in early infancy had poorer configural face processing than normal children when assessed in later childhood (Le Grand, Mondloch, Maurer, & Brent, 2001). This is suggestive of a sensitive or critical period in early infancy for the development of optimal configural face processing skills.

2.4 FACE PERCEPTION

The recognition of faces, like the recognition of any other visual object begins in the ganglion cells of the human retina. These cells project through the optic nerve to the lateral geniculate nucleus (LGN) of the thalamus. Beyond these primary perception sites, visual association cortex comprises two streams, with functional specialisation. The ventral visual stream projects forwards within the temporal lobe. This is involved in recognising ‘what’ an object is. The dorsal visual stream projects upward to the posterior parietal lobe and, on one formulation at least, processes information concerned with ‘where’ something happens (Mishkin & Ungerleider, 1983). The ventral visual stream that projects through the temporal lobes is primarily concerned with all kinds of visual object (including face) recognition (see back to figure 2.1).
2.4.1 The fusiform face area

Prosopagnosia (the failure to recognise previously familiar faces) can occur subsequent to a number of types and extents of brain injury. However, common to the majority of patients is damage to one particular region of inferior temporal cortex, dubbed the fusiform face area. A landmark post-mortem study by Meadows delimited the anatomically critical regions for acquired prosopagnosia to include the fusiform gyrus and possibly the lingual gyrus of the right temporal lobe (Meadows, 1974). It was further believed that the presence of other posterior lesions might contribute to the syndrome. Brain imaging techniques in typically developing adults have confirmed the role of the fusiform gyrus and inferior temporal lobes in face processing.

Studies using event-related potentials (Bentin, Allison, Puce, Perez, & et al, 1996), positron emission tomography (Sergent, Ohta, & MacDonald, 1992), and functional magnetic resonance imaging (Clark et al., 1996; Clark, Maisog, & Haxby, 1998; Kanwisher, McDermott, & Chun, 1997; Puce, Allison, Gore, & McCarthy, 1995; Puce, Allison, Asgari, Gore, & McCarthy, 1996) have unambiguously supported Meadows' clinical neuroanatomical observations. Viewing faces is associated with increased activity in the fusiform gyrus. Where hemispheric asymmetry occurs, as is found in most patient studies (De Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994), the right rather than the left hemisphere is implicated. The middle part of the right fusiform gyrus shows activation in most reported studies and has been named the ‘Face Fusiform Area (FFA)’ (Kanwisher et al., 1997). Earlier behavioural studies using
unilateral presentation of face images also generally demonstrated right-hemisphere (left visual field) superiority in face recognition (Sergent & Bindra, 1981).

However, despite demonstrations that the fusiform gyri clearly play an important role in face recognition, many argue that the role of this region is not specific to faces. Rather it may specialised for the type of configural processing that the recognition of faces recruits. Does the recognition of any other classes of stimuli involve this type of visual processing mediated by the fusiform gyri?

2.4.1.1 Intra-class discrimination

The idea that face recognition was only unique in so far as it required subtle intra-class discriminations was first championed by Damasio and colleagues (Damasio, Tranel, & Damasio, 1990). Inter-class discrimination can be considered as discriminating between different object categories e.g. a shoe, a table, and a football. Intra-class discrimination, on the other hand would require us to discriminate between different types of the same class of object, for example discriminating between different pairs of shoes. While recognising faces frequently involves subtle intra-class discriminations between many similar exemplars, this is not so for most other visual identification tasks. You need to be able to discriminate the face of your mother from that of a stranger.
but with objects it is often adequate to simply recognise the object class e.g. a shoe, or a table.

Damasio and his colleagues have argued extensively that prosopagnosia is (only) a form of visual object agnosia, selective for intra-class discrimination. When intra-class discrimination of non-face objects is assessed, prosopagnosia is frequently accompanied by other selective agnosias at this level (Damasio, Damasio, & Van Hoesen, 1982; Damasio et al., 1990; Henke, Schweinberger, Grigo, Klos, & Sommer, 1998). Prosopagnosics can have difficulty discriminating between different makes of car, just as they have difficulty discriminating between different faces. Gauthier and colleagues compared brain activation for discrimination of objects at an inter-class level (e.g. car or bird) or intra-class level (e.g. Honda or Ferrari) (Gauthier et al., 2000). Intra-class level decisions activated the fusiform gyrus. This property, rather than any intrinsically face-like 'pre-wiring' may account for the role of the fusiform gyrus in face processing. A similar conclusion may be drawn from studies on visual expertise.

2.4.1.2 Expertise

Experience is required to make fine-category discriminations within a homogenous class of stimuli. The typical decrement in recognising objects when inverted as opposed to upright is magnified for faces, for which inversion severely disrupts recognition. Dog and bird experts show similar
inversion decrements for images within their expert category as do typical individuals when shown faces (Diamond & Carey, 1986; Rhodes, Tan, Brake, & Taylor, 1989). In one experimental study, participants were trained to become experts at recognising “greebles”. Greebles are visual patterns that are not faces but are of a similar level of complexity, with a high degree of visual similarity between exemplars. Participants that had been trained to recognise these patterns were faster and more accurate at recognising greebles than non-trained participants (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997). However, this advantage disappeared when images were inverted. This suggests that the experience served to enhance upright recognition by way of enabling configural processing. Since inversion disrupts configural processing, no advantage could be seen for the stimuli when in this orientation. Moreover, it has been found that activation of the fusiform gyrus increases with expertise at discriminating greebles (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999). This perhaps implies that the configural processing learning in these participants was mediated in part by this neural region.

The ability to recognise faces can also be predictive of the ability to become expert at making other visual discriminations. Berbaum and Platz report that pathologists who are good at discriminating visually similar pathological specimens are also more accurate at recognising faces, suggesting a common neural substrate involved in both tasks (Berbaum & Platz, 1988). Considering such findings, Tarr and Gauthier suggest that the fusiform face area should more appropriately be renamed a ‘flexible fusiform area’ (for subordinate-level visual processing) (Tarr & Gauthier, 2000).
The finding that the cortical substrates and (configural) processing characteristics for faces need not be confined to such images suggests that faces may be special in degree rather than in kind. However, for most of us, faces constitute a domain that is emotionally salient, contains very many exemplars that require individual recognition, and is structurally (visually) homogeneous. The unique combination of these factors leads to a (relatively) unique mode of processing for faces compared to other sorts of visual stimuli. This type of processing would appear to be heavily dependent on the normal functioning of the fusiform gyri.

2.4.1.3 Damage to the fusiform

What happens when the functional integrity of the fusiform gyrus is impaired? The way in which damage to this region can result in prosopagnosia has already been considered. However, for many prosopagnosic patients, the exact extent of the brain damage is often not known. It is important not to equate prosopagnosia with fusiform damage. Many patients with prosopagnosia are thought to have specific difficulty with configural aspects of face processing – they see the face as individual parts rather than an integrated whole with spatial relationships between the independent elements (Levine, 1989).

Patients may be able to extract other information from the face such as gender or emotional expression (Sacks, 1985), which in some cases can be less reliant on configural processing. Such patients can be as good (or better!)
at recognising faces when they are presented inverted as they are when they are presented upright. Patient LH (whose brain damage may include but is by no means confined to the fusiform gyri) showed this pattern (de Gelder & Rouw, 2000). One could argue that he could not discriminate faces that were upright because of poor configural processing, but inverted faces do not invoke configural processing and therefore could be processed by an intact piecemeal processing system. This would suggest that his part-based recognition system is functioning but in some way, this is prevented from being used to recognise upright faces for which configural processing is typically recruited. LH would seem to be using a faulty configural processing to analyse upright faces although an intact piecemeal system would be more effective. Do upright faces, either innately or through experience, so strongly recruit configural processing that we can not override the recruitment of this type of processing even when the system is faulty?

Prosopagnosic patients are typically not reported to have social difficulties except for those directly resulting from their ability to recognise faces.

2.4.1.4 Developmental prosopagnosia

In a handful of individuals with prosopagnosia the deficit is thought to be congenital in origin and there is no known acquired neurological insult (Bentin, Deouell, & Soroker, 1999; de Haan & Campbell, 1991; Duchaine, 2000; Nunn, Postma, & Pearson, 2001). In several of these patients, the face recognition
deficit would appear to be qualitatively different to that experienced by patients with acquired lesions. Some developmental prosopagnosic patients are able to match concurrently presented faces, with difficulties appearing to be more concerned with memory for faces (Bentin et al., 1999; Kracke, 1994). Furthermore, while patients with acquired prosopagnosia often show covert recognition for faces that they explicitly claim not to recognise, this would not appear to be the case for patients with developmental prosopagnosia. Three patients with developmental prosopagnosia failed to show any covert recognition of faces. This could be linked to a failure to establish a store of accurate facial memories, which would have been possible for patients with acquired prosopagnosia pre-lesion (Barton, Cherkasova, & O'Connor, 2001). However, some covert recognition has been detected in one child with developmental prosopagnosia (Jones & Tranel, 2001).

In addition, where other aspects of face processing have been assessed, the difficulties seem to be wider reaching in developmental cases. Face recognition difficulties are often accompanied by problems with facial emotion recognition (Ariel & Sadeh, 1996; Kracke, 1994) (but see (Jones et al., 2001)) and difficulties with lip-reading and judging direction of eye gaze (de Haan et al., 1991). In addition, a number of these patients have been reported to experience social adjustment difficulties, for example patients AB and HD (Kracke, 1994; McConachie, 1995).

Therefore, patients with developmental prosopagnosia would appear to have, at least in some ways, qualitatively different impairment to those with acquired
prosopagnosia. Furthermore, one study has assessed configural processing abilities of an individual with developmental prosopagnosia and found them to be intact (Duchaine, 2000). None of these developmental patients are known to have neurological abnormalities so the findings provide no clear indication of the neural regions involved in their anomalous abilities. However, it is interesting to note that in these congenital cases, where other face processing abilities have been examined, no face identity recognition specific impairment like those found in acquired prosopagnosia, has been reported. Perhaps whatever the cause of face recognition difficulties congenitally or in early development, there will be many knock on affects to other elements of face processing systems? This is an important consideration, and caution needs to be drawn in modelling developmental profiles on acquired disorders (Karmiloff-Smith, 1997; Karmiloff-Smith, 1998).

As is pointed out by de Haan et al (de Haan, Humphreys, & Johnson, 2002), the fact that early neural damage often fails to have a significant impact on face recognition abilities is suggestive of a system that is either plastic following disruption or relatively widely distributed. For example, it has been found that less than 50% of children experiencing perinatal unilateral lesions to either hemisphere have any detectable face recognition impairments (Mancini, de Schonen, Deruelle, & Massoulier, 1994). In a similar study, it has been reported that face recognition impairments are more likely to result from early damage to the parietal lobes than to the temporal lobes (Ballantyne & Trauner, 1999).
2.4.1.5  *Face processing in developmental disorders*

In individuals with both autism and William's syndrome, anomalies in the configural processing of faces (thought to be mediated by the fusiform gyri) have been noted.

Youngsters with autism tend to perform at the level of much younger children on tasks that require them to match face features both within and without a supporting face context. They resemble mental-age matched controls when matching isolated face features, but fail to show any facilitation when the features are embedded in a whole face (Teunisse & de Gelder, 1994).

People with autism can also be less sensitive than controls to face inversion (Hobson, Ouston, & Lee, 1988; Langdell, 1978). Davies et al (Davies, Bishop, Manstead, & Tantam, 1994) found that high-functioning youngsters with autism and Asperger syndrome were impaired on a task that required the detection of configural similarity within an array of dots as well as detecting the configural similarity of faces. This suggests that a 'configural processing anomaly' might be a general feature of autistic processing style. This is consistent with the notion that individuals with autism rely on a (default) cognitive style that uses local detail rather than global pattern (Happe, 1999).

Functional brain imaging indicates that faces may not engage a special circuit in people with autism. People with autism have been found to show relatively reduced activation of fusiform regions by faces compared with objects (Pierce,
Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000). Similarly, individuals with autism fail to show normal ERP amplitude differences to familiar, as opposed to unfamiliar faces while they do show differential amplitudes for familiar versus unfamiliar objects (Dawson et al., 2002).

Despite having relatively spared face recognition abilities, individuals with William's syndrome also demonstrate anomalous configural face processing. They perform poorly on tasks that require configural face processing (Karmiloff-Smith, 1997) tending to rely on featural processing. Further evidence of anomalous configural face processing has been reported, where individuals with Williams syndrome are found to show a reduced face-inversion effect (Deruelle, Mancini, Livet, Cassse-Perrot, & de Schonen, 1999).

Atypical cognitive processes may be mediating face processing in this syndrome. Individuals with Williams Syndrome have been found not to show the typical gamma burst in EEG activity associated with viewing faces (Grice et al., 2001). This activity has been linked to the perceptual integration of features and its absence in WS may suggest that such processing is not critical to face recognition in this syndrome.
2.4.1.6 Beyond the Fusiform face area...

While all and any face processing task appears to enhance activation in the face-fusiform regions, the processing of facial identity – both the learning of new faces and the recall or recognition of learned ones – along with understanding social characteristics of the face, requires activation of more extensive networks. Here too, right rather than left-sided structures are critical. What is less clear is exactly which structures are implicated in which aspects of face processing.

2.4.2 Face Perception (continued)

2.4.2.1 Parietal lobe

Although it is the temporal lobe that is primarily concerned with identifying and recognising objects and faces, it would seem that the parietal lobe possibly has a role to play given the complex visuo-spatial nature of faces. This role may be more important in the establishment of face expertise than in adult skilled face recognition. Prenatal and peri-natal lesions to the parietal lobes (of either hemisphere) are known to result in residual deficits in face recognition, being suggestive of the importance of the parietal lobes in the development of face recognition (Ballantyne et al., 1999). One of the functions of the parietal lobes is to perform mental rotation type manipulations with stimuli so that they
can be represented from differing viewpoints (Vanrie, Beatse, Wagemans, Sunaert, & Van Hecke, 2002). Our initial experience with a new face is typically from a particular viewpoint. Perhaps, as children, our inferences about what a face looks like from different angles are partly based on mentally rotating the face. This processing may then influence the development of object (or face) recognition, which is represented more in temporal areas. Additionally, Adolphs and colleagues (1996) using lesion analysis, report that damage to the right inferior parietal cortex correlated with recognition of facial expressions of emotion.

2.5 FACE RECOGNITION AND FACE MEMORY

2.5.1 Fusiform Gyrus

The fusiform gyrus may be involved in simple perceptual memory for faces. Repetition priming effects have been observed in right fusiform for famous faces and in the left inferior occipital region for both familiar and unfamiliar faces (Henson, Shallice, Gorno-Tempini, & Dolan, 2002). The inference is that the fusiform gyrus has two-way connections to other cortical and sub-cortical regions. The fusiform response is unlikely to be specific to faces, since it also exhibits an attenuated response to repeated exposure of familiar non-face stimuli (Henson, Shallice, & Dolan, 2000).
2.5.2 Hippocampus

In PET studies, activity in the right parahippocampal gyrus has been generated by face recognition tasks (Sergent et al., 1992). This structure, rostral and medial to the fusiform gyrus, projects to hippocampal regions. The role of the hippocampus and neighbouring regions, including the amygdalae, in all aspects of learning is well known, and has been confirmed in imaging studies (Haxby et al., 1996). The process of forming new face-name associations is supported by hippocampus, in addition to the fusiform and dorso-lateral prefrontal regions (Sperling et al., 2001). These changes in hippocampal activity may form part of a consolidation process for face learning that lasts for a few years (Haist, Bowden, & Mao, 2001).

In patients with acquired hippocampal lesions, faces are one of many classes of material that are poorly learned and remembered. However, as with other material tested in such populations, faces learned a long time before damage can be relatively spared. This suggests that some aspects of established face knowledge are represented in, and accessed through, other cortical systems. The lateralisation that is seen in the fusiform gyrus, with right hemisphere lesions being particularly implicated in producing prosopagnosia, is also seen in the hippocampus where right hemisphere lesions may be particularly critical to face memory abilities (Baxendale, 1997). Suggesting differential roles for the hemispheres, Seidenberg et al (Seidenberg et al., 2002), found that patients with left hippocampal damage had a selective impairment in naming famous faces, while those with right hippocampal damage were impaired.
across all components of face memory, face recognition, semantic identification and face naming.

2.5.3 Amygdala

As a central operator in the limbic system, the amygdala is important in learning and memory for events or stimuli that have emotional or social valence. The amygdala is thought to enhance memory for arousing material (Phelps et al., 1998) possibly by modulating other regions that are involved with brain storage. Activity of the amygdala while participants view emotionally provocative stimuli correlates with the degree to which the stimuli are retained in long term memory (Cahill, 1996; Cahill et al., 2001b; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000). Since faces are emotionally arousing stimuli it is suggested here that the amygdala would also be involved in remembering faces.

One study suggests how this might be so. When faces were encoded with a 'deep' strategy (making judgements of pleasantness) they were remembered better in a recognition test. Additionally, activity was found to be enhanced in the amygdala relative to a shallow encoding condition (judging right/left orientation (Bernstein, Beig, Siegenthaler, & Grady, 2002). This suggests that our emotional reactions to faces may also modulate our subsequent ability to remember them.
In what ways could activity of the amygdala enhance memory for faces? With regard to emotionally charged events more generally, evidence suggests that the amygdala interacts with endogenous stress hormones released during these events to modulate memory storage in other brain regions (Cahill, 2000; Cahill & McGaugh, 1996). During the perception of faces showing a fearful expression, the amygdala may influence the activity of the fusiform gyrus and other regions involved in face processing (Morris et al., 1998) possibly enhancing our perception of these stimuli. However ‘modular’ face processing may be, it is still susceptible to influences from other processing systems.

Activity of the amygdala when viewing faces is also modulated by familiarity of the faces. Less activity is elicited by faces of people with whom we are familiar than by faces that are unknown to us (Gobbini, Leibenluft, Santiago, & Haxby, 2002). Haxby, Hoffman, & Gobbini (2002) suggest that this reduction in activity may be associated with feeling more at ease and less guarded when one is with close acquaintances as opposed to strangers – the amygdala responds to threat (Isenberg et al., 1999).

In a study addressing the relationship between face memory and medial temporal lobe structures, an intriguing association was noted between amygdala volume and scores on a face recognition memory task (Mackay et al., 1998). The males who attained the highest scores on this task had significantly smaller right amygdala volumes than the males who attained the lowest scores. This is perhaps suggestive of the importance of structural elements of amygdala development in face recognition memory.
2.5.3.1 Damage to the amygdala

Patients who have bilateral amygdala damage, as a consequence of surgery or neural disease have been found to exhibit a number of difficulties in the processing of faces. Most notably, individuals can develop post lesion difficulties in recognising facial expressions of emotion; in particular those emotions with negative valence (this evidence is considered later in this chapter). In addition to these emotion recognition difficulties, problems with recognising faces can also exist; whereby the ability to learn new faces encountered post-lesion is severely affected (Calder et al., 1996). Sometimes this is detectable in laboratory tests of face learning and memory (Calder et al., 1996; Tranel & Hyman, 1990a) but this isn’t always the case (Adolphs, Tranel, Damasio, & Damasio, 1995a).

Difficulties can present irrespective of whether the damage to the amygdalae occurs in adulthood or childhood. For example, patient SM had a congenital disease (Urbach-Wiethe) which produced bilateral calcification of her amygdala in early childhood if not before (Adolphs et al., 1995a). Therefore much of her development would have been experienced without normal amygdala function. However, like patients with acquired damage in adulthood, SM had difficulties with unfamiliar face memory (Tranel & Hyman, 1990b), suggesting that there is limited neural plasticity for these aspects of face memory.
When face recognition difficulties are present in either congenital or acquired cases with bilateral amygdala lesions, they are usually less severe and probably of a different nature to those experienced by prosopagnosic patients. An inability to adequately match concurrently presented faces has also been noted in some (Jacobson, 1986) but not all individuals with this neurological insult (Tranel et al., 1990a). Poor face memory may be part of a wider impairment in declarative memory for any emotional material. Since amygdala activation is associated with enhanced memory for emotionally salient stimuli, it is not surprising that damage to this region can result in impaired memory for emotionally arousing material (Adolphs, Cahill, Schul, & Babinsky, 1997).

Do patients with amygdala damage have difficulties with social functioning? Patient S.M., with developmental damage, is described as being ‘somewhat coquettish & disinhibited…(she) often makes mildly inappropriate sexual remarks’ (Tranel et al., 1990a). This same patient is also described as having a ‘history of inadequate social decision making, somewhat inappropriate social behaviour’ (Adolphs et al., 1995a). The first case with acquired amygdala damage to be described was a female adult patient referred to as DR. Jacobson notes a number of unusual social characteristics about this patient including; marked placidity, blunting of affect, social anxiety and absence of anger (Jacobson, 1986). She was also reported to be somewhat apathetic and failed to make any new friendships or attachments post operatively.
Although both of these patients have difficulties in social adjustment, they may be conceived to be qualitatively slightly different in nature, which perhaps relates to the age at which amygdala damage occurred. More evidence that this might be the case emerges from animal literature on the subject.

Since the observations made by Heinrich Kluver, bilateral amygdala lesions have long been known to impact on social interactions for Rhesus monkeys (see (Nahm, 1997) for a review). Amygdalectomised monkeys are known to demonstrate increased social affiliation and decreased anxiety during social encounters, in particular with unfamiliar monkeys (Emery et al., 2001). Neurons within the medial amygdala respond selectively to features of the social environment in this species (Brothers, Ring, & Kling, 1990). In macaques it is also possible to study the affect of lesions at different ages and assess the developmental consequences. Selective amygdala lesions have been produced in two week old monkeys, leading to somewhat different affects on social behaviour to those found in adult lesioned monkeys (Prather et al., 2001). In contrast to adult monkeys, who have been found to show decreased fear of inanimate objects and increased social affiliation, these monkeys demonstrated LESS fear of inanimate objects but MORE fear during dyadic social interactions. Therefore, it is of critical import to consider the impact of damage to the developing human brain separately (but alongside) to damage to the more developed adult brain. The consequences may be different.
2.5.3.2 The amygdala and autism

Individuals with autism, who by definition have difficulties in social functioning, have also been reported to have anomalous amygdala function (Howard et al., 2000). Decrements have been reported on tests of incidental face learning (Boucher & Lewis, 1992), memory for recently presented faces (Ellis, Ellis, Fraser, & Deb, 1994), and recognition of familiar faces (Boucher, Lewis, & Collis, 1998). Memory for other (non-social) objects appears to be at an appropriate level. It has been reported that control children remembered faces better than objects, while children with autism show no such distinction (Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998). This possibly reflects the enhanced emotional significance of faces for typically developing children but not for children with autism.

2.5.4 Orbito-frontal cortex

Just as the amygdala receives both efferent and afferent projections from the fusiform gyri, the orbito-frontal cortex is anatomically connected to the amygdala (Amaral & et al., 1992; Rolls, 2000). Within the macaque orbito-frontal cortices there are cells that appear to respond selectively to faces (Thorpe, Rolls, & Maddison, 1983). Different face recognition tasks may make differential demands on the face recognition system. Recognising newly learned faces may cause relatively more medial frontal activation, in particular the right medial orbito-frontal region, whereas recalling well-remembered faces may depend more on the posterior visual areas (Wiser et al., 2000). The
frontal lobes may also be recruited under restricted viewing conditions. Increased degradation of the face image is also reported to be coupled with increased activation of medial frontal regions (Grady, McIntosh, Horwitz, & Rapoport, 2000).

The orbito-frontal cortices additionally would appear to be involved in the processing of other information relevant to social functioning. For example, in normal individuals, judging expressions from another person's eyes produces activation of the amygdala, STS, and regions of prefrontal cortex (Baron-Cohen et al., 1999). Some cortical imaging studies also suggest that OFC is selectively involved in the performance of Theory of Mind tasks (Gallagher et al., 2000; Goel, Grafman, Sadato, & Hallett, 1995; Stone, Baron-Cohen, & Knight, 1998).

Damasio and his co-workers have discussed the role of the orbito-frontal cortex in social functioning (Damasio, 1996; Damasio, 1999). One of their key claims is that ventromedial parts of the inferior frontal cortex have a critical role in moderating activity flowing to the cortex from subcortical structures, including the amygdala and parts of the thalamus. One role of the orbito-frontal regions appears to be in modulating social interactions.

It has been noted since the classic study of Phineas Gage (see (Damasio, Grabowski, Frank, Galaburda, & Damsio, 1994)) that lesions of prefrontal cortex affect social behaviour. Abnormalities in behaviour consequent to lesions to this area could reflect an underlying difficulty in altering behavioural
responses when the emotional significance of stimuli changes (Dias, Robbins, & Roberts, 1996).

2.5.4.1 The orbito-frontal cortex and autism

Based on behavioural tests (including social orientation), it has been suggested that children with autism have pathologies of orbito-frontal regions (Dawson, Meltzoff, Osterling, & Rinaldi, 1998). And individuals with autism fail (in a selective fashion) tasks that have been shown to activate this region in typically developing individuals such as reading the language of the eyes and theory of mind tasks (Baron-Cohen, Leslie, & Frith, 1985).

2.5.5 Anterior middle temporal gyrus & other regions

Functional imaging studies consistently reveal that the recognition of known famous or familiar faces, compared to unknown faces, activates the anterior temporal regions, in particular the middle temporal gyrus (Gorno-Tempini et al., 1998; Leveroni et al., 2000; Nakamura et al., 2000; Sergent et al., 1992).

Involvement of these regions would not seem unique to the processing of famous faces. PET technology has been used to investigate the processing of famous faces and famous buildings (Gorno-Tempini & Price, 2001). Activation of the left middle temporal gyrus was common to both famous (versus non-famous) faces and buildings, suggesting that this region might be critical in
storing unique semantic associations that are not shared by other perceptually similar category members, rather than having a specific role in famous face recognition. This is supported by the fact that this area is also found to be activated by the perception of familiar outdoor scenes (Nakamura et al., 2000). A recent study by Shah and colleagues indicates that person familiarity in general, accessed by either face or voice information, is associated with increased neural activity in the posterior cingulate cortex (Shah et al., 2001). This again points to the involvement of multi-purpose systems in the higher level processing of faces. However, it could be that the involvement of the posterior cingulate was more related to task demands than to the face recognition aspect of the study. Subjects were required to attend to faces but at the same time press a button to indicate the appearance of a random stimulus. It is possible that such attentional demands make the task more effortful, and therefore require recruitment of the posterior cingulate.

2.6 FACIAL EXPRESSIONS OF EMOTION

Neural regions beyond the fusiform gyrus are involved with the processing of affect in faces and are additionally implicated in the personal experience of affect.
2.6.1 The amygdala

The role of the amygdala in the recognition of fearful facial expressions in typically developing individuals was first reported by Morris and colleagues, who noted increased activation in the amygdala when participants viewed fearful as opposed to happy faces (Morris et al., 1996). Numerous studies using a variety of imaging techniques have since confirmed these findings. When activation elicited by viewing fearful faces is contrasted against activation associated with viewing other facial expressions, the amygdala is consistently found to be differentially activated by fearful faces (Breiter et al 1996; Phillips et al., 1998). However, not all studies have replicated these findings (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998) although this may be in part due to the rapid habituation of the amygdala response to fearful faces shown in the course of an experiment (Breiter et al., 1996).

It would seem that rather than responding selectively to fear the amygdala responds to stimuli that pose an immediate threat, of which a fearful facial expression is an obvious example. Angry faces would also seem to signal threat, this time from the person displaying the expression rather than from some other aspect of the environment. It is therefore interesting to note a number of studies that have also found amygdala activation in response to facial expressions of anger (Hariri, Bookheimer, & Mazziotta, 2000) and there is a suggestion that this region also responds to sad facial expressions (Blair, Morris, Frith, Perrett, & Dolan, 1999).
From a developmental perspective, it has been argued that emotional facial expressions are first perceived in terms of pleasure and arousal (Bullock & Russell, 1984). They suggest that fear and anger would initially both be assigned the meaning of unpleasant/high arousal and the ability to discriminate between these two expressions relies on close attention to specific facial features. In this way it might be hypothesised that the amygdala is involved in the unpleasant or high arousal aspect of recognising fearful and angry faces but that what ultimately allows us to distinguish between them is high-level visual processes elsewhere in the brain and their interaction with the amygdala.

The amygdala is also thought to be involved in the processing of more complex facial displays. Baron-Cohen et al. (2000) found that interpreting higher level mental states from pictures of people's eyes also gave rise to amygdala activation in healthy control participants.

Amygdala lesions in humans can lead to impaired formation of conditioned autonomic responses to aversive stimuli (Desmedt, Garcia, & Jaffard, 1998). LeDoux (1995) suggests that involuntary and voluntary responses to fear are mediated by different neural networks emanating from the amygdala. This region would seem to be critical to personal experience and appropriate reaction to fear inducing stimuli. However, interest in this region with regard to facial expressions of emotion arose from the discovery that subsequent to bilateral lesioning, difficulties in recognising facial expressions of emotion conveying negative valence, in particular those displaying fear, were evident
(Adolphs, Tranel, Damasio, & Damasio, 1995b; Young et al., 1995). Fear is the most commonly affected emotion, although difficulties with the identification of anger and sadness are also common (Adolphs et al., 1999; Adolphs, Tranel, Damasio, & Damasio, 1994; Calder et al., 1996) although less so in patients with isolated lesions. See Chapter Six for a full consideration.

Where other aspects of reading social information from the face have been studied, for example assessing direction of eye gaze (Calder et al., 1996) or judging trustworthiness and approachability (Adolphs, Tranel, & Damasio, 1998), these aspects also appear to be affected by amygdala lesions.

Damage to amygdala can result in a multitude of difficulties in interpreting the face as a social cue. Difficulties may vary between individuals, possibly in part due to differences in extent of damage or the amount of connective tissue involved in the lesion. However, it is clear that the amygdalae are structures that are of critical import in enabling us to understand and interpret faces in a normal way. As was reviewed in the previous section of this chapter, individuals with amygdala lesions can also have difficulties with recognising faces and face memory and may have anomalous social behaviour. An isolated case in the literature (SM) is described who had congenital amygdala mineralisation, bilaterally due to Urbach-Wiethe disease (Adolphs & Tranel, 1999; Tranel et al., 1990a). This is perhaps the only pure case that allows us to evaluate the developmental consequences of damage to this region. In this case...
case difficulties in emotion recognition (for fear, surprise and anger),
alongside difficulties in face recognition memory and social adjustment exist.

2.6.1.1 The amygdala and autism

Concerning the involvement of the amygdala in face processing and social
adjustment there are indications that the functional integrity of this region may
be impaired in autism. In normal individuals, judging expressions from another
person's eyes produces activation of the amygdala, STS, and regions of
prefrontal cortex. This, however, is not the case for individuals with autism
(Baron-Cohen et al., 1999; Baron-Cohen et al., 2000) who fail to activate the
amygdala. In addition facial emotional expressions would appear not to
activate this region in individuals with autism as is found in typically
developing individuals. Critchley et al. (2000) found that individuals with
autism did not activate a cortical 'face area' when explicitly judging emotional
expressions and also failed to activate the left amygdala when processing was
implicit.

At a structural level, researchers have reported both increased (Abell et al.,
1999) and decreased (Aylward et al., 1999) amygdala grey matter volumes in
individuals with autism. Relative size is possibly influenced by whether the
individuals are high or low functioning. Individuals with Asperger's syndrome
have been found to have significantly greater left amygdala volume than
individuals with classic autism (Haznedar et al., 2000).
Dysfunction of the amygdala may be one causal factor underlying face recognition difficulties in individuals with autism (Baron-Cohen et al., 2000; Howard et al., 2000). The amygdala has also been implicated in psychopathy, where children with such tendencies are found to have difficulties recognising fearful and sad facial expressions (Blair, Colledge, Murray, & Mitchell, 2001).

2.6.2 The insula and basal ganglia

The basal ganglia have been widely implicated in the recognition of facial expressions of disgust. The basal ganglia are a group of sub-cortical nuclei in the telencephalon, and include the caudate nucleus, the globus pallidus, and the putamen, which are important parts of the motor system. Distinct neural substrates for fear and disgust have been identified (Phillips et al., 1997). Viewing facial expressions of disgust was found to produce activation of the right anterior insula.

Similar results were found in an fMRI study looking at emotion recognition in faces (Sprengelmeyer, Rausch et al, 1998) which identified differential neural substrates for the recognition of fear, anger and disgust. Disgusted faces activated the right putamen and thalamus and the left insula cortex whilst also increasing activation in medial frontal cortex.
In primates, the anterior insula is connected to the ventro posterior medial thalamic nucleus, which is thought to contain neurons which respond to pleasant and unpleasant tastes (Yaxley, Rolls, & Sienkiewicz, 1988). Furthermore, the anterior insula contains neurons that respond selectively to taste (Plata Salaman, Smith Swintosky, & Scott, 1996). It has also been found, in human PET studies, that the anterior insula is activated while tasting salt (Kinomura et al., 1994). It is suggested that activation of the anterior insula, during perception of facial expressions of disgust, implies that appreciation of visual stimuli depicting other's disgust is closely linked to the perception of unpleasant tastes and smells (Kinomura et al., 1994). As with the multiple functions of the amygdala, the neural areas concerned with the perception of facial expressions of disgust appear also to be implicated in the subjective experience of this emotion. In fact the insula may be key in the conscious experience of emotion more generally (Morris, 2002).

Initial interest in the neural substrate of disgust also arose from the identification of selective impairments in a patient group. Sprengelmeyer and colleagues reported that patients with Huntington's disease had particularly severe difficulty recognising facial expressions of disgust, although the recognition of other emotions was also affected to some extent (Sprengelmeyer, Young, Calder, Karnat, & et al, 1996). Less severe impairment of the other emotions may reflect a general deterioration in Huntington's disease, in which there seems to be a progression from specific impairments to more general impairments of all cognitive functions as the disease progresses.
One group (Gray, Young, Barker, Curtis, & Gibson, 1997) have looked at
disgust recognition in the earliest stages of Huntington's disease, in patients
who were gene carriers but who were either asymptomatic or showed only
minor symptoms of the disease. People symptomatic with Huntington's
disease have often suffered some degeneration of many regions of the brain.
In the early stages it seems to be the basal ganglia which show the most
degeneration, so testing patients in the early stages of the disease was used
as a way of tapping the importance of these structures in the recognition of
disgust. It was found that Huntington's gene carriers showed a highly selective
deficit in the recognition of disgust alongside intact intellectual functioning and
normal ability on other tasks of face processing, including recognition of the
other basic emotions from facial expressions. It is likely that the putamen and
insula can respond to multiple social signals of disgust and not just those
conveyed by facial expressions. Damage to these regions has been linked
both to impairments in recognising vocal expressions of disgust and in the
personal experience of feelings of disgust (Calder, Keane, Manes, Antoun, &
Young, 2000).

Individuals with Obsessive Compulsive Disorder (OCD) have been shown to
have impaired recognition of facial expressions of disgust (Sprengelmeyer et
al., 1997). This may well be linked to their abnormal experience of disgust in
relation to the false contamination alarm that such patients can experience
(Stein, Liu, Shapira, & Goodman, 2001). One possibility is that in a dynamic
way, the excessive and abnormal experience of a particular emotion is linked
to difficulties in recognising the emotion in the facial displays of others. The emotion of disgust may be experienced more frequently and intensely in some patients with OCD and as a response to stimuli that would perhaps not ordinarily evoke this emotion. This experience could in turn be linked with some dysregulation of the system involved in recognising this emotion in others.

2.6.3 Orbito-frontal cortex

Functional imaging studies have revealed activation in the orbito-frontal cortices when typically developing adults view emotionally expressive faces (George et al., 1993; Phillips et al., 1997; Sprengelmeyer et al., 1998). There would appear to be less specificity in response to different facial expressions than in the amygdala or insular cortices, with studies reporting activation linked with a variety of different emotions, including those conveying both positive and negative affect.

The orbito-frontal cortex may have a specialised role in the perception of angry facial expressions. Increasing intensity of angry facial expression has been found to be associated with enhanced activity in the orbito-frontal cortex and the anterior cingulate cortex (Blair et al., 1999). The authors suggest that when a facial expression of anger activates the orbito-frontal cortex, the activation may serve to suppress current behaviour through either inhibition or activation of alternative behaviours.
Even relatively small lesions of orbito-frontal regions may result in impairments in the ability to identify affect from facial and vocal expressions of emotion (Hornak, Rolls, & Wade, 1996). Temporary pharmaceutical disruption of the function of the orbito-frontal cortices using diazepam has also been found to selectively impair the recognition of angry facial expressions (Blair & Curran, 1999). Furthermore, as was reviewed in the previous section, damage to this region can result in anomalous social behaviour. Additionally, anomalous function of the area has been suggested in individuals with autism.

2.7 INTERPRETING SOCIAL INFORMATION OTHER THAN EXPRESSION FROM THE FACE

2.7.1 Superior Temporal Sulcus

One region that may serve to connect the lateral and medial systems involved in face processing (that are schematically represented in figure 6.1) is the superior temporal sulcus (STS). This is a lateral temporal structure with projections to medial structures including the amygdala and orbito-frontal cortex. This region receives inputs from both the dorsal visual stream of the parietal cortex and the ventral stream of the temporal cortex, affording it a role in the integration of form and movement information. STS is activated during viewing of biological motion (Grossman et al., 2000) and would seem to be particularly responsive to facial movement including movement of the lips and
movement of the eyes. However, the posterior superior temporal sulcus is also activated during the perception of static pictures of faces (Chao, Martin, & Haxby, 1999; Hoffman & Haxby, 2000). Haxby and colleagues suggest that this activity may reflect the involvement of this area in evaluating potential movement or the aspects of the face that change with movement (Haxby et al., 2002). STS has back-projections to inferotemporal face processing regions and may be involved, not only in integrating facial form with more dynamic facial information, but also in moderating the development of inferotemporal regions and their function.

2.7.1.1 Mouth movements

In humans, viewing mouth movements is found to elicit activity within the STS (Puce, Allison, Bentin, Gore, & McCarthy, 1998). Typically developing individuals, even those with no hearing difficulties, will make use of movements of the lips, jaw and tongue in understanding spoken language – a process that is normally referred to as lip-reading. Lip-reading may be more important in situations where sound quality is reduced for example in a noisy room but is used continuously and often unconsciously, allowing us to disambiguate spoken sounds. Lip movements that are inconsistent with auditory speech are confusing to us and frequently produce hearing errors, such that a sound intermediate to the one presented auditorily and the one presented visually is perceived (McGurk & MacDonald, 1976).
The superior temporal sulcus has also been found to be involved in the perception of lip-reading in functional imaging studies (Calvert, Bullmore, Brammer, Campbell, & et al, 1997). STS is known to be activated by watching stilled images of speaking faces (Calvert & Campbell, 2002; Sams et al., 1991) although the lateralisation of STS activation to speech and non-speech gestures can differ (Campbell et al., 2001).

2.7.1.2 Eye gaze

Perceiving direction of gaze is important to humans as a social species. It provides us with important social information, such as the location or object another is interested in. It can also be used to express intimacy and social control (Kleinke, 1986; Kleinke & Pohlen, 1971). A number of neural regions are implicated in gaze processing. Perrett and his colleagues (Perrett, Hietanen, Oram, & Benson, 1992; Perrett, Rolls, & Caan, 1982) have identified cells within primate STS that are responsive to whether head and eyes are facing or averted from the viewer. These cells are thought to be important in signalling the direction of another individual’s attention.

In a positron emission tomography study (PET) of human volunteers, parieto-temporal regions including the STS were activated during perception of gaze (Wicker, Michel, Henaff, & Decety, 1998). The STS showed significantly more activation when participants were monitoring eye gaze (either mutual or averted gaze) than for a condition in which the actor looked down such that
the eyes appeared closed. Similar results have been found using MRI technology (Puce et al., 1998). Here participants viewed a face in which the eyes were averted to the left or to the right. Eye movement was found to activate several focal regions of visual cortex including bilateral STS. More recently, direct gaze has been found to activate STS to a greater degree than averted gaze (Calder et al., 2002). Lesions to the STS region in monkeys have been found to impair judgements of eye gaze direction (Campbell, Heywood, Cowey, Regard, & Landis, 1990; Heywood & Cowey, 1992).

If the ways in which gaze is used in social interactions are considered, there are essentially two separate functions that it performs, the meaning of which is influenced by other contextual factors. We use gaze to decide where a person is looking or directing his or her attention in the external world and we also use gaze to decide if someone is looking at us. In the first instance we might want to follow their gaze in order to ascertain what is of interest to the other person, and in the second situation we would need to assess why the person was looking at us in order to know how to respond to them. It would seem that these two functions of gaze, although much overlapping and used together in everyday situations, would seem to rely on at least partially separate neural substrates both of which have anatomical connections with the STS (Seltzer & Pandya, 1994; Stefanacci & Amaral, 2000).
2.7.2 Intra-parietal sulcus

Gaze directed away from the viewer has been found to activate regions of the brain that deal with spatial attention. Laterally averted gaze produces increased activity in the intra-parietal sulcus (George, Driver, & Dolan, 2001). Haxby and colleagues (Haxby, Hoffman, & Gobbini, 2000), and Wicker et al (Wicker et al., 1998) also report activation of this parietal region when viewers discriminate line of sight from a face image, perceiving where an actor is looking. This region is involved in spatial attention and given that humans shift their attention reflexively to the direction of gaze of another (Driver et al., 1999) it is easy to conceive how this area is functionally important to our reaction to seen gaze.

2.7.3 Orbito-frontal cortex

Activation in response to averted gaze has also been reported to occur within the orbito-frontal cortex (Calder et al., 2002). This region has also been associated with theory of mind performance. The authors propose that the reason why averted gaze may differentially activate this region is that more computation is involved to work out the goals and intentions of a person with averted gaze relative to a person with direct gaze.
2.7.4 Amygdala

Several independent neuroimaging studies report distinct patterns of cortical activation depending on whether eye gaze is directed at the viewer or averted. A gaze monitoring study has reported that the right amygdala is specifically engaged when viewers watch a face making direct eye contact with them (Kawashima et al., 1999). Exploring passive face processing, it has been reported that engaged gaze activates the amygdala bilaterally (George et al., 2001). This activity was also found to enhance activity in the fusiform regions, again exemplifying the cross talk in the complex system. Direct gaze is a socially salient cue to which we must respond rapidly as it can signal both threat and affiliative approach and the amygdala would seem to be a key structure in signalling this.

In one patient with amygdala damage (DR), ability to judge direct gaze has been assessed and was found to be suboptimal (Young et al., 1995). Furthermore, individuals with autism, where anomalous amygdala function has been proposed are impaired both at laboratory tests of eye gaze (Howard et al., 2000) and at making appropriate eye contact and joint attention behaviours in everyday functioning (Charman et al., 1997).

2.8 A DISTRIBUTED FACE PROCESSING NETWORK

The middle parts of the fusiform gyri (the ‘face fusiform’ area) appear to be the critical ‘gateway’ to the face-processing circuitry - but thereafter many cortical
sites are recruited, depending on task, stimulus properties and individual 
differences. We should not expect less. Faces are probably the most visually 
complex, intrinsically meaningful visual stimuli with which we interact. They 
form part of a cognitive, an affective, and a social nexus within which we 
function. At least two interconnected right-dominant systems suggest 
themselves in face processing - a medial system (hippocampus, orbito-frontal 
cortex, amygdala) related to learning, social and affective value and salience 
of faces, and a lateral system (fusiform gyrus, superior temporal sulcus and 
middle lateral temporal gyri) that may be implicated in long-term face-
knowledge and the perception and production of a range of face acts. 
Different face processing tasks make differentially weighted demands on the 
same systems.

2.9 PREDICTIONS ABOUT FACE PROCESSING IN TURNER 
SYNDROME

In Chapter One, evidence for face processing deficits in TS was reviewed as a 
possible explanation for the social difficulties experienced by women with the 
syndrome. In most studies that had assessed this ability, face matching was 
found to be sub-optimal in both children and adults with the syndrome. In the 
current chapter, various additional aspects of face processing have been 
considered, including face recognition memory, famous face recognition and 
the recognition of facial expressions of emotion. The type of processing 
thought to be important for optimal face processing was also considered, with
an exploration of three partially distinct types of configural processing. None of these other types of face processing have been studied in Turner syndrome although all would seem to play an important role in normal social interaction.

If face-processing difficulties are related to social functioning difficulties in Turner syndrome, it is important to understand the nature of these difficulties more fully. In considering the exploration, in Chapter One, of the ways in which gene/behaviour relationships can be studied, could face processing difficulties be an endophenotypic marker for the anomalous social function experienced by women with Turner syndrome?

2.9.1 HYPOTHESES

1 TS women will have impaired face processing skills in the domains of...
   a. face matching
   b. face recognition memory
   c. familiar face recognition
   d. all aspects of facial emotion recognition
   e. configural face processing

2 Face processing abilities will correlate with visuo-spatial abilities in women with TS

3 Face processing abilities will correlate with social adjustment abilities in women with TS

4 Face processing abilities will correlate with age at which oestrogen supplementation commences for women with TS
CHAPTER SUMMARY

This chapter began by considering why there is such great interest in what to all intents and purposes would seem like a non-specific skill – our immense ability to recognise a limitless amount of faces. The fact that this ability could be selectively impaired following brain damage led to experimental techniques being applied which in turn led to notions of ‘special’ mechanisms that are important for face recognition. The right hemisphere typically would seem to play a greater role in face processing then left hemisphere. But moving away from the modularity research that dominated the 1980s and 90’s this chapter considered the many different cortical structures that contribute to a wide number of different aspects of face recognition.

Firstly, it considered evidence for the importance of configural visual processing in face recognition and the ways in which this type of processing has been measured. The proportion of this chapter dedicated to considering the role of the fusiform gyrus in face recognition goes just a small way towards reflecting the amount of journal coverage that this tiny brain region has been given over the past decade or so. This region of the inferior temporal lobe really does seem to have a unique ability to analyse visual stimuli to the level that is necessary to discriminate between the vast number of faces that we encounter. However, while the adequate function of this cortical structure may be ‘necessary’ for normal face recognition, it is by no means ‘sufficient’ and the remainder of this chapter focused upon the neural systems connected to the fusiform gyri that are also important to face processing.
A number of regions outside the fusiform gyri are recruited by different face processing tasks. Face perception may additionally involve parietal lobe regions. Face recognition memory would appear to make use of medial brain structures involved in memory and affective learning more generally including the hippocampus, amygdala and orbito-frontal cortex. The processing of facial expressions of emotion is also found to call on these sites and additionally places demands on the insula and basal ganglia. Other information from the face that is of social relevance includes eye gaze and lip movements and for these tasks the superior temporal sulcus would appear to have a particularly important role.

In considering the different elements of the face processing networks, I have highlighted the involvement of a number of these regions in other aspects of social functioning. It has been demonstrated that damage to various components of these neural circuits often results in difficulties with face processing and frequently in more wide-reaching difficulties in social functioning. The co-morbidity of these impairments demonstrates the interdependency of the functional mechanisms involved in face perception and social behaviour.

The neural circuits involved in the processing of faces are all highly interconnected and undoubtedly rely on much feedback and cross talk, particularly in the development and setting up of these specialised systems.
Finally, it was considered how our knowledge of face processing could inform our investigations of face processing in Turner syndrome. Many different aspects of face processing, in addition to face matching will be assessed in women with TS with the hypothesis being that impairments will be seen in all these domains. In Chapter Three, the mechanisms and neural regions involved in face processing will be used to inform a study of face processing in Turner syndrome.
3 CHAPTER THREE - METHODOLOGY

3.1 GROUP SELECTION CONSIDERATIONS AND CHARACTERISTICS

Standardised IQ assessments of girls and women with Turner syndrome frequently reveal depressed Performance IQs where Verbal IQ is within the normal range, reflecting their difficulties in visuo-spatial functioning. Since women with TS have an unusual profile of cognitive abilities, it would be difficult to match groups in terms of both Verbal and Performance IQ without having a control group that was not representative of the general population.

In the experiments reported in this thesis, participants were matched on a group basis in terms of Verbal IQ, as assessed by the Weschler Adult Intelligence Scale (WAIS). Performance IQ was then entered as a covariate in the group comparisons, using parametric statistics.

3.2 KARYOTYPE SPECIFICITY

Karyotypic differences within the TS population have not been satisfactorily dealt with in many previous studies with women with TS. As the studies reviewed in Chapter One demonstrate, different karyotypes, and ultimately the
presence or absence of different genes on the X-chromosome can have an impact on the phenotypic expression of Turner syndrome. In order to make conclusions about the importance of any genetic mechanisms to the resultant phenotype it is necessary to consider different karyotypes individually. The first study includes only those women who have been identified to have monosomie (45,X) Turner syndrome. None of the cases were found to have any evidence of mosaicism in the cell lines analysed.

As was also highlighted in Chapter One, the parental origin of the single remaining X-chromosome in monosomie TS has been reported to affect phenotypic expression, specifically concerning socio-cognitive abilities. Study One focused on individuals who have inherited their single X from their mother (45,X\textsuperscript{m}). Since girls with this karyotype have been found to have greater social adjustment difficulties (Skuse et al., 1997), it was hypothesised that face processing difficulties would be most readily detectable in this sub-group.

### 3.3 SAMPLE RECRUITMENT

Twenty three individuals with Turner syndrome (45,X\textsuperscript{m}) were recruited from a National survey of Turner syndrome, through the Child Growth Foundation and through a specialist clinic at the Middlesex Hospital. Formal written consent was obtained. Participants were invited to take part in this further phase of the research. An outline of the type of tasks to be administered was given, along with an estimate of the duration of the test session. Participants
then returned a slip, in a pre-paid envelope, indicating whether or not they were interested in taking part and furthermore the times of day and days of the week that would most convenient for them to be tested. Positive responses were followed up by a telephone call to arrange a test session and answer any questions that the subject may have about the study. For a small number of participants, testing arrangements were made through the participants’ parents.

Control participants were recruited by means of posters that were placed within Great Ormond Street Hospital, The Institute of Child Health and University College London. The posters advertised the study as involving taking part in some ‘fun psychological tests’ and informed participants that they would be paid £15 for their participation. Participants were invited to take part if they were female, between 18 and 36 years of age and had been resident in the UK for more than three years.

3.3.1 Response rates

Thirty 45,X\textsuperscript{m} women were approached to participate in the study. Twenty-five women consented to take part in the study, three declined and a further two failed to respond. Two of the participants were later excluded from analyses for reasons detailed below. Forty-five women responded to the advertisement for control participants. A screening interview on the telephone enabled the exclusion of individuals who
had known psychiatric or neurological disease (past or present), and of those who had not been resident in the UK for at least the past three years. Of the remainder of volunteers, participants were chosen for participation according to availability.

3.4 GROUP CHARACTERISTICS

3.4.1 Age

The women in both the TS and control groups were young adults, all between the ages of 18 – 36 years and groups were matched for age ($t (44) = .27$, $p = .79$). Age characteristics are shown in table 3.1.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XX (females)</td>
<td>23</td>
<td>25.30</td>
<td>4.53</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>45,X&lt;sup&gt;m&lt;/sup&gt; (Turner syndrome)</td>
<td>23</td>
<td>24.91</td>
<td>5.28</td>
<td>18</td>
<td>36</td>
</tr>
</tbody>
</table>

3.4.2 Ethnicity

Participants were asked to indicate their ethnicity as being one of the following White, Indian/Pakistani, Asian, African/Caribbean or other. All women in the TS group were of Caucasian ethnicity as were the majority of control
participants, except one who was African/Caribbean and another who was Indian/Pakistani.

### 3.4.3 Educational level

Participants indicated the highest educational level that they had attained out of the following options: No exam qualifications, GCSE/O-Level, Secretarial or technical, A-Level, Professional qualification without University degree (e.g. SRN, teaching diploma, HNC, TEC), University degree (or equivalent). Proportions for each educational level can be seen in table 3.2. The control females on average attained a higher level of educational qualification, with a mean rank that was significantly higher than that for the TS women according to Mann-Whitney test statistics ($46,XX$ females $=27.76$, $45,X^m$ TS $= 19.24$, $U=166.5$, $p=.03$).
<table>
<thead>
<tr>
<th>Educational qualifications</th>
<th>46,XX (females)</th>
<th>45,Xm (Turner syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
</tr>
<tr>
<td></td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GCSE/O-Level</td>
<td>3  13.0</td>
<td>7  30.4</td>
</tr>
<tr>
<td>Secretarial/Technical</td>
<td>-</td>
<td>2  8.7</td>
</tr>
<tr>
<td>A-Level</td>
<td>3  13.0</td>
<td>5  21.7</td>
</tr>
<tr>
<td>Professional qualification</td>
<td>5  21.7</td>
<td>3  13.0</td>
</tr>
<tr>
<td>University degree</td>
<td>12  52.2</td>
<td>6  26.1</td>
</tr>
</tbody>
</table>

3.4.4 Social class

Participants occupations were classified according to the Standard Occupational Classification 2000 (Office of National Statistics, 2000). Thirty percent of the TS women were in the two highest groups (managers/senior officials, and professional occupations), 26% were in the following two groups (associate professional and technical occupations, and administrative and technical occupations), and 44% in the lower groups. For the control group, the respective percentages were 21%, 75% and 4%. Proportions for each level can be seen in table 3.3. The mean rank of the women in both groups was highly similar according to Mann-Whitney test statistics (46,XX females =22.13, 45,Xm TS = 24.87, U=233.00, p=.48).
Table 3.3: Social group classification

<table>
<thead>
<tr>
<th>Occupation</th>
<th>46,XX (females) n=23</th>
<th></th>
<th>45,Xm (Turner syndrome) n=23</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Unemployed (not classified)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>1. Managers/Senior officials</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>2. Professional occupations</td>
<td>4</td>
<td>17.4</td>
<td>6</td>
<td>26.1</td>
</tr>
<tr>
<td>3. Associate professional &amp; technical</td>
<td>10</td>
<td>43.5</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>4. Administrative &amp; secretarial</td>
<td>8</td>
<td>34.8</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>5. Skilled trades</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>6. Personal Service</td>
<td>1</td>
<td>4.3</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>7. Sales/Customer service</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>8. Elementary</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4.3</td>
</tr>
</tbody>
</table>
3.4.5 IQ

Participants were excluded if their Verbal IQ was below 70. This led to the exclusion of one individual with TS but none of the control volunteers. Controls were matched to the TS group for Verbal IQ. The IQ distributions of the groups can be seen in table 3.4. The women with 45,Xm (TS) had a significantly lower mean Performance IQ as is typically reported. However, groups were matched for Verbal IQ.

Table 3.4: Mean WAIS IQ scores

<table>
<thead>
<tr>
<th></th>
<th>46,XX (females)</th>
<th>45,Xm (TS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>mean 99.57</td>
<td>mean 98.30</td>
<td>sd 11.64</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>mean 105.70</td>
<td>mean 94.52</td>
<td>sd 11.44</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>mean 102.30</td>
<td>mean 96.30</td>
<td>sd 11.58</td>
</tr>
</tbody>
</table>

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3.5 MEASURES OF GENERAL FUNCTIONING

3.5.1 Performance IQ (PIQ)

The Picture Completion, Block Design and Digit Symbol sub-tests of the WAIS-R (Wechsler, 1981) were administered and scores pro-rated to provide an estimate of Performance IQ (Ward & Ryan, 1996). A short version was used due to time constraints and the sub-tests chosen because they correlate strongly with full Performance IQ.

3.5.2 Verbal IQ (VIQ)

To give an estimate of Verbal IQ, four sub-tests of the WAIS were used: Information, Digit Span (which is also related to verbal memory), Arithmetic and Similarities. These sub-test scores were then pro-rated. A short version was used due to time constraints and the sub-tests chosen because they correlate strongly with full Verbal IQ (Ward et al., 1996).

3.5.3 Verbal memory

The word subtest of the Recognition Memory Test (RMT, (Warrington, 1984)) was administered. In this test, 50 printed words were shown individually to participants, to rate as pleasant or unpleasant. Before being shown the words, participants were told that it was a ‘test of memory for words’.
Immediately after presentation, the words were presented one at a time, each one accompanied by a new foil. A forced choice procedure required the participant to choose the one that had been presented previously. The dependent variable was choice accuracy (/50).

3.6 TESTS OF FACE RECOGNITION

3.6.1 The Benton Test of Facial Recognition - short form (Benton, Hamsher, Varney, & Speen, 1983)

This test provides a standardised procedure for assessing discrimination of face images presented as halftone images. It is a graded test. The first part requires matches of identical face images, where one image is presented on one sheet and the recognition set on the sheet below. In the harder parts of the test, a front view image of a face has to be matched for identity to three faces from a set seen from different viewing angles (3/4 or full face), and under different lighting conditions (from above, left or right). Raw scores were adjusted to give estimated long form scores (Benton et al., 1983).

3.6.2 Warrington face recognition task

This was a forced choice recognition test for halftone images of male faces that used an identical presentation procedure as the word recognition test.
above (Warrington, 1984). This recognition task was administered directly after the word sub-test of the Warrington recognition memory test.

### 3.6.3 Familiar face recognition

This test was computer administered. First, a set of photographs of 50 famous people was chosen, all of which were named accurately on presentation by at least 17 out of 20 women (age range 18-36 years) who did not take part in the experiment proper. The face-images were downloaded from copyright-free sites on the worldwide web and digitally manipulated to generate halftone images of similar size and general appearance. The identities of the famous individuals in each group (cropped and uncropped) are shown in table 3.5 with identification rates (out of twenty) for the initial standardisation study.

In the experiment itself, participants were asked to name the individual within 20 seconds of display onset. There were two presentation conditions, one for each half-set of 25 faces. In the *cropped* condition, the facial features were close-cropped using a rectangular frame to remove facial outline and hairstyle, but leaving eyes, nose and mouth fully visible. Under these conditions, only facial features, and their configuration (i.e. relative distances between features and overall disposition with respect to each other) could be used to identify the face. In the other condition, *the whole head* condition, faces were presented whole, including hairstyle and general contour. Examples of cropped and uncropped images are shown in figure 3.1.
Table 3.5: Identification rates of the famous people from the initial standardisation experiment.

<table>
<thead>
<tr>
<th>Group 1 (cropped)</th>
<th>Group 2 (uncropped)</th>
</tr>
</thead>
<tbody>
<tr>
<td>name</td>
<td>Correct id /20</td>
</tr>
<tr>
<td>Arnold Schwarzenegar</td>
<td>20</td>
</tr>
<tr>
<td>Charlie Chaplin</td>
<td>20</td>
</tr>
<tr>
<td>Princess Diana</td>
<td>20</td>
</tr>
<tr>
<td>Elvis</td>
<td>20</td>
</tr>
<tr>
<td>Queen Mother</td>
<td>20</td>
</tr>
<tr>
<td>Richard Branson</td>
<td>20</td>
</tr>
<tr>
<td>Tony Blair</td>
<td>20</td>
</tr>
<tr>
<td>Cherie Booth/Blair</td>
<td>20</td>
</tr>
<tr>
<td>William Hague</td>
<td>19</td>
</tr>
<tr>
<td>Hugh Grant</td>
<td>19</td>
</tr>
<tr>
<td>Leonardo DiCaprio</td>
<td>19</td>
</tr>
<tr>
<td>Madonna</td>
<td>19</td>
</tr>
<tr>
<td>Tom Cruise</td>
<td>19</td>
</tr>
<tr>
<td>Richard Gere</td>
<td>19</td>
</tr>
<tr>
<td>Joan Collins</td>
<td>18</td>
</tr>
<tr>
<td>Andre Agassi</td>
<td>18</td>
</tr>
<tr>
<td>Einstein</td>
<td>18</td>
</tr>
<tr>
<td>Elton John</td>
<td>18</td>
</tr>
<tr>
<td>Harrison Ford</td>
<td>18</td>
</tr>
<tr>
<td>Terry Wogan</td>
<td>18</td>
</tr>
<tr>
<td>Carol Vorderman</td>
<td>18</td>
</tr>
<tr>
<td>Catherine Zeta-Jones</td>
<td>17</td>
</tr>
<tr>
<td>Paddy Ashdown</td>
<td>17</td>
</tr>
<tr>
<td>Michelle Pfeffer</td>
<td>17</td>
</tr>
<tr>
<td>Prince William</td>
<td>17</td>
</tr>
</tbody>
</table>
Scoring took account of distinguishing information given by the respondent when they were unable to name the face. Responses were scored correct when distinctive semantic information (i.e. a specific role played by a TV actor) was given. These scores were further corrected for knowledge of the individual. Following presentation of the faces, participants were given the names of the individuals seen and asked what they knew about them. Recognition scores were calculated based on only those individuals for whom they demonstrated adequate individual knowledge (*Corrected score*).
3.6.4 Incidental face recognition

In this computer-based test, unfamiliar face images that had been seen earlier in the test session (part/whole and face inversion – for details, see next section) were presented for recognition. The target set comprised 22 grey-scale face images and 22 distracter faces chosen to be similar in general appearance to the target faces. The new and old faces appeared one at a time in a randomised order in the centre of the computer screen for old/new decision. The dependent variable was accuracy of recognition, measured using a sensitivity measure, Pr', which takes account of both hits and correct rejections (Snodgrass & Corwin, 1988).

3.7 TESTS OF CONFIGURAL FACE PROCESSING

These tests were designed to probe face-processing style, without implicating memory for known faces directly. They assess three partially distinct areas of configural processing.
3.7.1 Mooney Face recognition (Sensitivity to first-order relations)

Mooney faces are hand-painted images of human faces rendered in photographic half tone (Mooney, 1957). It has been suggested (de Haan & Campbell, 1991) that the perception of these patterns as faces may require the ability to detect (facial) shape from shading. It is also thought to require gestalt-closure abilities (holistic processing). According to Maurer's definitions of configural processing discussed in Chapter Two (Maurer, Le Grand, & Mondloch, 2002), detecting the presence of a face in these stimuli requires sensitivity to first-order relations. Foils were also constructed from parts of Mooney images in which no face was present (see figure 3.2).

Figure 3.2: A Mooney face (on the left) and a foil (on the right).

Images were presented on a computer screen. In the practice series, 3 faces and one foil were seen. In the main experiment, there were 25 faces and 5 foils – these appeared in a randomised order in each block. There were two blocks giving 60 trials in total. Participants pressed a key to indicate whether a face was present. If they indicated the presence of a face, they then pressed a
key to indicate ‘yes’ or ‘no’ to the following questions: ‘Is it male?’ & ‘Is it young (under 50)?’ The dependent variable was the Pr’ prime score based on ‘correct’ and ‘incorrect’ responses.

3.7.2 Whole and part-face matching. (Holistic processing)

According to Maurer (Maurer et al., 2002), the reason that we are better at matching whole faces than individual parts of faces is that we process faces in a holistic way that ‘glues together’ the features. If individuals’ process faces in this manner then they should demonstrate an advantage for matching whole faces compared to just the eyes or just the mouths. In addition, different face parts are of different emotional significance with the upper face (eyes) generally conveying more information about feelings, thought and intentions (Baron-Cohen, Wheelwright, & Joliffe, 1997). Perhaps then, accuracy for matching upper and lower face stimuli may differ according to the social and emotional competencies of the individual. Indeed, children with autism have been found to be selectively impaired at using the eye region to identify faces (Langdell, 1978). This task examined accuracy at matching whole full-face images compared with matching just the upper face or just the lower face. A similar procedure was used to that outlined above (X-AB recognition paradigm, using similar presentation schedules). Twelve matched pairs of faces were seen under three presentation conditions (96 trials). A pair of items presented for
recognition followed the target image, which was presented first. The stimuli could be whole face, upper-face or lower-face (represented in figure 3.3). Condition (whole/upper/lower) was unpredictable from trial to trial. Participants again chose the left or right image in the recognition array by pressing the left or right marked key of the computer keyboard. The dependent variables were the percentage of correct responses for each of the three conditions.

Figure 3.3: Examples of a whole, lower and upper face stimulus set.

3.7.3 Upright and inverted face matching (Sensitivity to second-order relations)

What Daphne Maurer (Maurer et al., 2002) describes as sensitivity to second-order relations can be assessed using a facial inversion task. Sensitivity to second-order relations involves representing the distances between face features. This ability is thought to underlie skilled adult face recognition but is disrupted when faces are inverted and the distance relations between the parts altered. If individuals are processing faces in a configural manner,
sensitive to the second-order relations, they should be more accurate at matching faces when presented in an upright orientation rather than when they are inverted.

In this task, a face image appeared on the computer screen for matching to an immediately aftercoming target. The orientation of the image varied unpredictably. It could be upright in both presentation and recognition phase – or it could be upside-down in both phases.

Each trial proceeded as follows: Following practice (24 trials – of which 12 were upright and 12 inverted, where no feedback was given) a fixation cross appeared for 250 msecs followed by a face image for 250 msecs. This was followed by a laterally arranged pair of face images, one of which was the previously seen face. Participants were instructed to press the key on the side at which the target appeared. The process is represented diagrammatically in figure 3.4. The only feedback given during the experiment was non-specific praise. The 32 grey-scale images (16 pairs) were matched in terms of sex, age, luminance, contrast and general appearance. Each pair appeared 4 times in the upright condition and 4 times in the inverted condition, giving 128 trials. Image size was approximately 8cm by 6cm on the computer monitor used in testing. The dependent variables were the percentage of correct choices for the upright and the inverted face conditions, for each participant.
Both faces presented simultaneously until response is made

Figure 3.4: Example of a trial from inversion experiment.
3.8 FACIAL EXPRESSION CATEGORISATION

3.8.1 The Ekman-Friesen Test of Affect Recognition

Participants were shown 60 photographic half-tone face images derived from the Ekman set (Ekman & Friesen, 1976). In these, 10 different individuals posed the six basic emotions: happiness, surprise, fear, sadness, disgust and anger, using the FACS posing method (Ekman et al., 1976) (examples are shown in figure 3.5). These were shown as single, card-mounted (15cm x 10cm) images to participants. The six emotion labels were also provided. Participants selected one of six emotion labels to match to the face. The dependent variable was the number of correct responses (/10) for each expression.
Figure 3.5: Examples of the six 'basic' facial expressions of emotion used in the Ekman-Friesen task.
3.9 OVERALL PROCEDURE

All participants were tested individually in a quiet room either within their own home or at the Institute of Child Health. Tests were administered in a single session lasting approximately 2 ½ hours, with appropriate breaks given as necessary to minimise fatigue. The order of administration of the tasks was identical for all participants. The session commenced with tests of face processing style: inverted face matching, part-whole face matching and Mooney faces, followed by tests of face recognition: Famous face recognition, Benton face recognition, the emotion recognition task and the Warrington memory task. The WAIS was administered at the end of the test session with the final task being the incidental face memory task. It was not possible for the experimenter to be blind to the group membership of the participants.
recognition and full scale IQ do not remain significant after Bonferroni corrections for multiple comparisons.

Hypothesis Two was not supported. Performance IQ, used here as a measure of visuo-spatial processing, failed to correlate with face processing skills in either the TS women or the control female participants.

4.6.2 Face processing and social function

It was predicted that face-processing abilities would correlate with social function. For twenty of the twenty-three participants with TS, Autism Quotient subscale scores were available (see Chapter One for a description) (Baron-Cohen et al., 2001). This self-report questionnaire asks participants to respond to fifty questions (of which 10 comprise the social sub-scale) indicating whether the statements are true of them or not. The TS women had scores ranging between 0 and 10, with a mean score of 2.8, which is higher than you would expect in a normal population {Baron-Cohen, Wheelwright, et al. 2001 878 /id}.

Contrary to predictions made in Hypothesis Three, this scale failed to correlate with any measured indices of face processing ability. It may be that there is no direct relationship between the two abilities. However, it is possible that a self-report questionnaire is not the best way to assess social function in this population. At an observational level, it has been noted that there may be
some lack of insight into their social difficulties. In order to assess the validity of the ASQ social subscale in this population, the relationship was assessed between one of the items and an objective behavioural measure that could be seen to tap the ability in question.

One of the items in the questionnaire is 'I find it easy to work out what someone is thinking or feeling just by looking at their face'. The Ekman-Friesen test of affect recognition looks at just this ability (Ekman et al., 1976). Forty five percent (9/20) of the TS women had accuracy scores of 50% (5/10) or less for recognising the emotion of fear in facial expressions. Despite this, only 25% of the women with TS answered the question on the ASQ to indicate that they were aware that they did not ‘find it easy to work out what someone was thinking or feeling just by looking at their face.’ Furthermore when these results were probed further it did not appear to be the women with the lowest fear recognition scores that were indicating that they had difficulty in this domain (see table 4.3).

The women who indicated on the questionnaire that they found it easy to 'work out what someone was thinking or feeling just by looking at their face' were LESS accurate at recognising fear from facial expressions than their counterparts who said that they DID NOT ‘find it easy to work out what someone was thinking or feeling just by looking at their face.’ This difference was not significant according to an Independent samples t-test (t=-.987, df=18, p=.337). However, the result does suggest that the validity of this self-report questionnaire may be questionable, at least in this population. This item
addressing the ability to tell what someone is feeling from their face is not
good at discriminating women with TS who have poor fear recognition abilities
from those who are good at recognising fear from facial expressions.

Hypothesis Three was not supported. Face-processing abilities failed to
correlate with a questionnaire measure of social adjustment. However, the
validity of the social adjustment instrument in this population is questionable.
### Fear recognition score /10

<table>
<thead>
<tr>
<th>'I find it easy to work out what someone is thinking or feeling just by looking at their face'</th>
<th>'I DO NOT find it easy to work out what someone is thinking or feeling just by looking at their face'</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=15</td>
<td>n=5</td>
</tr>
<tr>
<td>2 (39)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>3 (43)</td>
<td>7 (46)</td>
</tr>
<tr>
<td>3 (37)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>3 (37)</td>
<td>7 (52)</td>
</tr>
<tr>
<td>4 (43)</td>
<td>8 (54)</td>
</tr>
<tr>
<td>4 (32)</td>
<td></td>
</tr>
<tr>
<td>5 (48)</td>
<td></td>
</tr>
<tr>
<td>5 (43)</td>
<td></td>
</tr>
<tr>
<td>6 (39)</td>
<td></td>
</tr>
<tr>
<td>6 (42)</td>
<td></td>
</tr>
<tr>
<td>7 (49)</td>
<td></td>
</tr>
<tr>
<td>7 (54)</td>
<td></td>
</tr>
<tr>
<td>8 (44)</td>
<td></td>
</tr>
<tr>
<td>9 (54)</td>
<td></td>
</tr>
<tr>
<td>10 (56)</td>
<td></td>
</tr>
</tbody>
</table>

Mean = 5.47 (44)  Mean = 6.60 (48)

Table 4.3: Comparison of individual participant scores for fear recognition dependent on whether they indicated they found it easy to tell what someone was feeling by looking at their face. (In brackets are total emotion recognition scores out of 60)
4.6.3 Face processing and oestrogen supplementation

All of the TS women were receiving oestrogen supplementation due to an innate deficiency. Contrary to Hypothesis Four, age at which oestrogen supplementation commenced failed to correlate with any of the test variables in this study.

4.6.4 Correlations between face recognition and configural face processing

Pearson correlations were computed separately for each group. Table 4.4 shows no significant correlations between any of the face recognition measures for females with TS. However, for the control females (table 4.5) the Warrington face recognition and Famous face recognition tasks were significantly positively correlated, although this was the case for no other measures.
Table 4.4: Pearson correlations between tests of face recognition – TS females

<table>
<thead>
<tr>
<th></th>
<th>Benton face recognition</th>
<th>Warrington face recognition</th>
<th>Famous face recognition</th>
<th>Incidental face recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=23 Benton</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrington Face recognition</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famous face recognition</td>
<td></td>
<td>.362</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Incidental face recognition</td>
<td></td>
<td>.201</td>
<td>.264</td>
<td>1.00</td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td>.340</td>
<td>.284</td>
<td>.172</td>
</tr>
</tbody>
</table>

Table 4.5: Pearson correlations between tests of face recognition – Control females

<table>
<thead>
<tr>
<th></th>
<th>Benton face recognition</th>
<th>Warrington face recognition</th>
<th>Famous face recognition</th>
<th>Incidental face recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=23 Benton</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrington Face recognition</td>
<td></td>
<td>.109</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Famous face recognition</td>
<td></td>
<td>.324</td>
<td>.435*</td>
<td>1.00</td>
</tr>
<tr>
<td>Incidental face recognition</td>
<td></td>
<td>.210</td>
<td>.339</td>
<td>.239</td>
</tr>
</tbody>
</table>

*p<.05 (two-tailed)
In performing correlations on the configural face processing tests, new variables were calculated for the Inversion and Part/Whole task to reflect the critical configural processing ability. For the face inversion task, the difference between the upright and inverted conditions was the DV:

\[
\text{Inversion decrement} = \text{upright accuracy} - \text{inverted accuracy}
\]

For the Part/Whole task the difference between whole face matching and Part face matching was computed:

\[
\text{Holistic processing} = \frac{\text{whole matching} - (\text{upper face} + \text{lower face matching})}{2}
\]

Within the tests of configural face processing, for both the TS and control groups the only correlations to reach significance were the ones between holistic processing and inversion decrement (see table 4.6). Neither of these measures correlated with Mooney face recognition.

Correlation matrices were then computed between tests of face recognition and tests of configural face processing, separately for both groups. The only significant correlation in either group was between Mooney face recognition and incidental face recognition for the control females (Pearson correlation .517, p<.05). The correlation was no longer significant after Bonferroni corrections for multiple comparisons. No other associations between configural face processing and face recognition approached significance.
Table 4.6: Correlations between measures of configural face processing – TS women

<table>
<thead>
<tr>
<th></th>
<th>Mooney face recognition (sensitivity to 1&lt;sup&gt;st&lt;/sup&gt; order relations)</th>
<th>Whole-part face recognition (holistic processing)</th>
<th>Upright-inverted Face recognition (sensitivity to 2&lt;sup&gt;nd&lt;/sup&gt; order relations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooney face recognition (sensitivity to 1&lt;sup&gt;st&lt;/sup&gt; order relations)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing)</td>
<td>-.137</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2&lt;sup&gt;nd&lt;/sup&gt; order relations)</td>
<td>-.120</td>
<td>.615**</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 4.7: Correlations between measures of configural face processing – Control females

<table>
<thead>
<tr>
<th></th>
<th>Mooney face recognition (sensitivity to 1&lt;sup&gt;st&lt;/sup&gt; order relations)</th>
<th>Whole-part face recognition (holistic processing)</th>
<th>Upright-inverted Face recognition (sensitivity to 2&lt;sup&gt;nd&lt;/sup&gt; order relations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooney face recognition (sensitivity to 1&lt;sup&gt;st&lt;/sup&gt; order relations)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing)</td>
<td>.389</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2&lt;sup&gt;nd&lt;/sup&gt; order relations)</td>
<td>.258</td>
<td>.447*</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed)  
** p<.01 (two-tailed)  
*** p<.001 (two-tailed)
Correlations between emotion recognition variables were then assessed. The only significant correlation was for the TS women between Anger and Sadness recognition (Pearson correlation co-efficient = .657, p=.001) which remained significant after Bonferroni corrections for multiple comparisons. No other correlations were significant.

4.6.5 Face memory and emotion recognition

Patients with amygdala lesions are reported to be specifically impaired in classifying and responding to fearful facial expressions (Adolphs et al., 1999). This deficit in emotional facial expression recognition can be associated with an additional impairment in face identity memory (Young et al., 1995). From this, a new hypothesis was formulated.

Face recognition memory performance would be correlated with the recognition of fear from facial expressions.

Bivariate correlations (Pearson’s test) were calculated for individual expression scores below ceiling level (surprise, anger, disgust, sadness and fear, but not happiness) with face recognition scores and configural face processing scores. These were run separately for each subject group. The results are shown in table 4.8 and 4.9.

‘Fear’ scores – and only fear scores - correlated strongly with recognition accuracy in controls. However, in TS, the correlation failed to reach
significance, and the pattern of correlations generally seemed more variable. Bonferroni corrections for multiple testing failed to eliminate the significant correlations between fear and Warrington face memory (p<.005). A test of differences was applied to the independent correlations for each group (Pearson), following the 'Hyperstat' method (davidmlane.com/hyperstat). This tests the difference between the magnitudes of two correlations. This gave $z = 1.96$, $p = .03$ for the Warrington task, although a similar pattern of results failed to reach significance for the familiar faces task ($z=1.32$, $p=.09$). Only the correlation of fear with Warrington recognition scores was significantly greater in the controls than in the TS group. Thus, Hypothesis Five was partially supported. Fear and face recognition abilities were correlated in control participants.

\[ z = \frac{r_1 - r_2}{\sqrt{\frac{1}{n_1 - 3} + \frac{1}{n_2 - 3}}} \]
Table 4.8: Correlations between emotion recognition scores and face recognition and configural processing measures – TS females.

<table>
<thead>
<tr>
<th>N=23</th>
<th>Happiness recognition</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton face recognition</td>
<td>-.199</td>
<td>.139</td>
<td>.306</td>
<td>.361</td>
<td>.512*</td>
<td>.270</td>
</tr>
<tr>
<td>Warrington face recognition</td>
<td>-1.32</td>
<td>.004</td>
<td>.315</td>
<td>.102</td>
<td>.425*</td>
<td>.218</td>
</tr>
<tr>
<td>Famous face recognition</td>
<td>-2.32</td>
<td>.527**</td>
<td>.218</td>
<td>-.083</td>
<td>.393</td>
<td>.195</td>
</tr>
<tr>
<td>Incidental face recognition</td>
<td>.001</td>
<td>.267</td>
<td>.218</td>
<td>.247</td>
<td>.712***</td>
<td>.382</td>
</tr>
<tr>
<td>Mooney face recognition (sensitivity to 1st order relations)</td>
<td>.069</td>
<td>.202</td>
<td>.149</td>
<td>-.024</td>
<td>-.009</td>
<td>-.053</td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing)</td>
<td>-.309</td>
<td>.072</td>
<td>-.006</td>
<td>.335</td>
<td>-.192</td>
<td>.397</td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2nd order relations)</td>
<td>-.022</td>
<td>-.117</td>
<td>.237</td>
<td>-.197</td>
<td>.213</td>
<td>-.356</td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed)  
** p<.01 (two-tailed)  
*** p<.001 (two-tailed)  

- no longer remain significant after Bonferroni corrections for multiple comparisons
Table 4.9: Correlations between emotion recognition scores and face recognition and configurual processing measures – Control females.

<table>
<thead>
<tr>
<th></th>
<th>Happiness recognition</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton face recognition #</td>
<td>-.152</td>
<td>.366</td>
<td>.214</td>
<td>.090</td>
<td>.187</td>
<td></td>
</tr>
<tr>
<td>Warrington face recognition #</td>
<td>-.370</td>
<td>.735***</td>
<td>.216</td>
<td>-.019</td>
<td>.121</td>
<td></td>
</tr>
<tr>
<td>Famous face recognition #</td>
<td>-.172</td>
<td>.564**</td>
<td>.205</td>
<td>-.028</td>
<td>.143</td>
<td></td>
</tr>
<tr>
<td>Incidental face recognition #</td>
<td>-.037</td>
<td>.387</td>
<td>.006</td>
<td>-.009</td>
<td>.069</td>
<td></td>
</tr>
<tr>
<td>Mooney face recognition (sensitivity to 1st order relations) #</td>
<td>.022</td>
<td>.376</td>
<td>.394</td>
<td>-.016</td>
<td>.216</td>
<td></td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing) #</td>
<td>.130</td>
<td>.029</td>
<td>-.129</td>
<td>-.098</td>
<td>.277</td>
<td></td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2nd order relations) #</td>
<td>.023</td>
<td>-.151</td>
<td>.190</td>
<td>.258</td>
<td>.196</td>
<td></td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed) ** p<.01 (two-tailed) *** p<.001 (two-tailed)

no longer remain significant after Bonferroni corrections for multiple comparisons.
The only correlation to remain significant in the TS group after Bonferroni corrections for multiple comparisons was that between Disgust and Incidental face recognition.

Are emotion recognition abilities correlated with configural face processing abilities? Pearson correlations were computed for all emotion recognition and configural face processing variables. Configural face processing scores failed to correlate with any of the emotion recognition scores for either group.

4.7 CHAPTER SUMMARY

Women with Turner syndrome (45,X<sup>m</sup>) performed more poorly than the control participants on all measures of face recognition. They had difficulties matching concurrently presented faces on the Benton face recognition task, and difficulties with various aspects of face learning and memory assessed by different tasks. They also performed poorly on a task assessing recognition of facial expressions of emotion. The women with TS performed at an overall lower level on the Ekman-Friesen pictures of facial affect than the control group. This deficit is primarily the result of difficulties with two negative emotions. Fear and (to a lesser extent) anger were both significantly impaired in women with TS.

The women with TS, however, showed typical sensitivity to configural aspects of faces and appeared able to process faces in a configural manner. They
demonstrated normal inversion effects, being more accurate at matching upright than inverted faces, were able to detect Mooney faces and were more accurate at matching whole faces than parts of faces.

Highly significant correlations were reported between fear recognition and face recognition memory for the control participants but not for the women with TS. Verbal and Performance IQ failed to correlate with any of the face processing measures in either group as did age at which oestrogen supplementation commenced for the women with TS.

Women with Turner syndrome with a single X-chromosome that is maternally inherited (45,Xm) display numerous subtle face-processing difficulties. As was predicted, they have poorer face recognition, learning, memory and emotion recognition from faces than control females. However, contrary to predictions they showed normal configural processing of faces.

With regard to the genetic mechanisms that may lead to the face recognition difficulties in TS, at least two possibilities exist. The women studied all had just one intact X-chromosome that had been inherited from their mother. Therefore, the phenotype observed could be the result of haploinsufficiency (insufficient dosage) for genes on the X-chromosome that would normally be expressed from both X-chromosomes in typically developing females.

However, the phenotype could also result from an insufficient dosage of genes that are expressed on the paternally inherited X-chromosome but which
are silenced on the maternally inherited X (the imprinting hypothesis). If this second scenario were true, face recognition difficulties would not be evident in females who had a single paternal X-chromosome (45,X\textsuperscript{p}). Study Two tested the hypothesis that an imprinted gene(s), which is expressed only on the paternal X-chromosome, influences the development of face and emotion recognition abilities. It was therefore predicted that women with TS and a paternal X-chromosome would not have the face and emotion recognition difficulties seen in women with a maternally inherited X-chromosome. This was based on the previous finding that women with a single paternally derived X-chromosome had better social adjustment than those with a single maternally derived X-chromosome.
5  CHAPTER FIVE - STUDY TWO – TESTING THE IMPRINTING HYPOTHESIS

5.1.1 OVERVIEW

From Study One, it emerged that individuals with Turner syndrome who had inherited their single X-chromosome from their mother (45,X<sup>m</sup>) performed more poorly than a control group on various tasks of face recognition. Covarying for Performance IQ did not ameliorate group differences. This suggests that the difficulties with face processing in this population may be relatively independent of the visuo-spatial (& parietal) deficits encountered by many women with TS. Moreover, typical configural face processing abilities were evident on tasks designed to establish face perception skills, suggesting that infero-temporal structures involved in face recognition may develop relatively normally. Difficulties with faces experienced by these women may therefore be related to their social-affective value.

Previous research has suggested that the social cognitive dysfunction in Turner syndrome may be significantly greater for women who have inherited their single X from their mother (45,X<sup>m</sup>) than for those who have inherited their single X from their father (45,X<sup>p</sup>) (Skuse et al., 1997). Genomic imprinting may therefore be at work; whereby genes are differentially expressed depending
on the sex of the parent that passes on the gene. Skuse proposed that a
genetic locus (or loci) might exist on the X-chromosome that is expressed
when inherited paternally but silenced when inherited maternally. This locus
was proposed to influence social cognition since women with a single
maternally inherited X-chromosome were found to exhibit greater socio-
cognitive dysfunction than those with a single paternally inherited X.

If face processing difficulties in TS are linked to social cognitive dysfunction
then one might expect to find fewer difficulties in the women who have a
paternally inherited X (45,X\textsuperscript{p}) than those women with a maternally inherited X.

To test whether face recognition difficulties would be present and if so, to
what degree, among TS women with a paternally inherited X, a new sample of
women (half of whom had a maternally inherited X, and half of whom had a
paternally inherited X) was investigated. The sixth hypothesis to be tested
was...

6 Women with TS with a paternally inherited X-chromosome will have better
face processing skills than women with TS with a maternally inherited X-
chromosome.

The parental origin of the single X-chromosome was determined using
cytogenetic analyses as described elsewhere (Jacobs et al., 1997). The
analysis took place at the Wessex Regional Genetics Laboratory in
collaboration with Professor Jacobs and Dr. Thomas. For seventy percent of
individuals with monosomic TS the single X has been inherited from the mother with the remainder inherited from their father (Jacobs et al., 1997). This study selected equal numbers of each group of individuals, matched for age and Verbal IQ, in order to assess group differences.

5.2 METHODOLOGY

5.2.1 Sample recruitment

Forty individuals with monosomic Turner syndrome (45,X) were recruited from a National survey of Turner syndrome, through the Child Growth Foundation and through a specialist clinic at the Middlesex Hospital. All participants had previously consented to taking part in an ongoing TS research project at the Institute of Child Health but none of the participants were the same as those used in Study One. Participants were recruited by the same procedure as described for Study One. The experimenter was blind to the parental origin of the intact X-chromosome. Two participants were unable to participate. Nineteen individuals with a 45,X<sup>m</sup> karyotype and nineteen with a 45,X<sup>p</sup> karyotype participated in the study.
5.2.2 Sample characteristics

5.2.2.1 Age

The women in both the 45,X\textsuperscript{m} and 45,X\textsuperscript{p} groups were young adults, all between the ages of 16 – 44 years. The groups were matched for age (t (32.26) = .872, p=.390), with characteristics shown in table 5.1.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X\textsuperscript{m} (maternal)</td>
<td>19</td>
<td>24.21</td>
<td>9.48</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>45,X\textsuperscript{p} (paternal)</td>
<td>19</td>
<td>21.89</td>
<td>6.65</td>
<td>16</td>
<td>38</td>
</tr>
</tbody>
</table>

5.2.2.2 Ethnicity

Participants were asked to indicate their ethnicity as being one of the following: White, Indian/Pakistani, Asian, African/Caribbean or other. All of the 45,X\textsuperscript{p} women classified themselves as White. Amongst the 45,X\textsuperscript{m} individuals, all were White except one who classified herself as Other.
5.2.2.3 Educational level

Participants indicated the highest educational level that they had attained out of the following options: No exam qualifications, GCSE/O-Level, Secretarial or technical, A-Level, Professional qualification without University degree (e.g. SRN, teaching diploma, HNC, TEC), University degree (or equivalent).

Proportions for each educational level were similar across the groups as can be seen in table 5.2. The mean ranks of the groups were not significantly different according to Mann-Whitney test statistics ($45,X^m = 19.05$, $45,X^o = 19.95$, $U = 172$, $p = .79$).
Table 5.2: Maximum level of educational qualification achieved

<table>
<thead>
<tr>
<th>Educational qualifications</th>
<th>45,X&lt;sup&gt;m&lt;/sup&gt; (maternal)</th>
<th>45,X&lt;sup&gt;p&lt;/sup&gt; (paternal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=19</td>
<td>n=19</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>GCSE/O-Level</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>Secretarial/Technical</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A-Level</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Professional qualification</td>
<td>4</td>
<td>21.1</td>
</tr>
<tr>
<td>University degree</td>
<td>2</td>
<td>10.5</td>
</tr>
</tbody>
</table>

5.2.2.4 Social class

Participant-occupations were classified according to the Standard Occupational Classification 2000 (Office of National Statistics, 2000). The classification included nine groupings: 1. Managers/Senior officials, 2. Professional occupations, 3. Associate professional and technical occupations, 4. Administrative/secretarial occupations, 5. Skilled trades, 6. Personal service occupations, 7. Sales/Customer service occupations, 8. Process/plant/machine occupations, 9. Elementary occupations. None of the participants were classified as belonging to groups 1, 5 or 7, as can be seen from table 5.3. The mean rank of the women is not significantly different for the two karyotypes (45,X<sup>m</sup> = 16.39, 45,X<sup>p</sup> = 21.75, U=121.5, p=.09).
### Table 5.3: Social group classification

<table>
<thead>
<tr>
<th>Occupation</th>
<th>45,X&lt;sup&gt;m&lt;/sup&gt; (maternal)</th>
<th>45,X&lt;sup&gt;p&lt;/sup&gt; (paternal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=19</td>
<td>n=19</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Unemployed (not classified)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1. Managers/Senior officials</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Professional occupations</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>3. Associate professional &amp; technical</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>4. Administrative &amp; secretarial</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>5. Skilled trades</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6. Personal Service</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>7. Sales/Customer service</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8. Elementary</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
5.2.2.5 IQ

As with Study One, participants were to be excluded if their Verbal IQ was below 70. None of the participants had Verbal IQ within this range. Groups were matched in terms of both Verbal and Performance IQ and consequently for full scale IQ. The IQ distributions of the groups can be seen in table 5.4. For both TS groups Performance IQ was significantly lower than Verbal IQ, as is typically reported (within sample t-test: \(45,X^m - t (18) = -3.03, p=.007\); \(45,X^p - t (18) = -3.92, p=.001\)).

<table>
<thead>
<tr>
<th></th>
<th>45,X^m (maternal)</th>
<th>45,X^p (paternal)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=19</td>
<td>n=19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>sd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>99.37</td>
<td>99.44</td>
<td>.91</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>88.47</td>
<td>90.44</td>
<td>.88</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>93.68</td>
<td>95.22</td>
<td>.91</td>
</tr>
</tbody>
</table>

5.2.3 Materials

The tasks administered were the same as those used in Study One with an identical overall procedure. The incidental face recognition task was not
included in this test battery and a new short version of the Mooney faces task was created – this included the ten most difficult to recognise Mooney face stimuli alongside the same 5 foils. The test session took place within a quiet room at the Institute of Child Health or within the participant's own home. Each session lasted for just less than 2 ½ hours.

5.2.4 Statistical procedures

The groups did not differ significantly on any of the background variables considered and therefore none were entered as covariates in the following analyses. For all variables (separately for each group), the assumption of normality of distributions was tested using one-sample Kolmogorov-Smirnov tests. For two variables (Warrington recognition memory for words and Ekman-Friesen recognition of happy faces), significantly skewed distributions were detected for both groups. It was not possible to normalise these distributions using appropriate transformations, as there was a high level of ceiling performance on both tasks. The analyses were therefore repeated using non-parametric statistics.
5.3 RESULTS

5.3.1 Face recognition tests

Group performance was compared for the Benton face recognition task, the Warrington recognition memory task, and the famous face recognition task using independent samples T-tests. Table 5.5 shows that there were no significant differences between the women with a maternal X (45,X<sup>m</sup>) and those with a paternal X (45,X<sup>p</sup>) on any of these measures. The face recognition impairments seen in women with Turner syndrome with a maternal X in Study One are identical to those in women with Turner syndrome with a paternally inherited X-chromosome.

Since two tasks had skewed distributions that could not be corrected using appropriate transformations, analysis was repeated using non-parametric statistics, which confirmed the lack of group difference on these tasks. For Warrington word recognition memory the mean ranks of the groups using a Mann Whitney-U test were 45,X<sup>m</sup> = 16.47, 45,X<sup>p</sup> = 22.53 (U=123, p=.10). For Happy face recognition the ranks were 45,X<sup>m</sup> = 19.00, 45,X<sup>p</sup> = 20.00 (U=171, p=.55).
Table 5.5: Group comparisons for tests of face recognition accuracy

<table>
<thead>
<tr>
<th>Variable</th>
<th>45,Xᵐ</th>
<th>45,Xᵖ</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Benton face recognition</td>
<td>19</td>
<td>43.42</td>
<td>.67</td>
</tr>
<tr>
<td>Warrington recognition memory (faces)</td>
<td>19</td>
<td>36.26</td>
<td>.22</td>
</tr>
<tr>
<td>Warrington recognition memory (words)</td>
<td>19</td>
<td>47.53</td>
<td>.35</td>
</tr>
<tr>
<td>Famous faces (cropped)</td>
<td>19</td>
<td>66.08</td>
<td>.86</td>
</tr>
<tr>
<td>Famous faces (uncropped)</td>
<td>19</td>
<td>79.93</td>
<td>.52</td>
</tr>
<tr>
<td>Famous faces (total)</td>
<td>19</td>
<td>72.88</td>
<td>.31</td>
</tr>
</tbody>
</table>

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There is a non-significant trend towards better performance of the 45,X^0 women on two of the tasks considered (Benton face recognition (p=.08) and Famous face recognition for cropped faces (p=.07)). The results from the 45,X^0 women can be compared to those of the control group from Study One in order to assess their relative degree of impairment (see table 5.6).

Performance on all face recognition tasks (except for the Benton) is found to be significantly impaired in the 45,X^0 women, even after correcting for multiple comparisons.
Table 5.6: Face recognition in 45, Xp women compared to control females from Study One.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control females (study 1)</th>
<th>45, Xp</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Benton face recognition</td>
<td>23</td>
<td>47.08</td>
<td>3.40</td>
</tr>
<tr>
<td>Warrington recognition memory (faces)</td>
<td>23</td>
<td>42.48</td>
<td>4.54</td>
</tr>
<tr>
<td>Warrington recognition memory (words)</td>
<td>23</td>
<td>48.61</td>
<td>2.39</td>
</tr>
<tr>
<td>Famous faces (cropped)</td>
<td>23</td>
<td>94.93</td>
<td>3.77</td>
</tr>
<tr>
<td>Famous faces (uncropped)</td>
<td>23</td>
<td>98.29</td>
<td>2.15</td>
</tr>
<tr>
<td>Famous faces (total)</td>
<td>23</td>
<td>96.61</td>
<td>2.56</td>
</tr>
</tbody>
</table>

* All results remain significant after Bonferroni corrections for multiple comparisons.
5.3.2 Tests of face processing style

5.3.2.1 Mooney faces

An independent samples T-test was applied to assess the effect of group (45,X^m vs. 45,X^p) on adjusted Pr' scores derived from performance on this task. There were no significant group differences (45,X^m = .41, 45,X^p = .42, t(1,36) = .75, p = .86).

5.3.2.2 Face inversion test

Accuracy in matching upright and inverted faces was examined by SPSS GLM procedures (repeated-measures analysis of variance). The dependent variable was orientation (upright or inverted), the group factor was presence or absence of TS. The groups performed at similar levels in their recognition accuracy for upright (45,X^m = 89.47% (sd 9.09), 45,X^p = 86.84% (sd 9.75)) and inverted faces (45,X^m = 77.63% (sd 14.78), 45,X^p = 77.96% (sd 10.28)). There was a main effect of orientation, in favour of upright faces (F(1,36) = 22.87, p < .001). There was no significant effect of group (F(1,36) = 0.16, p = .70) and no interaction between group and condition (F(1,36) = 0.47, p = .50). Turner syndrome women with either a single maternal or paternal X-chromosome matched upright faces more accurately than inverted faces.
5.3.2.3 Whole/part face matching

Accuracy measures for the whole face, upper face, and lower face matching, were entered into an ANOVA (SPSS GLM repeated measures) as 3 levels of a single dependent variable (part-of-face). The group factor was maternal or paternal single X-chromosome. There was a main effect of part-of-face: whole faces were more accurately discriminated \( (F(1,36) = 33.61, p < .001) \). There was no effect of group \( (F(1,36) = .16, p = .69) \) and no interaction between group and condition \( (F(1,36) = .95, p = .14) \). As figure 5.1 demonstrates, whole faces were more accurately matched than face parts for both TS groups.

Figure 5.1: Accuracy for matching whole faces and parts of faces. Bars show mean. Error bars show standard error.
5.3.3 Facial emotion recognition

Accuracy (raw scores) for each facial expression category were entered into a MANOVA (SPSS GLM multivariate). Figure 5.2 shows the pattern of distribution of raw accuracy scores. No significant differences between the individual emotions were found for women with a single paternal X-chromosome compared to those with a maternal X. Total emotion recognition score also failed to show any significant group differences.

![Bar chart showing facial emotion recognition accuracy for six 'basic' emotions](image)

Figure 5.2: Facial emotion recognition accuracy for the six ‘basic’ emotions. Bars show mean. Error bars show standard error.

The results do confirm, however, that women with TS (45,X) have a specific decrement in fear and (to a less marked extent) anger recognition. According to the standardised norms for fear recognition, derived from Ekman and
Friesen (Ekman & Friesen, 1976), the women are performing on average nearly 5 standard deviations (45,X\textsuperscript{m} = -4.91, 45,X\textsuperscript{p} = -4.82) below the level that would be expected for this task. This is clinically significant and is line with the data obtained in Study One for 45,X\textsuperscript{m} women (z score = -5.5).

Attesting to the fact that the fear recognition deficit is disproportionately worse than for any other emotions, paired sample T-tests for the group as a whole show that fear is significantly less well recognised than any other emotion including anger (t=3.14, p=.003).

Comparing the 45,X\textsuperscript{p} women to the control females from Study One, it can be seen that the only emotion that they recognise significantly less accurately is fear, with an effect size of 1.05.
Table 5.7: Ekman-Friesen facial affect recognition for 45,X⁰ women compared to control females from Study One.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control females (Study 1 n=23)</th>
<th>45,X⁰ (n=19)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Happiness</td>
<td>23</td>
<td>10.00</td>
<td>0</td>
</tr>
<tr>
<td>Sadness</td>
<td>23</td>
<td>8.52</td>
<td>1.31</td>
</tr>
<tr>
<td>Surprise</td>
<td>23</td>
<td>8.82</td>
<td>1.03</td>
</tr>
<tr>
<td>Fear</td>
<td>23</td>
<td>8.30</td>
<td>1.33</td>
</tr>
<tr>
<td>Anger</td>
<td>23</td>
<td>8.17</td>
<td>.83</td>
</tr>
<tr>
<td>Disgust</td>
<td>23</td>
<td>8.48</td>
<td>1.20</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>52.30</td>
<td>2.79</td>
</tr>
</tbody>
</table>

* Remains significant after Bonferroni corrections for multiple comparisons
5.3.4 Correlational analyses

In Study One, correlations between the face processing measures were explored. It was pointed out that deficits in both fear recognition from faces and facial recognition memory are associated with compromised integrity of the amygdalae and wondered whether the degree of impairment in these domains might be associated in our TS population. It emerged that the recognition of fear from facial expressions was strongly correlated with face recognition accuracy for the control participants but not for the women with TS with a maternally inherited X-chromosome (45,X<sup>m</sup>). In this study the performance of TS women with maternally (45,X<sup>m</sup>) and paternally (45,X<sup>p</sup>) inherited X-chromosomes was compared. It was predicted that the same correlations would also fail to reach significance in women with a paternally inherited X-chromosome.

Hypothesis Seven. Recognition of fearful facial expressions will not be correlated with recognition memory for faces in TS individuals with a paternally derived X-chromosome.

Bivariate correlations (Pearson’s test) were calculated for individual expression scores below ceiling (surprise, anger, disgust, sadness and fear, but not happiness) with face recognition scores. These were run separately for each participant group. The findings are summarised in table 5.8 and 5.9.
Table 5.8: Correlations between emotion recognition scores and face recognition and configural processing measures – 45,X<sup>m</sup> TS females.

<table>
<thead>
<tr>
<th>N=19</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition</td>
<td>.456&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-.277</td>
<td>.256</td>
<td>.397</td>
<td>.210</td>
</tr>
<tr>
<td>Warrington</td>
<td>-.201</td>
<td>.000</td>
<td>.025</td>
<td>.254</td>
<td>-.173</td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famous</td>
<td>-.294</td>
<td>-.049</td>
<td>-.171</td>
<td>-.227</td>
<td>.029</td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mooney</td>
<td>-.064</td>
<td>.169</td>
<td>-.196</td>
<td>-.121</td>
<td>-.053</td>
</tr>
<tr>
<td>face recognition (sensitivity to 1&lt;sup&gt;st&lt;/sup&gt; order relations)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-part</td>
<td>.470&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-.347</td>
<td>.248</td>
<td>.252</td>
<td>.397</td>
</tr>
<tr>
<td>face recognition (holistic processing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upright-inverted</td>
<td>.125</td>
<td>.006</td>
<td>-.150</td>
<td>-.183</td>
<td>-.246</td>
</tr>
<tr>
<td>Face recognition (sensitivity to 2&lt;sup&gt;nd&lt;/sup&gt; order relations)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed)  
** p<.01 (two-tailed)  
*** p<.001 (two-tailed)  

no longer remain significant after Bonferroni corrections for multiple comparisons.
Table 5.9: Correlations between emotion recognition scores and face recognition and configural processing measures – 45,Xq TS females.

<table>
<thead>
<tr>
<th>N=19</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton face recognition</td>
<td>.270</td>
<td>.241</td>
<td>.142</td>
<td>.384</td>
<td>.303</td>
</tr>
<tr>
<td>Warrington face recognition</td>
<td>- .045</td>
<td>.755***</td>
<td>- .193</td>
<td>.193</td>
<td>.351</td>
</tr>
<tr>
<td>Famous face recognition</td>
<td>- .054</td>
<td>.667**</td>
<td>-0.006</td>
<td>.288</td>
<td>.705***</td>
</tr>
<tr>
<td>Mooney face recognition (sensitivity to 1st order relations)</td>
<td>.345</td>
<td>- .174</td>
<td>.214</td>
<td>-.081</td>
<td>.067</td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing)</td>
<td>.249</td>
<td>.134</td>
<td>-.166</td>
<td>.111</td>
<td>.170</td>
</tr>
<tr>
<td>Upright-inverted face recognition (sensitivity to 2nd order relations)</td>
<td>- .190</td>
<td>.349</td>
<td>.180</td>
<td>-.044</td>
<td>.246</td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed) ** p<.01 (two-tailed) *** p<.001 (two-tailed)

* no longer remain significant after Bonferroni corrections for multiple comparisons
As was the case in Study One, none of the correlations between the face recognition memory and fear recognition variables were significant for the 45,X<sup>m</sup> TS women as can be seen from figures 5.3 and 5.4. The pattern of correlations were strikingly different for the TS women with a paternal X-chromosome (45,X<sup>p</sup>) shown in figures 5.5 and 5.6. Here, despite very similar mean scores, there were highly significant correlations between fear recognition and both Warrington face recognition memory and famous face recognition. These correlations mirror those found for control participants in Study One. Famous face accuracy was also correlated with anger recognition in 45,X<sup>p</sup> TS women.

The Hyperstat method (as described in study 1) was applied to test for significant differences between the magnitudes of two correlations. The correlation between fear recognition and Warrington face recognition was significantly greater for 45,X<sup>p</sup> females than for 45,X<sup>m</sup> females (z=2.78, p=.002). The correlation between fear recognition and famous face recognition was also significantly greater in those females with a 45,X<sup>p</sup> karyotype (z=2.42, p=.008). Similarly, anger recognition and famous face recognition scores were correlated to a significantly greater degree in women with 45,X<sup>p</sup> TS than those with 45,X<sup>m</sup> TS (z=2.40, p=.008).
Recognition memory for faces
Mean=36.26, SD=5.22

Fear recognition
Mean=6.21, SD=2.39

Rsq = 0.0000

Figure 5.3: Scatter plot of the correlation between fear recognition and Warrington recognition memory for faces in 45,Xm TS women. Displaying line of best fit and 95% confidence intervals.

Famous face recognition
Mean=72.88, SD=18.31

Fear recognition
Mean=6.21, SD=2.39

Rsq = 0.0024

Figure 5.4: Scatter plot of the correlation between fear recognition and Famous face recognition in 45,Xm TS women. Displaying line of best fit and 95% confidence intervals.
Recognition memory for faces
Mean=37.79, SD=5.35

Fear recognition
Mean=6.11, SD=2.87

Rsq = 0.5706

Figure 5.5: Scatter plot of the correlation between fear recognition and Warrington recognition memory for faces in 45,X⁰ TS women. Displaying line of best fit and 95% confidence intervals.

Famous face recognition
Mean=83.06.88, SD=18.65

Fear recognition
Mean=6.11, SD=2.87

Rsq = 0.4451

Figure 5.6: Scatter plot of the correlation between fear recognition and Famous face recognition in 45,X⁰ TS women. Displaying line of best fit and 95% confidence intervals.
5.4 CHAPTER SUMMARY

Study Two sought to test the hypothesis that women with Turner syndrome with a single paternal X-chromosome would have better face processing abilities than women with TS with a single maternal X-chromosome. Nineteen women with a single paternal X were compared to nineteen women with a single maternal X on the tasks described in Chapter Three. The experimenter was blind to the parental origin of the single X-chromosome in these TS women.

Hypothesis Six, that women with a paternal X-chromosome would have better face processing skills compared to those with a maternal X-chromosome was not supported. Women with TS with a single paternal X-chromosome performed at equivalent levels to those with a single maternal X-chromosome on all tasks of face processing. Confirming that the scores were indicative of a deficit in 45,Xp women, they were performing at significantly lower levels than the control females from Study One on most of the tasks. TS women with a single paternal X-chromosome were impaired at face recognition memory and at recognising fear from facial expressions, but they too showed normal configural processing of faces.

From this, a new hypothesis was formulated - that women with a paternal X-chromosome would show identical correlations between tests of emotion recognition and face recognition to those seen in women with a maternal X-chromosome. This hypothesis was not supported. Correlation patterns
between face recognition and emotion recognition differed according to parental origin of the single X-chromosome. As in Study One, TS individuals with a maternal X-chromosome showed no correlation between their ability to recognise the emotion of fear in faces and face recognition memory. However, for women with TS with a paternal X-chromosome, like the typically developing females in Study One, these abilities were highly correlated.
6 CHAPTER SIX - DISCUSSION

STUDIES ONE AND TWO

6.1 FACE PROCESSING IMPAIRMENTS IN TURNER SYNDROME

Study One explored whether a karyotypically homogenous group of individuals with TS (45,X\text{m}) would show impairment on numerous tasks of face recognition ability. These tasks could be conceptualised as covering four broad domains: face matching, face recognition memory, emotion recognition and configural face processing. Women with Turner syndrome (45,X\text{m}) were found to perform at below average levels on face matching, face memory and emotion recognition tasks but showed normal configural processing of faces.

Study Two assessed the same face processing abilities in a new group of women with Turner syndrome, this time comparing those with a maternally inherited X-chromosome (45,X\text{m}) to those with a paternally inherited X-chromosome (45,X\text{n}). It was found that the parental origin of the single X-chromosome had little effect on levels of performance on these tasks. The women with a paternal X-chromosome had an equivalent deficit at face and emotion recognition, also showing normal configural face processing.
There were some subtle group differences between TS women with a maternal and those with a paternal X-chromosome that are examined towards the end of this chapter. However, for the most part, since the groups failed to differ on any key variables, TS will be used to refer to women with either a maternally or paternally inherited single X.

What aspects of the TS psychological phenotype might be able to account for the impaired performance on these measures of face processing? As was reviewed in Chapter One, individuals with TS are known to have a number of cognitive and neuropsychological abnormalities that can be broadly categorised into two domains – visuo-spatial dysfunction and socio-cognitive dysfunction. In line with the visuo-spatial deficits, structural and metabolic abnormalities in occipital-parietal brain regions have been reported (Clark, Klonoff, & Hayden, 1990; Clark et al., 1990). However no neural basis has been proposed for the socio-cognitive anomalies.

As is typically found (Collaer, Geffner, Kaufman, Buckingham, & Hines, 2002), the women with Turner syndrome had Verbal IQ scores within the normal range, while Performance IQ (PIQ) scores were significantly depressed relative to the control group. Nevertheless, PIQ, which was entered as a covariate in the reported analyses, failed to materially affect the results. In addition, Performance IQ failed to correlate with a single measure of face processing in either the control or TS participants.
By examining each test in turn, it will be proposed that face and emotion recognition deficits in this syndrome are best explained not by parietal and visuo-spatial dysfunction but rather by functional abnormalities of medial brain systems supporting socio-cognitive processing.

The two groups of 45,X<sup>m</sup> TS females were combined and analysed with an additional set of control females. The results with these larger sample sizes replicated the results reported within this chapter (Lawrence et al., in press).

### 6.1.1 FACE MATCHING

As predicted in hypothesis 1a, individuals with TS were less accurate than controls at matching concurrently presented faces in the Benton face recognition test. This task is the accepted clinical test for face recognition impairment. While individuals with Turner syndrome performed more poorly than the control participants, the TS mean score was within the normal range and would not be classified as being clinically significant according to test criteria. Just five (8%) of the sixty-one women with Turner syndrome obtained scores that would be deemed clinically significant. Thus a reduced ability in face matching is seen in some individuals with TS but abilities are within the normal range for most participants.

Our data fit with previous studies that have used this task in women with TS. Most studies that have assessed face matching in TS report decrements of a similar severity (Reiss et al., 1993; Romans, Stefanatos, Roeltgen, Kushner,
& Ross, 1998; Ross, Kushner, & Zinn, 1997; Ross et al., 1997; Romans et al., 1998). The only study not to report a significant decrement on this task was that of (Murphy et al., 1994). However, despite their result failing to reach significance, the TS women in their study performed slightly worse than the control group, to a comparable degree as was observed in the 45,X<sup>m</sup> women in this current study. The current study had more power to detect the subtle effect.

### 6.1.2 Face recognition memory

While previous studies have identified face-matching difficulties in girls and women with Turner syndrome, none to our knowledge have assessed face recognition memory abilities. Three independent tasks were used to assess different aspects of face recognition memory in our participants. Hypothesis 1b was supported, all three tasks identified deficits for women with TS.

The first task, which is used to identify clinical impairments in face memory, was the Warrington Recognition Memory Test. As with the Benton face recognition task, the scores of the TS women were depressed on this task in comparison to the control females. The deficit, however, appeared to be relatively more severe. Overall the women with TS had a mean recognition score that was lower than any of the means for the brain lesion groups reported in the original test standardisation (Warrington, 1984), which is indicative of a clinically significant impairment.
Poor performance on the face recognition component of this task was seen alongside normal performance on the word recognition memory component, which is indicative of the impairment not being part of a generalised non-specific memory impairment. However, since both the TS and control participants performed at near ceiling levels on the word recognition aspect of this task, the possibility is left open that subtle word recognition memory impairments may be detectable using a more sensitive task. Furthermore, without testing recognition memory for other visual stimuli, for example the recognition of doors (Doors and People Test, (Baddeley, Emslie, & Nimmo-Smith, 1994) it is not possible to know whether the recognition deficit is specific to faces. Additional investigations are needed to clarify whether other visual recognition difficulties exist in this group.

Impaired face memory was confirmed on the two additional tasks that assessed this capacity. Individuals with TS recognised fewer familiar (famous) faces than did the control participants, a result that was not related to general knowledge for the individuals in question. The faces used in this study were chosen because they were all very highly recognisable to an independent control population on which the test was standardised. Therefore, poor performance on this task reflects difficulties with face memory that translate to abilities in every-day life.

On the familiar face recognition memory task, individuals with TS demonstrated a relatively greater decrement when the faces had their
external features cropped. Cropping of faces removes the hair and jaw line and in removing these features that it may be possible to analyse in a more piecemeal way, a greater reliance is placed on configural processing for face recognition (Campbell et al., 1998). The ability to recognise famous faces when their external features are cropped is one that emerges in late childhood and is thought to coincide with a shift towards the greater use of configural processing in face perception (Campbell et al., 1998). This suggests that women with TS may differ from controls in their reliance on facial configurations in the storage and encoding of representations of known faces. This is in contrast to normal sensitivity to configural aspects of faces on the processing tasks. However, since recognition accuracy for both cropped and uncropped faces was reduced in TS and the interaction only held for those with a maternal X (45,X") interpretation is somewhat problematic.

A test of incidental face recognition assessed the ability to learn new faces under conditions where the participants were not aware they would subsequently be tested for recognition. Here too individuals with TS performed at a level lower than that of controls, demonstrating that difficulties in remembering faces can be detected using a number of different test procedures and reducing the chance that any deficit simply reflects a problem with some idiosyncratic aspect of task design.
6.1.3 Facial emotion recognition

The ability of our participants to identify facial expressions of emotion was assessed using another clinically utilised task of face processing ability. The women with TS showed an overall impairment on the Ekman-Friesen test of affect recognition. Such a result is in line with previous studies of women with TS that have shown deficits in identifying positive and negative affect in faces (McCauley, Kay, Ito, & Treder, 1987).

No previous studies of TS have reported recognition scores separately for the different emotions. Given the involvement of different neural circuitry in the recognition of different emotions it was felt that it was important to analyse results at this level. Since this study was conducted, Ross and colleagues have published a paper that looked at the recognition of individual emotions in TS individuals, the results of which are not entirely consistent with what was found here, despite apparently using the same experimental measure (Ross et al., 2002).

For the studies within this thesis, analysing each emotion individually, fear was the least accurately identified facial expression, showing a highly significant and specific decrement in TS compared with controls. Recognition of angry faces was also significantly poorer in TS than controls. By contrast, other expressions (happiness, sadness, disgust and surprise) showed no group-specific decrement. However, since happiness recognition was at near ceiling
levels for both groups it is not possible to know whether a deficit for this emotion would be detectable with a more sensitive measure.

Deficits in fear recognition were highly significant with effect sizes of greater than 1 for both $45,X^m$ and $45,X^p$ TS women. A less marked deficit in anger recognition was also evident. However, the decrement for fear recognition was particularly severe, with paired sample t-tests revealing that it was significantly less well recognised than any of the other emotions (including anger) in both TS groups. Contrary to hypothesis 1d, ALL aspects of emotion recognition were not impaired. Difficulties in this domain were highly specific.

Ross's group came to a similar conclusion that facial emotion recognition was impaired in TS (Ross et al., 2002). However, they found the greatest impairments to be in the recognition of anger and surprise. It is possible that the lack of a significant deficit emerging for fear recognition may have something to do with the large standard deviations for the recognition of this emotion in both the control and TS sample. It was by far the most inaccurately recognised emotion for both groups, with women with TS achieving 53% accuracy (sd 29) and control females scoring 62% (sd 25). The women with TS are thus performing at a similar level to our TS women ($45,X^m = 56\%$, $45,X^p = 61\%$) but their control participants are scoring considerably below both our control participants (mean 83%) and the participants in the original task standardisation (89.5%) (Ekman & Friesen, 1976). Perhaps the discrepancy seen between the current results and those obtained by Ross et al is mediated by differences in the control populations used rather than the TS
performance profile. Nothing about the control population used by Ross et al seems particularly remarkable, although 28% of participants were non-white. The Ekman stimuli are comprised of white Caucasian faces. Despite the fact that there is much evidence to suggest that the six emotions used in the study are cross-culturally valid, the brain is known to respond differentially to own and other race faces (Golby, Gabrieli, Chiao, & Eberhardt, 2001; Hart et al., 2000; Hart et al., 2000). And furthermore there does seem to be a small within-group advantage in recognising facial expressions (Elfenbein & Ambady, 2002a; Elfenbein & Ambady, 2002b; Elfenbein et al., 2002a). It is unlikely that this could account for the magnitude of the reduced recognition rate in Ross’s control participants but it may go some way to explaining the poor recognition of fear identified in this population.

6.1.4 Configural Face Processing

In teasing apart configural processing, Maurer (Maurer, Le Grand, & Mondloch, 2002) has proposed three different aspects of configural processing that are, broadly speaking, thought to be tapped by the three configural processing tasks used in this study. Inter-correlations between configural face processing tasks suggest that common mechanisms may support some aspects of configural processing. For both the control and TS females, the magnitude of the part-whole effect correlated with the magnitude of the inversion effect. This suggests that the types of configural processing thought to underlie performance on these two tasks are closely related. The
part/whole effect is thought to rely on holistic processing, while the face inversion effect is thought to rely upon sensitivity to second-order relations. These proposed different types of configural processing might depend on overlapping functional mechanisms. However, the Mooney face recognition task (thought to assess sensitivity to first-order relations) failed to correlate with either of the other configural processing tasks, perhaps suggesting a reliance on different processes for this aspect of configural processing.

Despite having poor face recognition abilities, the women with TS resembled controls in showing marked sensitivity to configural aspects of faces, with hypothesis 1e not being supported. They were at least as good as controls at detecting faces in the Mooney stimuli, demonstrating normal sensitivity to what Maurer terms ‘first-order relations’ (Maurer et al., 2002). The women also displayed the normal pattern on the part/whole-matching task, being more accurate when matching whole faces than either just the upper or lower half of the face. This would suggest that, like typically developing women, women with TS process faces in a holistic manner. The upper face is more expressive than the lower face in terms of conveying information about emotion, thoughts and feelings (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). It was predicted that women with TS may look less at the upper face, and consequently would be less proficient at matching faces from the eye region. Individuals with autism can be less accurate at recognising faces from the eye region (Langdell, 1978). However, both the women with TS and the control participants were equally accurate at matching upper and lower face parts.
On the face inversion task, the normal detrimental effect of inversion on face matching was seen for both the control participants and the women with TS. Since this effect is thought to be mediated by our sensitivity to the second-order relations in upright but not inverted faces, it would appear to suggest that women with TS are able to process faces in terms of the spatial distances between face parts. This finding is at odds with a study by (Waber, 1979), which found that women with TS had impaired memory for upright faces but intact memory for inverted faces. Participants were shown two sets of 24 photographs of unfamiliar faces. The first set was presented upright and the second set inverted. After each set in turn, a series of pairs of faces were presented, asking the participant to decide which they had just seen. At test, the faces were in the same orientation as at presentation.

From Waber's study one would predict that women with TS fail to show typical sensitivity to second order spatial relations on the matching task. One possible explanation for this discrepancy is that Waber's task involved a memory component, while the current study utilised an immediate matching procedure. The fact that this current study found some evidence of configural anomalies on a memory task (famous face recognition) may provide support for this interpretation. However, this effect may be mediated by ceiling effects for the recognition of whole famous faces.

The effect in Waber's study may not be due to configural processing per se but rather to memory processes. As was considered in Chapter Two, memory
for faces may be enhanced by their emotional significance. Emotional significance is presumably reduced for inverted faces, since they are less salient stimuli. In this sense, normal memory for inverted but not upright faces could also be explained in terms of a lack of facilitation to memory of the emotional significance of upright faces. It may prove useful to consider such an interpretation when reviewing the discrepant evidence for a face inversion effect in autism.

Another possibility is that the tasks presented here were not sensitive enough to detect what may be a subtle impairment in configural processing. Close to ceiling levels of accuracy were achieved in the whole face conditions which may make any differences in configural sensitivity difficult to detect. Despite, showing normal configural processing the women with Turner syndrome did perform more poorly than controls at face matching, even if the impairment was not clinically significant. Perhaps subtle anomalies in configural face processing exist that could not be detected using the Mooney face recognition task and the inversion and part/whole matching tasks? Future investigations could benefit from using recent stimuli devised by Daphne Maurer (Maurer et al., 2002) that systematically manipulate configural and featural aspects of the face-image, and could provide more conclusive data. The relatively short exposure duration of the images in the inversion and part-whole tasks leaves open the possibility that the task may have 'forced' a configural processing style where one would not normally be recruited. Studying the effect of long and short exposure duration in such tasks is another possible direction for future investigations.
However, on the tasks designed to tap configural face processing, women with Turner syndrome showed typical sensitivity to configural aspects of faces. This was surprising. The hypothesis was that in this developmental syndrome, as in others in which face recognition decrements are reported; configural processing would be delayed or deviant in relation to chronological age. In Williams syndrome and autism, face processing anomalies are accompanied by poor configural face processing abilities when the individuals are tested on similar tasks to those used here (Deruelle, Mancini, Livet, Cassse-Perrot, & de Schonen, 1999; Hobson, Ouston, & Lee, 1988).

The finding of apparently intact configural perceptual processing of faces in TS necessitates the modification of ideas about the necessary and sufficient conditions for face recognition to develop to age-appropriate levels. While configural-processing abilities may be a necessary precondition for remembering faces, such abilities (as measured by these tasks) are not, in themselves, sufficient for age-appropriate face recognition skills to develop. Face recognition was reliably impaired in women with Turner syndrome. Anomalous configural face processing cannot account directly for the face recognition difficulties identified in this syndrome. This has also been found to be the case for a patient with developmental prosopagnosia, who had severe face recognition difficulties but intact configural face processing skills (Duchaine, 2000). This supports the idea that intact configural processing is not the only skill necessary for developing good face recognition skills.
Since a number of tasks of both face recognition and configural face
processing were administered, the chance of alpha inflation generating a
spuriously significant finding may be increased. However, on the four main
tasks of facial recognition (Benton, Warrington, Famous faces and Incidental
Recognition) Bonferroni corrections failed to reduce the significance of the
results except for on the Famous Faces task.

6.2 NEURO-BIOLOGICAL BASIS

Are there any possible explanations at the level of neuro-cognitive systems for
the deficits in face processing identified in this developmental syndrome?
Four systems; face perception, visuo-spatial abilities, general memory skills,
and socio-affective processing are now considered as possible explanations.

6.2.1 Face perception and configural processing – occipito-temporal
cortex

One could suggest that perceptual anomalies within the occipito-temporal
cortex, or more specifically the fusiform gyri, might be causally involved in this
impairment. Evidence from a multitude of sources points to the role of the
fusiform gyri in the perceptual and configural processing of faces (Bentin,
Allison, Puce, Perez, & et al, 1996; Kanwisher, McDermott, & Chun, 1997;
Meadows, 1974; Bentin et al., 1996; Kanwisher et al., 1997). However,
although the women with TS were impaired at the Benton face recognition
task compared to the control females, their scores were for most part not
indicative of clinically significant impairments. In fact 92% of women with TS
scored within the normal range on the task, indicating that any deficits in face perception are relatively subtle. Furthermore, women with TS showed normal configural processing of faces, which would imply that the mechanisms underlying face perception operate in a similar manner in TS and typically developing women.

Although fear may be the most visually difficult emotion to discriminate (Rapcsak et al., 2000), disgust is typically the next most difficult. If face perception were at the route of the difficulties TS women have in recognising facial expressions of emotion, you would not predict such a specific fear related decrement but rather graded performance across the emotions associated with their difficulty of visual discrimination.

It is of course possible that the subtle difficulties with face matching, identified on the Benton task, would feed through to storage and retrieval, impacting too (and perhaps to a greater extent) on face memory. However, surprisingly Benton face recognition scores failed to correlate with any measures of face recognition memory in either the control or TS women. Configural face processing also failed to predict test performance in either group. These factors all suggest that an underlying difficulty with face perception does not serve as a good explanation for the array of deficits seen in TS.

6.2.2 Visuo-spatial – Parietal lobes

Another explanation for the TS impairment on tests of face recognition could be the abnormalities in the structure and function of occipital-parietal brain
regions that have been noted in numerous studies of women with TS (Clark et al., 1990; Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995; Reiss et al., 1995). Women with TS typically have poor visuo-spatial function and this study replicated earlier reports by showing lower Performance IQ's relative to the control group.

Although damage to the parietal lobes in adulthood is not generally noted to be associated with face recognition difficulties, it may be the case that these regions are important in establishing skilled face recognition abilities. Ballantyne and Trauner (Ballantyne & Trauner, 1999) assessed the face recognition abilities (using the Benton task) of a series of 40 children and adults who had suffered from perinatal strokes. The methodology of combining adults and children in such a study is questionable, particularly considering the developmental changes in face processing ability that occur through late childhood and adolescence. However, individuals who had suffered damage to temporal, frontal and parietal regions all performed significantly more poorly than controls on this task. More importantly, the greatest impairments were seen for individuals whose strokes had occurred within the parietal lobes, irrespective of hemisphere. Difficulties for the parietal damage participants were relatively mild and of a similar severity to those seen in our TS women (approximately one standard deviation below the control group).

If parietal lobe abnormalities in Turner syndrome were contributing to their face recognition difficulties a correlation between Performance IQ (which is
often used as a basic index of parietal lobe function) and face recognition skills would be expected. However, Performance IQ failed to correlate with the Benton face recognition task, or any other measures of face recognition in either the control or TS females. Deficits in visuo-spatial functioning do not appear to be a good explanation for the face processing deficits observed in TS. The lack of correlation between face processing abilities and Performance IQ is surprising. One might assume that the visuo-spatial skills tapped by Performance IQ would play some role in the development of face processing abilities. However, these results suggest that their role, if any, is minimal and the face processing deficits identified in TS can not be explained by sub-optimal visuo-spatial abilities.

Whilst considering Performance IQ (PIQ), it is worth noting that the correlations between Performance IQ and Verbal IQ were remarkably similar for the women with TS and the control participants. In Study One the Pearson correlation coefficient for the control participants was .576 (p=.004) and for the women with TS the coefficient was .571 (p=.004). This observation suggests that there is a constant decrement in Performance IQ in the TS group. This is similar conceptually to the decrement in stature seen in this population (Brook, Gasser, Werder, Prader, & Vanderschueren-Lodewyckx, 1977) where height can be predicted on the basis of parental height. Given that the cause of short stature in this population is largely due to SHOX gene haploinsufficiency (Rao et al., 1997), it is worth considering the possibility that a similar mechanism, due to single gene haploinsufficiency, could account for
the Performance IQ deficit in these women. Both height and PIQ would appear to vary in a constant manner according to pre-defined criteria.

6.2.3 Generalised memory impairment – Hippocampus

Face recognition memory deficits were detected alongside normal recognition memory for words (although see above), suggesting that all aspects of memory are not equally impaired. Similarly, although memory for famous faces was found to be at below average levels in the women with TS that were studied, their memory for other semantic information about these same individuals was equivalent to that of the control participants. Memory for faces would seem to be impaired, but memory for words and semantic information is intact. The fact that the memory impairment observed is non-generalised would appear to preclude dysfunction of the hippocampus providing a viable explanation for the face recognition difficulties observed. Although memory for faces can be impaired following lesions to this region (Seidenberg et al., 2002), given the lack of stimulus specificity in the role of the hippocampus in laying down new memories (Papanicolaou et al., 2002), one would expect memory for other types of stimuli to be affected too. Amnesiacs, suffering from either partial or total loss of memory, are equally impaired at both the word and face recognition sub-tests of the Warrington (Aggleton & Shaw, 1996). Furthermore, patients with developmental amnesia of perinatal origin also have quite generalised memory difficulties with recall and episodic
memory (Vargha-Khadem, 2001) although face memory does not appear to have been explicitly tested.

The middle temporal gyrus appears to play a role in the recognition of famous faces (Leveroni et al., 2000) but is not systematically activated during the viewing of unfamiliar faces. Since the memory deficits in the TS women were not confined to famous faces, dysfunction of this area would also appear to be an unlikely explanation for the memory deficits observed.

6.2.4 Socio-affective processing – amygdala and related circuitry

I will now argue that the most plausible explanation for the profile of face processing deficits seen in TS is dysfunction of socio-affective processing associated with the amygdala and related circuitry. To recap, the difficulties experienced by the TS women are in face matching (minor difficulties), face recognition memory (clinically significant difficulties), and recognising fear and, to a lesser extent, anger from facial expressions (clinically significant). Configural face processing abilities were at an age appropriate level, as was the ability to recognise other facial expressions of emotion. The uneven profile of intact and impaired abilities means that explaining the deficit in terms of an impaired face processing ‘module’ is not appropriate.

In Chapter Two it was argued that one reason why humans have a remarkable capacity to learn and remember faces is that memory systems
function differently for emotionally significant stimuli. For most human beings, faces are arguably the most emotionally significant stimuli that we deal with on a regular basis. Having an emotional response to a face within socio-affective neural systems may then aid our later memory for that face.

The amygdala is thought to enhance memory for arousing material (Phelps et al., 1998) possibly by modulating other regions involved with brain storage. This mechanism is possibly mediated by the release of endogenous stress hormones that can be triggered by amygdala activation (Cahill, 2000; Cahill & McGaugh, 1998; Cahill, 2000). Activity of the amygdala while participants view emotionally provocative stimuli correlates with the degree to which these stimuli are retained in long term memory (Cahill, 1996; Cahill, 2000; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Cahill, 1996; Canli et al., 2000).

Although this reasoning has not before been directly applied to face learning and memory, it seems an obvious parallel to draw. Recognising faces may involve the amygdala to the extent that the task may automatically engage emotion-based processing. In direct relation to face memory, it has been demonstrated that making emotional judgements about faces (pleasantness) as opposed to non-emotional decisions (directionality) evokes greater amygdala activity (Bernstein, Beig, Siegenthaler, & Grady, 2002). In this study, making emotional decisions during encoding also evoked better memory for the faces. If faces have abnormal significance for women with TS, then learning or categorising faces will be specifically affected.
One way to assess the hypothesis that compromised amygdala function could underlie the face memory difficulties observed in this population would be to test memory for other emotionally salient (non-face stimuli) (for example using tasks such as those employed by (Cahill et al., 2001). It would be predicted that this type of memory would also be impaired but to my knowledge has not previously been assessed in Turner syndrome.

This reasoning may be able to explain the face memory impairments identified in TS but can such an explanation be applied to the other face processing difficulties identified in this syndrome?

Firstly, the TS women were also reported to have a mild decrement at face matching. During the perception of faces showing a fearful expression, the amygdala can influence the activity of the fusiform gyrus and other regions involved in face processing (Morris et al., 1998) possibly enhancing our perception of these stimuli. Therefore, if the amygdala is not responding in the normal way to the emotional significance of faces, any top down influences on infero-temporal regions may be disrupted, affecting face-matching skills.

Individuals with TS also had selective impairments in the recognition of fear (and for 45,X° women anger) from facial expressions of emotion. As was reviewed in Chapter Two, the involvement of the amygdala in processing fearful and angry facial expressions has been attested to by functional imaging studies (Morris et al., 1996; Phillips et al., 1998b; Phillips et al., 1998a). It’s role in the processing of fearful faces is particularly well supported
e.g. (Breiter et al., 1996). Other emotions that would seem to rely more heavily on different neural circuitry were recognised normally in these women. For example, women with TS were as good as controls at recognising facial expressions of disgust – this facial expression is believed to activate the insula and basal ganglia (Phillips et al., 1997; Phillips et al., 1998a; Phillips et al., 1997).

It is understood that fear is the most difficult of the six basic emotions to recognise (Rapcsak et al., 2000). Therefore, it is conceivable that a specific difficulty at recognising fear could be caused by problems in general visual discrimination. If however, the problem was one of visual discrimination you would expect the other emotions to be affected in some sort of graded way, which was not the case. Disgust which is also a hard emotion to recognise (Ekman et al., 1976), was labelled accurately by the experimental group. In a more recent study (Elgar et al., 2002) recognition of emotions based just on the upper half of the face – from the bridge of the nose upwards, was assessed. From this portion of the face, fear was not the hardest emotion to recognise for control participants; rather disgust was significantly less well recognised than any other emotion. Despite this, the TS women performed at the same level as the control group for disgust recognition but were again specifically impaired at fear recognition. There would seem to be something specific about the emotion of fear itself, rather than just that it is hard to discriminate, that is producing the TS specific decrement in this task.
The entirely unexpected and robust finding that in controls ‘fear’ scores accounted for a significant portion of the variance for face recognition memory accuracy, could reflect a mediating role for the amygdala in the support of both face recognition and fear classification. Unlike control subjects, the correlation of ‘fear’ with face recognition memory scores was not significant for women with Turner syndrome and a single maternal X-chromosome. A possible explanation is that when the amygdala develops anomalously, other systems come to support face recognition and emotion recognition (although possibly not fear). The lack of correlation in TS (45,X^m) could suggest that the growth and connectivity of the amygdala is anomalous, reducing the functional link between fear and face recognition. However, for women with TS and a single paternal X-chromosome, the typical female correlation was found with good fear recognition abilities being associated with good face recognition memory abilities. This suggests that the functional link between these two tasks may be mediated by a different mechanism to that which mediates the general decrement in task performance seen for these tasks in both 45,X^m and 45,X^p women. Subtle differences between women with a single paternal and those with a single maternal X-chromosome are discussed more fully in Chapter Seven.

Socio-affective processing and the amygdala would appear to be involved, to varying degrees and in different ways in all of the face processing tasks that are seen to be performed suboptimally by the women with TS. Although, I suggest that the amygdala may be functionally anomalous in TS, it is probably
better to think about a set of structures including the amygdala. The amygdala has many projections to neighbouring regions of cortex and other regions involved in social cognition, such as other medial temporal areas and orbito-frontal cortex. These structures are both structurally and functionally heavily interconnected. The consideration of the role of the amygdala in this chapter does not consider the role of the amygdala in isolation but rather deals with its function within a system.

Do patients who have experienced damage to their amygdalae have a behavioural profile similar to that observed in the women with TS?

6.2.4.1 Patients with amygdala damage

As was previously reviewed in Chapter Two, a handful of patients have been reported who have damaged amygdalae. In one case the damage is due to congenital Urbach-Wiethe disease that produced bilateral calcification of the amygdala. For the other cases damage has been sustained in adulthood either due to surgery (for example to alleviate epilepsy) or as a result of neural disease (e.g. encephalitis). Table 6.1 gives details of a number of cases that have been described in peer-reviewed journals – many have been studied on several occasions. Where details have been provided the sex, age at insult, cause of insult and extent of damage are recorded.
<table>
<thead>
<tr>
<th>Patient</th>
<th>authors</th>
<th>gender</th>
<th>Age of damage</th>
<th>Cause of damage</th>
<th>Extent of damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.R.</td>
<td>(Young et al., 1995) (Adolphs et al., 1999) (Broks et al., 1998) (Calder et al., 1996) (Tranel &amp; Hyman, 1990)</td>
<td>Female</td>
<td>34-37 years</td>
<td>Surgical</td>
<td>At least 25% of left amygdala and &gt;4% of right</td>
</tr>
<tr>
<td>SM</td>
<td>(Adolphs, Tranel, Damasio, &amp; Damasio, 1994) (Adolphs et al., 1999) (Adolphs, Tranel, Damasio, &amp; Damasio, 1995) (Adolphs &amp; Tranel, 2000)</td>
<td>Female</td>
<td>Congenital</td>
<td>Urbach-Wiethe disease</td>
<td>Bilateral total calcification of the amygdala – minimal other damage</td>
</tr>
<tr>
<td>E.P.</td>
<td>(Hamann &amp; Adolphs, 1999) (Adolphs et al., 1999)</td>
<td>Male</td>
<td>73</td>
<td>Encephalitis</td>
<td>Complete bilateral amygdala plus extensive other</td>
</tr>
<tr>
<td>G.T.</td>
<td>(Hamann et al., 1999) (Adolphs et al., 1999)</td>
<td>Male</td>
<td>59</td>
<td>Encephalitis</td>
<td>Complete bilateral amygdala plus extensive other</td>
</tr>
<tr>
<td>LV</td>
<td>(Adolphs et al., 1999)</td>
<td>Female</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 100%</td>
</tr>
<tr>
<td>JS</td>
<td>(Adolphs et al., 1995)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 100%</td>
</tr>
<tr>
<td>UB</td>
<td>(Adolphs et al., 1995)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 50%</td>
</tr>
<tr>
<td>LDV</td>
<td>(Adolphs et al., 1995)</td>
<td>Female</td>
<td>?</td>
<td>?</td>
<td>Right amygdala</td>
</tr>
<tr>
<td>AK</td>
<td>(Adolphs et al., 1995)</td>
<td>Female</td>
<td>?</td>
<td>?</td>
<td>Right amygdala 100%</td>
</tr>
<tr>
<td>SB</td>
<td>(Adolphs et al., 2000)</td>
<td>Female</td>
<td>?</td>
<td>?</td>
<td>Right amygdala 50%</td>
</tr>
<tr>
<td>CS</td>
<td>(Adolphs et al., 2000)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 75%</td>
</tr>
<tr>
<td>MA</td>
<td>(Adolphs et al., 2000)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 100%</td>
</tr>
<tr>
<td>JM</td>
<td>(Adolphs et al., 1999)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Left amygdala 100%</td>
</tr>
<tr>
<td>SM</td>
<td>(Calder et al., 1996) (Broks et al., 1998)</td>
<td>Male</td>
<td>55</td>
<td>Herpes Simplex Encephalitis</td>
<td>Bilateral complete amygdala &amp; extensive other</td>
</tr>
<tr>
<td>SP</td>
<td>(Adolphs et al., 1999)</td>
<td>Male</td>
<td>?</td>
<td>?</td>
<td>Surgical</td>
</tr>
<tr>
<td>DBB</td>
<td>(Adolphs et al., 1999)</td>
<td>Female</td>
<td>20's</td>
<td>Surgical</td>
<td>Complete left, partial right amygdala – no other</td>
</tr>
<tr>
<td>GR</td>
<td>(Aggleton et al., 1996)</td>
<td>Female</td>
<td>67</td>
<td>Herpes Simplex Encephalitis</td>
<td>Extensive right amygdala plus extensive other, some left amygdala plus other</td>
</tr>
<tr>
<td>JC</td>
<td>(Broks et al., 1998)</td>
<td>Female</td>
<td>51</td>
<td>Herpes Simplex Encephalitis</td>
<td>Extensive bilateral amygdala plus other temporal lobe</td>
</tr>
<tr>
<td>YW</td>
<td>(Broks et al., 1998)</td>
<td>Male</td>
<td>57</td>
<td>Herpes Simplex Encephalitis</td>
<td>Left amygdala and hippocampus</td>
</tr>
</tbody>
</table>

Table 6.1: Summary of characteristics of patients with amygdala damage
<table>
<thead>
<tr>
<th>Patient</th>
<th>Face matching</th>
<th>Face recognition memory</th>
<th>Facial emotion recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Happiness</td>
<td>Surprise</td>
</tr>
<tr>
<td>D.R</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>SM</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GT</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>LV</td>
<td>49&lt;sup&gt;th&lt;/sup&gt; centile</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>JS</td>
<td>8&lt;sup&gt;th&lt;/sup&gt; centile</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>UB</td>
<td>49&lt;sup&gt;th&lt;/sup&gt; centile</td>
<td>?*</td>
<td>+</td>
</tr>
<tr>
<td>LDV</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; centile</td>
<td>?*</td>
<td>+</td>
</tr>
<tr>
<td>FR</td>
<td>77&lt;sup&gt;th&lt;/sup&gt; centile</td>
<td>?*</td>
<td>+</td>
</tr>
<tr>
<td>AK</td>
<td>32&lt;sup&gt;nd&lt;/sup&gt; centile</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>SB</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>JM</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>SE</td>
<td>40/54</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>SP</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>DBB</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>GR</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>JC</td>
<td>34/54</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>YW</td>
<td>45/54</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>RB</td>
<td>46/54</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

* Recognition or naming of famous faces is impaired.

Table 6.2: Summary of face processing impairments in patients with amygdala damage – where inconsistencies arise between studies, impairment is reported.
In table 6.2 the behavioural profile of these patients on various tests of face processing is summarised. As can be seen, the behavioural profiles of all the patients are by no means identical. Some patients, like DBB are reported to have no difficulties at recognising facial expressions of emotions. While for others, (for example DR) many aspects of face processing appear to be problematic. As a rule of thumb, damage would appear to have to affect both amygdalae in order to produce significant difficulties. DR, SM, GT, JM and SP all have bilateral amygdala and significant difficulties in fear recognition (and face recognition memory where tested). The patients with lesions affecting either just the left or just the right amygdala are not reported to have difficulties in recognising fear from facial expressions, although some have difficulties matching faces on the Benton task.

It is important to remember that the effects of any lesion will cause changes to a whole system, to all areas with which there are interconnections. In addition, some of the patients have lesions that extend beyond the amygdala into neighbouring regions, so it is not always clear what particular aspect of the damage may have produced the difficulties identified. Many inferences can be drawn, however, by considering the commonalities in the profiles of patients who have in common damage to a particular region, in this instance, the amygdala.

Each aspect of face processing that was assessed in Turner syndrome will now be considered with regard to these patients, in order to assess how closely the behavioural profile of women with TS matches that of patients with amygdala damage.
6.2.4.1.1 Face matching

The women in the current study with Turner syndrome had minor difficulties matching faces. Perception of faces and face matching is often reported to be relatively intact in patients with amygdala damage (Young et al., 1995) (DR). However, other patients perform face-matching tasks very poorly (Adolphs et al., 1995) (JS and LDV) although these patients also have more extensive damage. The majority of the women with TS performed within the normal range on the Benton face matching task, despite having a relatively depressed mean score in relation to the control group. The mean score across the three TS groups studied for the Benton task was 43.6/50. This is very similar to scores obtained by the four amygdala damage patients studied by Broks et al (Broks et al., 1998). These patients had scores ranging from 34 (in the clinically impaired range) to 46 (in the normal range), with a mean score of 41.25. Like women with Turner syndrome, patients with amygdala damage would appear to sometimes have subtle difficulties at matching faces. However, these patients also have damage to brain regions outside the amygdalae. As was reasoned previously, the amygdala responds to emotionally significant faces and its activity can modulate activity in face processing regions such as the fusiform gyrus (Morris et al., 1998). If the amygdala is damaged or functioning abnormally, this feedback may be disrupted bringing about sub-optimal functioning of perceptual face processing. If this were the case it could be predicted that, in TS, activity within the amygdala during a face viewing task would not correlate with activity in fusiform regions, as it does for healthy volunteers.
6.2.4.1.2 Configural face processing

From studies one and two there was no evidence that women with TS did not process faces in the typical configural manner. Since configural face processing is thought to occur largely within the fusiform regions it could be argued both that it would, but also that it would not, be likely to be affected if the amygdala was functioning abnormally. Since amygdala activity modulates fusiform activity it could be contended that this may impact upon configural processing. Alternatively, it could be argued that since, at a functional level the amygdala does not appear to be involved in configural processing, such abilities should be unaffected, as is the case for the TS women studied. Configural face processing has not been systematically studied in patients with amygdala lesions. However, one study of patients with selective amygdalo-hippocampectomies found evidence for normal configural processing (Crane & Milner, 2002). Normal performance on the Mooney faces task was noted, which suggests that normal function of the amygdala is not necessary for sensitivity to first-order relations in configural processing.

6.2.4.1.3 Face memory

Women with Turner syndrome are impaired at learning to recognise new faces and have impaired recognition of familiar faces. It was reasoned earlier that since the amygdala appears to play a role in memory for emotionally significant events and stimuli, it should follow that it would be involved in face
memory. Faces are emotionally significant to most humans. If patients have
damage to their amygdala it would be predicted that face memory would be
affected. In a re-analysis of psychometric data, Aggleton and Shaw (Aggleton
et al., 1996) found that all four patients with amygdala damage performed
more poorly on the face recognition than the word recognition subtest of the
Warrington. They were the only brain-damage group, amongst thirteen groups
with specific brain damage, to show this pattern. Their mean scores of 37/50
for face recognition and 48.5/50 for word recognition are comparable to those
obtained by the TS women in the current study (45,X<sup>m</sup> Studies One and Two:
36.43 for faces and 48.00 for words; 45,X<sup>p</sup>: 37.79 for faces and 49.32 for
words). Face recognition memory has not been assessed in many patients
with amygdala damage but the similarity between the results of these few
patients and females with TS is striking. DR, SM and GR, all with bilateral
amygdala damage also have face specific memory difficulties.

6.2.4.1.4 Recognising facial expressions of fear

Women with TS had a very specific deficit in recognising fear from facial
expressions. For women with a 45,X<sup>m</sup> karyotype this deficit extended to anger
recognition. It was reasoned earlier that the most plausible explanation for this
lay in dysfunctional amygdalae rather than problems at a perceptual level. In
patients with bilateral amygdala damage the recognition of fear from facial
expressions would also appear to be differentially affected. Of the eleven
patients considered in tables 6.1 and 6.2 who had fear recognition assessed,
it was impaired in nine. The recognition of other emotions was much less
frequently affected. The recognition of sadness was impaired in four patients, while disgust and surprise were each impaired in three patients. After fear, the next most frequently affected emotion was anger (recognition impaired in more than 50% (6/11) of bilateral damage patients) which was the other emotion that was also affected in TS.

Given that TS is a developmental syndrome, it is perhaps more important to consider the implications that an abnormally functioning amygdala may have on development. A critical patient to consider is SM, an individual with a rare congenital disease (Urbach-Wiethe) that primarily affects epithelial tissue (Adolphs et al., 2000). SM has selective bilateral calcification of amygdala tissue, which is believed to have been sustained in early childhood. She has relatively normal face matching skills on the Benton (85th centile), but is impaired at unfamiliar face learning and memory (Tranel et al., 1990) and at recognising fearful, angry and surprised facial expressions (Adolphs et al., 1999; Adolphs et al., 1995; Adolphs et al., 1999). Like women with TS, SM is also reported to have anomalous social behaviour. She has been described as being 'somewhat coquettish and disinhibited...often makes mildly inappropriate sexual remarks' (Tranel et al., 1990) and is also said to have 'a history of inadequate social decision making and somewhat inappropriate social behaviour' (Adolphs et al., 1995).

Depending on how early SM developed calcification of her amygdalae, this could point towards limited capacity of the developing human brain to reorganise the processing of faces, following amygdala damage, in a way that optimally supports face and emotion recognition skills. It is therefore plausible
that a congenital cause of compromised functional integrity of the amygdala, as I am postulating in TS, could have implications extending into adulthood for face and emotion recognition abilities.

Bilateral damage to the amygdalae would appear to produce a similar behavioural profile to that observed in women with TS. Face matching is at relatively normal levels with indication of slight impairment in some cases. Face recognition memory is compromised, and this would appear to be alongside normal memory for words. Finally the recognition of fear and anger from facial expressions of emotion is compromised. On the basis of these similarities and the theoretical reasoning about why a deficit in amygdala function could account for the behavioural profile seen in TS, it was hypothesised that the structural integrity of the amygdalae would be impaired bilaterally in women with TS.

### 6.2.4.2 Social skills and face recognition

How can the proposal that socio-emotional processing and dysfunction of the amygdala are at the heart of face processing difficulties in TS when there is no correlation between social functioning and face processing abilities in these women? Social dysfunction was assessed using the Autism Spectrum Quotient self-report questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Item analysis revealed that the use of a self-report questionnaire of social function may not be valid for women with TS. The
women with TS who responded that they found it easy 'to work out what someone is thinking or feeling just by looking at their face' were no more accurate at recognising facial expressions of fear than were the TS women who indicated that they did not find it easy. If anything the women who said they found it easy were slightly less accurate. This item does not appear to be good at discriminating women with TS who have difficulties in this area. In future, it may be wise to obtain measures of social functioning from multiple sources in an attempt to establish the validity of different assessment strategies.

6.3 CHAPTER SUMMARY

Studies one and two revealed that women with Turner syndrome have poor face and emotion recognition abilities alongside intact configural processing of face stimuli. This profile of abilities is suggestive of possible neural circuits that may be compromised in these women. It is argued that explanations for the deficits based on face perception, visuo-spatial abilities and general memory can not adequately account for the behavioural profile observed. It is argued that anomalous socio-affective processing, particularly that which centres around the amygdala, is the most parsimonious explanation for the face processing deficits seen.
7 CHAPTER SEVEN – STRUCTURAL BRAIN IMAGING

7.1 RATIONALE

From Studies One and Two it emerged that individuals with monosomic TS (both 45,X⁰ and 45,X⁰) had difficulties with face and emotion recognition that were reminiscent of those experienced by patients with bilateral amygdala damage. Given the developmental nature of the difficulties in TS, it is important to note that their difficulties are also reminiscent of patient SM who sustained amygdala damage in early childhood (if not before) due to congenital disease (Adolphs & Tranel, 2000). Several neuroimaging studies have explored brain structure in TS, consistently revealing abnormalities in parietal regions along with variable structural differences in frontal and subcortical structures (Murphy et al., 1993; Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995; Reiss et al., 1995; Reiss et al., 1993). No studies have reported structural abnormalities in brain structures specifically implicated in social cognition, including the amygdala. An eighth hypothesis was formulated:

8 Women with TS have structurally abnormal amygdalae
The findings from the studies in this thesis precipitated a new investigation to be carried out in collaboration with Dr. Tina Good (Good et al., 2001a), who conducted the reported analyses. None of the previous studies that have looked at brain structure in TS have used Voxel Based Morphometry (VBM). This fully automated whole brain analysis technique is able to detect minute differences in brain volume. It was additionally chosen as the preferred method of analysis since the amygdala is difficult to identify and delimit from the hippocampus using Magnetic Resonance Imaging (MRI) and brain tracing techniques. Studies that employ different anatomical definition techniques produce varying estimates of amygdala volume. With those studies that employ the Watson criteria (Watson et al., 1992) producing significantly larger volumes than the remainder (Brierley, Shaw, & David, 2002). In a recent commentary, David and colleagues point out that amygdala volume measurements for healthy humans can vary by as much as 2,800 mm$^3$ between studies (David, Brierley, & Shaw, 2002). Furthermore, these estimates were up to five times greater than those reported in a recent post-mortem study (Chance, Esiri, & Crow, 2002). VBM avoids the subjectivity of region of interest (ROI) approaches, and since there is no possibility of observer or technique bias, results are comparable between laboratories.
7.2 METHODS

7.2.1 Participants

In order to characterise the brain structural phenotypes, high resolution MRI structural imaging was performed on twenty-one 45,X participants (all from studies one and two). Ten women had a single paternal X-chromosome and for the remaining eleven the single X was maternal in origin. The same imaging was also performed on 16 control females matched for age and Verbal IQ, see table 7.1.

Table 7.1: Age in years of study participants.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>age(yrs)</th>
<th>Verbal IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>46,XX (females)</td>
<td>16</td>
<td>23.46</td>
<td>3.73</td>
</tr>
<tr>
<td>45,X(^m) (Turner syndrome)</td>
<td>11</td>
<td>21.70</td>
<td>5.23</td>
</tr>
<tr>
<td>45,X(^p) (Turner syndrome)</td>
<td>10</td>
<td>22.60</td>
<td>6.50</td>
</tr>
</tbody>
</table>

Individual T-tests revealed no significant difference in the ages or Verbal IQ's of the women with TS (45,X\(^m\) or 45,X\(^p\)) and the control females.
7.2.2 Scanning techniques and analyses (from Good et al, submitted)

High resolution volumetric magnetic resonance (MR) imaging was performed on a Siemens 2T Magnetom scanner using an optimised MPRAGE sequence that affords enhanced grey/white matter contrast and segmentation. The acquisition parameters included: TR/TE/TI 11/4/1000, flip angle 12, matrix 256 x 224, FOV 256 x 224mm; 176 sagittal slices, 1mm isotropic voxels. Amygdala/hippocampal significance levels were small-volume corrected using sphere of 40mm diameter as a generous estimate of total amygdala volume.

An optimised method of voxel based morphometry (VBM) was used. This involves a number of fully automated pre-processing steps: extraction of brain; spatial normalization into stereotactic space; segmentation into grey and white matter and CSF compartments; correction for volume changes induced by spatial normalisation, and smoothing with a 10mm full width at half maximum (FWHM) isotropic gaussian kernel. After smoothing, each voxel represents the local average amount of grey (or white) matter in the surrounding region, the size of which is defined by the size of the smoothing kernel (Ashburner & Friston, 2000).

A customised grey matter template derived from all the TS patients and control participants was used in order to avoid any bias during the spatial normalisation step. The smoothed data were analysed using MATLAB 5.3 (MathWorks, Natick, Mass., USA) and statistic parametric mapping (SPM99) employing the framework of the General Linear Model. Regionally specific structural differences were assessed statistically using a two-tailed test, testing for increased or decreased grey matter. Significance levels were set at p<0.05, corrected for whole brain volume. The measure used is simply the proportion of brain tissue volume that is comprised of, or occupied by, grey matter. For discrete well-defined structures such as the amygdala this is equivalent to the volume of that structure. For less well-defined structures such as the orbito-frontal cortex, it is equivalent to grey matter density, in the sense that the proportion of
the volume of the brain in this region that is grey matter is significantly different in cases and controls. This measure is not equivalent to packing density of neuropil at a microscopic level.

The design matrix modeled the control group and the 45,X group (divided according to the maternal or paternal origin of the single X-chromosome). The mean global grey matter intensity was modelled as a covariate in order to facilitate the detection of regionally specific structural changes having discounted global differences. Age was included as a covariate.

This fully automated whole brain imaging technique enables detection of subtle changes in grey matter on a voxel-wise basis between groups of patients and normal participants. Classical MRI morphometric techniques are based upon region of interest type metrics, which are inherently subjective and operator dependent.

7.3 RESULTS

7.3.1 Voxel Based Morphometry

X-monosomic females possessed localised regions of altered brain structure compared with 46,XX controls, irrespective of the parental origin of their single X-chromosome. These abnormalities included regionally increased volumes of the amygdalae and increased grey matter in the orbito-frontal cortex bilaterally (Fig. 7.1).
Figure 7.1: Structural differences in grey matter volume, demonstrated by voxel-based morphometry. Comparison between 45,X TS females and normal 46,XX females. Increased grey matter is seen bilaterally in amygdala and orbito-frontal cortex of the TS sample. Significance levels set at p<.05, corrected. (Local maxima coordinates for amygdala: -37, -12, -24; -34, -6, -25; 21, -10, -24; 33, -6, -24 and for orbito-frontal cortex: -26, 28, -7).
Individual nuclei within the amygdala subserve different functions but with the scanning resolution available, distinguishing whether these substructures were differentially affected was not possible.

In addition, to structural differences in the amygdalae and orbito-frontal cortices of TS women, the volumes of the right occipito-parietal lobe also differed between TS women and female controls. A reduction in volume was identified in the right occipital-parietal lobe, the voxel of peak difference was at (x, y, z) 18, -61.5, 25.5. The occipital parietal anomalies are consistent with many previous reports (Reiss et al., 1995) as well as with identified visuo-spatial difficulties for women with TS.

Figure 7.2 Decreased right occipito-parietal volume in females with TS (45,X) compared with Control females (46,XX), Significance levels set at p<.05, corrected for whole brain volume. Local Maxima coordinates: 18, -61.5, 25.5.
7.3.2 Estimates of regional grey matter for individual participants

In an ideal situation, actual measurements of the regions of interest would have been computed for individual participants, using tracing methods. Unfortunately, this was not possible, so grey matter within a single voxel in each region of interest was used. Indices for individual participants for specific neural areas of interest were calculated based on amount of grey matter within a smoothed voxel from the region of interest. The voxels chosen for the analysis were those that were at the local maxima on the SPM map, that is they were the individual voxels showing the most statistically significant differences between the groups. This is not strictly a measure of either volume or density, and shouldn't be regarded as such. However, it does provide an estimate of grey matter for the specific regions in question. The derived indices represent grey matter in cubic mm per voxel (1.5mm x 1.5mm x 1.5mm) for the individual voxel considered. They will be referred to as indices of grey matter for particular regions. Estimates were derived from within the left amygdala, left orbito-frontal cortex and right occipito-parietal cortex. Dr. Tina Good calculated the grey matter indices in the same manner as has been used for other studies (Good et al., 2002).

7.3.2.1 Amygdala

In order to assess the validity of these estimates, I made group comparisons using SPSS. Grey matter (mm$^3$) was measured for the voxel (within the left amygdala) of maximum difference between the TS and control groups (34,-6,-
In figure 7.3, the distribution of indices of left amygdala grey matter can be seen for the TS and control females. There was little overlap between the women with TS and the control females, with the women with TS consistently having increased grey matter at this left amygdala voxel. The mean grey matter ($mm^3$) and variance for the TS groups were highly similar ($45,X^m$ mean = .45, sd = .07; $45,X^p$ mean = .46, sd = .06). However, the mean grey matter ($mm^3$) for the control females was reduced ($46,XX$ mean = .35, sd = .05). This difference held up in a General Linear Model Univariate analysis in SPSS. This revealed a main effect of group (df 2,34, $F=11.18, p<.0001$). Post hoc Tukey tests confirmed that the grey matter at this voxel for the TS women with a maternal and those with a paternal X-chromosome did not differ (mean difference = .0045, $p=.984$). However, both groups of TS women had significantly more grey matter than did control females ($46,XX$ vs. $45,X^m$ mean difference = .0967, $p=.001$; $46,XX$ vs. $45,X^p$ mean difference = .0923, $p=.002$). This analysis, based on an index of regional volume, supports the VBM group comparison, which found the control females to have significantly smaller amygdala volume than the TS women.
Figure 7.3: Cubic mm of grey matter within voxel 34,-6,-25 (the voxel of maximum difference within the left amygdala). Distribution of cubic mm of grey matter for females with TS and control females.

7.3.2.2 Orbito-frontal cortex

The same analysis was repeated for grey matter within the voxel of maximum difference within the OFC (-26, 28, -7) for individual participants. Again, just a small degree of overlap is seen between the amount of grey matter for the women with TS and the control females (see figure 7.4).
Group means of grey matter (mm$^3$) for this voxel were compared using General Linear Model Univariate analysis followed up by post-hoc Tukey tests. There was a main effect of group (F(2,34) = 7.32, p=.002). Post-hoc analysis revealed that the control females had significantly less grey matter at this voxel (mean .45, sd = .05) than women with TS with a maternal X-chromosome (45,X$^n$ mean = .53, sd = .07, p=.002). The difference was in the same direction but failed to reach significance for the comparison between control females and those with a paternal X-chromosome (45,X$^p$ mean = .50, sd = .05, p =.09). Grey matter for the two TS groups was not significantly different (p=.37). This analysis partially supports the findings of the main VBM
group comparison of OFC volumes. The women with TS, had more grey matter in the left orbito-frontal cortex voxel than did the control females, however, this only reached significance for the 45,X\textsuperscript{m} sub-group.

7.3.2.3 Occipito-parietal cortex

Finally, a group comparison was conducted, using grey matter (mm\textsuperscript{3}) for the voxel of maximum difference within the right occipital-parietal cortex (18, -61.5, 25.5). In figure 7.5, there is perhaps slightly less differentiation between the TS women and the control females than was seen for estimated amygdala and orbito-frontal volumes. However, univariate ANOVA revealed significant group differences between grey matter at this voxel within occipito-parietal cortex for the control participants and the women with TS (F = 8.1; p=.002).

Post hoc Tukey tests revealed that women with a single X-chromosome that was paternal in origin had significantly less grey matter within this voxel (mean = .32; sd = .12) than did the control females (mean = .46; sd = .05) (mean difference = -.143, p<.001). The difference was in the same direction for 45,X\textsuperscript{m} females (mean = .39; sd = .09) compared to controls although it just failed to reach significance using Tukey post-hoc analyses (mean difference .0771, p=.096). The TS individuals did not differ from each other according to the parental origin of their single X (mean difference = .066, p=.209). This is partially in line with the main group VBM analysis that revealed a significantly smaller occipito-parietal volume for both groups of women with TS compared to control females.
Figure 7.5: Cubic mm of grey matter within voxel 18,-61.5,25.5 (the voxel of maximum difference within the left orbito-frontal cortex). Distribution of cubic mm of grey matter for females with TS and control females.

The group differences using estimated brain volumes largely resemble those observed in the VBM analysis by Dr. Tina Good. This supports the validity of using such indices of grey matter for this particular sample. Ideally though, we would calculate the following analysis using actual measured volumes of the regions of interest.
<table>
<thead>
<tr>
<th></th>
<th>46,XX (females)</th>
<th>45,X&lt;sup&gt;m&lt;/sup&gt; (TS)</th>
<th>45,X&lt;sup&gt;p&lt;/sup&gt; (TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey matter index for left amygdala at voxel -34,-6,-25 (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Mean 0.35</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Std. Error</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Grey matter index for left orbito-frontal cortex at voxel -26,28,-7 (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Mean 0.45</td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Std. Error</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>Grey matter index for right occipito-parietal cortex at voxel 18,-61.5,25.5 (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Mean 0.46</td>
<td>0.39</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Std. Error</td>
<td>0.05</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Table 7.2: Summary Table of descriptive statistics for grey matter indices calculated from single voxels within the regions of interest. The derived indices represent cubic mm of grey matter in a single voxel (1.5mm x1.5mm x 1.5 mm).
I then assessed the correlation patterns between these indices of regional grey matter and the behavioural face processing tasks. The hypotheses were that:

9 Indices of amygdala grey matter would correlate positively with fear recognition accuracy and memory for faces.

10 Indices of orbito-frontal cortex grey matter would correlate positively with overall emotion recognition and face recognition accuracy.

11 Indices of occipito-parietal cortex grey matter would correlate positively with Performance IQ.

There were no apriori predictions about whether these correlations would hold for both the TS and control women or just one or other of these groups.

7.3.3 Correlations between brain structure and behaviour

For the majority of participants who were scanned, behavioural data from studies one and two had also been collected. This allowed correlations to be made between the grey matter indices for specific brain regions and performance on cognitive tasks.

7.3.3.1 Amygdala and emotion recognition and face recognition memory

Pearson correlations were run for indices of left amygdala grey matter and emotion recognition scores, for the TS women and controls separately. Table 7.3 and 7.4 show the correlation matrices for each group.
failed to correlate with grey matter ($mm^3$) at the voxel of maximum difference within the amygdala.

The only correlation, of those between indices of amygdala grey matter and face and emotion recognition, to reach significance was that between fear recognition and indices of left amygdala grey matter for $45,X^p$ TS females. This is consistent with Hypothesis Nine that fear recognition ability would be correlated with amygdala grey matter (or in this case, an index of it), although the relationship is positive rather than negative. However, it is also consistent with the idea that 1 in 50 analyses will be significant by chance at the 0.02 level. Since a number of correlations were made, it is important to be cautious in drawing any firm conclusions. The correlation is not significant after applying Bonferroni corrections for multiple comparisons. It would be important to replicate this potentially interesting result on an independent sample of women with this karyotype and with actual amygdala measurements rather than indices of grey matter for this region. Applying the hyperstat statistic to test for significant differences between correlations, it was found that the correlation between fear recognition and grey matter within amygdala voxel 34,-6,-25 approached a greater level of significance for $45,X^p$ TS females than for control females ($z=1.39, p=.08$). However there were no significant differences in the correlations for the two groups of TS women according to the parental origin of their X-chromosome ($z=1.00, p=.16$). Contrary to the second part of Hypothesis Nine, indices of left amygdala grey matter failed to correlate with Warrington face recognition memory or famous face memory ability or any other tests of face processing.
Table 7.3: Correlations between cubic mm of grey matter within one voxel of left amygdala at 34,-6,-25 and emotion recognition scores – 46,XX control females.

<table>
<thead>
<tr>
<th>Index of left amygdala grey matter</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
<th>Warrington face memory</th>
<th>Famous face recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>-.135</td>
<td>.242</td>
<td>-.224</td>
<td>.148</td>
<td>.084</td>
<td>.066</td>
<td>-.048</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.675</td>
<td>.448</td>
<td>.483</td>
<td>.647</td>
<td>.796</td>
<td>.838</td>
<td>.881</td>
</tr>
</tbody>
</table>

Table 7.4: Correlations between cubic mm of grey matter within one voxel of left amygdala at 34,-6,-25 and emotion recognition scores – 45,X<sup>m</sup> TS females.

<table>
<thead>
<tr>
<th>Index of left amygdala grey matter</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
<th>Warrington face memory</th>
<th>Famous face recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>.475</td>
<td>.364</td>
<td>.259</td>
<td>.426</td>
<td>.521</td>
<td>.247</td>
<td>.150</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.165</td>
<td>.302</td>
<td>.471</td>
<td>.220</td>
<td>.123</td>
<td>.492</td>
<td>.680</td>
</tr>
</tbody>
</table>
Table 7.5: Correlations between cubic mm of grey matter within one voxel of left amygdala at 34,-6,-25 and emotion recognition scores – 45,X0 TS females.

<table>
<thead>
<tr>
<th>Index of left amygdala grey matter</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
<th>Warrington face memory</th>
<th>Famous face recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=10</td>
<td>Pearson correlation</td>
<td>Sig. (2-tailed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-.207</td>
<td>.566</td>
<td>.716</td>
<td>.532</td>
<td>-.114</td>
<td>.521</td>
<td>.486</td>
</tr>
<tr>
<td></td>
<td>.020</td>
<td>.113</td>
<td>.754</td>
<td>.123</td>
<td></td>
<td>.154</td>
<td>.064</td>
</tr>
</tbody>
</table>

Figure 7.6: Correlations between indices of amygdala grey matter in mm² at 34,-6,-25 and fear recognition for 45,X0 TS.

Ettmah-Feiben - fear raw score

Index of left amygdala grey matter

Rsq = 0.5127
7.3.3.2 Orbito-frontal cortex and emotion recognition and face recognition memory

Bivariate Pearson correlations were also computed for indices of orbito-frontal cortex grey matter together with emotion recognition and face recognition memory variables. None of the correlations between these variables were significant. Hypothesis Ten, that orbito-frontal cortex grey matter (or an index thereof) would be correlated with emotion recognition and face recognition memory, was not supported. Grey matter within voxel -26, 28, -7 of the OFC also failed to correlate with any of the other measures of face processing.

7.3.3.3 Occipito-parietal cortex and Performance IQ

Pearson bivariate correlations were calculated for indices of right occipito-parietal cortex grey matter together with Verbal and Performance IQ, separately for each group. None of these correlations were significant. The hypothesis that Performance IQ would correlate with grey matter (or an index of grey matter) in this brain region was not supported. However, when TS and control females were analysed as a single group (n=32) a significant correlation between Performance IQ and indices of right occipito-parietal grey matter was observed (Pearson correlation .554, p=.005). For the group as a whole, individuals with more grey matter within voxel 18, -61.5, 25.5 of the occipito-parietal cortex had higher Performance IQ's. However, when the distribution of these scores is considered, it becomes clear that the significant
correlation coefficient does not reflect a simple linear trend (see fig. 7.5). Rather, the correlation results from two partially distinct clusters of participants, those with TS who have less grey matter within this voxel of occipito-parietal cortex and low Performance IQ and those without TS who have more grey matter in this voxel of occipito-parietal cortex and higher Performance IQ's.

Figure 7.7: Scatter plot showing the correlation between grey matter mm$^3$ at 18,-61.5,25.5 within the occipito-parietal cortex and Performance IQ for all participants.

Hypothesis Eleven was partially supported although the relationship between Performance IQ and an index of occipito-parietal grey matter does not appear to be linear.

Grey matter within this occipito-parietal cortex voxel failed to correlate with any of the measures of face processing.
7.3.3.4 Oestrogen and regional brain volumes

Bivariate Pearson correlations were run for age of commencement of oestrogen therapy and the indices of grey matter for the three brain regions. Grey matter indices for right occipito-parietal cortex (Pearson correlation $r^m$: .012, $p=n/s$; $r^p$: -.272, $p=n/s$), left orbito-frontal cortex (Pearson correlation $r^m$: -.69, $p=.057$; $r^p$: -.374, $p=n/s$) and left amygdala (Pearson correlation $r^m$: -.73, $p=.038$; $r^p$: -.314, $p=n/s$) did not systematically correlate with the age at which oestrogen replacement commenced. For $X^m$'s only, earlier oestrogen therapy was associated with greater amygdala grey matter at voxel 34,-6,-25. Most of the correlation coefficients were negative. This suggests that any subtle associations would be in the direction of earlier commencement of treatment being associated with greater regional grey matter.

7.4 DISCUSSION

From the behavioural results of Studies One and Two, it was hypothesised that women with TS would have structural differences in their amygdalae and/or related neural circuits. The current study revealed that this was the case. Imaging revealed increased grey matter in the amygdalae and orbito-frontal cortices bilaterally for women with compared to control females. The TS women had poor face and emotion recognition abilities, alongside normal configural processing of faces. As was reviewed in Chapters Two and Six, the amygdalae and orbito-frontal cortices have been implicated in face and emotion recognition. Evidence comes from both patients with brain damage and functional imaging studies of healthy participants. One study has
looked at configural face processing abilities in patients with amygdala
damage and found that, like the women in our study, patients were able to
detect faces in the Mooney face stimuli (Crane & Milner, 2002).

As demonstrated in Chapter Six, patients with damage to bilateral amygdalae
often have deficits in face recognition memory and fearful face recognition
(Calder et al., 1996). This is also the case for a rare individual who has
developmental damage to this region (Tranel & Hyman, 1990). However, the
women with TS do not have damage to their amygdala in either of these
senses. They do not have voids where their amygdalae would be, or even a
reduction of volume in this region. Women with TS have increased grey
matter bilaterally in their amygdalae.

From this, one could argue for a non-linear relationship between amygdala
volume and face recognition abilities. Decreased grey matter would seem,
according to patient studies, to be sub-optimal. However, it is not the case that
more is necessarily better. Increased grey matter, for women with TS, also
appears to be sub-optimal. Might there be a curvilinear relationship between
amygdala grey matter and certain face-processing abilities?

How can increased grey matter within a region be associated with reduced
abilities in the skills that it sub-serves? There are various explanations for
these results. It is possible that during neuronal development anomalous
pruning of the region occurred. This could in turn have produced anomalies in
function, due to an excess of neurons and dendrites. Pruning refines brain
regions so that they are best able to serve the functions for which they are used. A relatively increased brain volume may reflect sub-optimal pruning.

Another possibility is that the structural differences in themselves reflect functional differences. The functional difference may have developmentally induced structural adaptation of these areas. A study of London taxi drivers suggests a capacity for local plasticity change in the structure of the healthy human brain in response to environmental demands (Maguire et al., 2000). The posterior hippocampi of taxi drivers were significantly larger than those of non taxi-drivers. It was also found that the longer an individual had been a taxi driver, the greater the posterior hippocampal volume. This is suggestive of causality in the direction of taxi driving (and the spatial representation that it involves) leading to regional expansion within the hippocampus.

With regard to TS, there may be a congenital anomaly of social and emotion processing neural networks incorporating amygdala and OFC. The circuit may have to work ‘harder’ because it is functioning in a sub-optimal way; this could possibly bring about hypertrophy. In the same way that muscles may atrophy if they are not being used and hypertrophy if they are being overused, the anomalous function of this circuit could plausibly lead to structural volume increases in the amygdala and orbito-frontal cortices.

How could these alternative explanations of the structural imaging results be explored? In mice bred with the 45,X karyotype it may be possible to investigate neuro-architecture of the amygdala at various stages of development. If increased amygdala grey matter is also found in mice with a
single X-chromosome, it would be possible to investigate whether these
differences are present at birth or even earlier. If the structural differences are
the result of functional abnormalities it should be possible to identify a stage of
development where the cyto-architecture of the amygdala looks very similar in
mice with a 45,X karyotype to those with a 46,XX karyotype.

A developmental human study incorporating both structural and functional
imaging could prove invaluable in establishing the link between structure and
function. If it were possible to map the structural development of the amygdala
through childhood and adolescence, alongside the functional response of the
amygdala to fearful faces, insights may be gained into the inter-relationship
between structure and function.

In the task of emotion recognition used in Studies One and Two, explicit
classification of emotion was required. The amygdalae also activate in
response to implicit tasks. For example, the amygdala is known to be
intrinsically involved in fear conditioning (Morris, Buchel, & Dolan, 2001).
However, dissociations have been described whereby explicit processing can
be impaired with implicit processing remaining intact. It has been noted, since
the observations of Claparede, that patients are able to learn through classical
conditioning without being consciously aware of the learning that has taken
place (Kihlstrom, 1995). More recently, a patient with blindsight (GY) has been
reported who has amygdala responses to the presentation of fearful faces in
his blind field, despite being unaware of their existence (Morris, de Gelder,
Weiskrantz, & Dolan, 2001). It would be interesting to investigate whether
implicit responses to fearful faces are impaired in TS to the same degree as
their explicit recognition of these stimuli. If they are not, it might imply that an element of the impairment in TS is concerned with making cognitive sense of amygdala activity.

As was reviewed in Chapter Two, increased bilateral amygdala volumes have also been reported for individuals with autism/Asperger syndrome (Howard et al., 2000). This perhaps further suggests a link between increased amygdala volume and social dysfunction including poor face processing abilities. However, the picture in autism is by no means clear (Sweeten, Posey, Shekhar, & McDougle, 2002). Some studies have reported decreased amygdala volume in autistic subjects (Aylward et al., 1999), while others suggest increased grey matter may be lateralised to the left hemisphere (Abell et al., 1999). There is some suggestion that the difference between autism and Asperger syndrome and whether the individuals are high or low functioning may have some bearing on these discrepant findings. One study found significantly greater left amygdala volume in subjects with Asperger’s syndrome compared to those with autism (Haznedar et al., 2000). Assessing children with an autistic spectrum disorder, it has been found that amygdala enlargement is only present in those with strictly defined autism (Sparks et al., 2002).

Definition of what is meant by autism or Asperger’s syndrome may be a crucial factor in the variance between studies. Despite diagnostic criteria existing, there are clearly elements of subjectivity to the diagnosis of these disorders and it is not clear whether the two should be treated separately. Turner syndrome on the other hand is diagnosed on the basis of objective
genetic analysis. In the case of individuals with a 45,X karyotype, the findings of increased amygdalae and orbito-frontal cortex grey matter may have more chance of replication success. If the effect is genuine, any group of individuals chosen could be expected to be relatively homogenous since they would be known to have the same genetic basis for their condition.

Neuroanatomical studies in autism may give us some clues as to the nature of the increased volume of the amygdalae. Nine brains of autistic individuals were analysed in a post-mortem study, and in each case microscopic amygdala abnormalities were described (Kemper & Bauman, 1998). Small neuronal size was noted, as was increased cell packing density. In other studies, white matter deficits have been reported (McAlonan et al., 2002) and it is important to consider connections between regions, as well as the regions themselves in understanding how dysfunctional circuitry may contribute to behavioural manifestations. Similar studies would be useful in helping to establish what the increases in grey matter reflect for women with Turner syndrome.

Functional imaging studies are now being used to throw light on the processing mechanisms that may be different in individuals with autism and Asperger’s syndrome to those seen in the normal population (Baron-Cohen et al., 1999; Critchley et al., 2000; Baron-Cohen et al., 1999). Such studies can help to establish links between anomalies of the amygdalae and behaviour. Similar studies are needed for women with Turner syndrome in order to help determine whether the amygdalae and orbito-frontal cortices are functioning anomalously in this population.
Indices of grey matter for specific neural areas of interest were calculated for individuals based on grey matter volume within a smoothed voxel from within the region of interest. The voxels chosen for the analysis were those that were at the local maxima on the SPM map, that is they were the voxels showing the most statistically significant differences between the groups. The derived estimates represent grey matter volume in cubic mm per voxel (1.5mm x 1.5mm x 1.5mm).

To verify the validity of this technique, group comparisons were made for the three areas of interest using the estimated volumes. For left amygdala, left orbito-frontal cortex and right parietal cortex the indices of grey matter for each of the regions differed significantly between the groups. Mirroring the group VBM analysis TS women (with either a maternally or paternally inherited single X) had significantly greater grey matter within the voxel of maximum difference within their left amygdala. For the orbito-frontal cortex both groups of TS women had increased grey matter in the voxel of maximum difference compared to control females, although this did not quite reach significance for the 45,Xp women (p=.09). For the occipito-parietal cortex, both TS groups had reduced grey matter at the voxel of maximum difference compared to controls, this time the result was just outside significance for the 45,Xm women. The results of a group comparison using VBM analysis were largely replicated using index techniques that compute the amount of grey matter within a single voxel within the region interest. This provides some
validation to the process of using indices of regional grey matter from a single voxel.

A correlation was predicted between indices of left amygdala grey matter and the recognition of fear from facial expressions. This prediction arose from the observation that women with TS had larger amygdalae than karyotypically normal control females and also had poorer fear recognition scores. It was hypothesised that the larger the amygdalae, the poorer the fear recognition abilities. However, although this pattern holds for the group comparison, it is not the case when scores of individual participants are considered. Indices of amygdala grey matter were not correlated with fear recognition scores for control females. In addition, for women with TS and a single maternal X-chromosome there was a non-significant relationship between the ability to recognise fear from facial expressions and indices of left amygdala grey matter.

For women with TS and a single paternal X-chromosome, a significant positive correlation was found between these two variables. For these women, increased grey matter in the voxel of maximum difference within left amygdala was associated with better fear recognition abilities. This result is counterintuitive given the results of the group comparisons. Women with TS have overall larger amygdalae than control females and are worse at fear recognition. However, within the 45,Xp group it was the women with the lower indices of left amygdala grey matter that were scoring at the lowest levels on a test of fear recognition.
Could this unpredicted finding shed any light on the mechanisms underlying these structural differences? These results could suggest that hypertrophy of the amygdala may serve as a compensatory mechanism for anomalous amygdala function, such that increased size in patients with poor function can aid fear recognition abilities. Why this relationship should be seen only for TS individuals with a single paternal X-chromosome is not clear. It may be the case that with a larger sample it would be possible to detect a significant association for individuals with the 45,X\textsuperscript{m} karyotype (the correlation is certainly in the same direction and of a fair size – Pearson correlation = .364).

However, the difference between these correlations for women with a single maternal and those with a single paternal X-chromosome, may be a further indication of subtle genetic imprinting effects that are influencing the development and function of the amygdala. Without knowing whether increased grey matter detected by VBM reflects increased volume of the amygdala or increased density one cannot make any strong predictions. However, this interesting finding stresses the need further to conduct detailed studies of amygdala structure in women with Turner syndrome, which can assess both volume (in absolute terms) and density.

The fact that women with a paternal X-chromosome, despite having similar structural amygdala differences to 45,X\textsuperscript{m} women, and similar fear recognition scores, show a striking correlation between these variables is suggestive of possible different functional mechanisms underlying fear recognition in these two groups of women. One way to elucidate whether this is the case would be to use functional imaging techniques to investigate the brain regions involved in the processing of fearful faces in these women.
It was also predicted that indices of left orbito-frontal cortex grey matter would correlate with emotion recognition and face recognition memory ability. This was not found to be the case. Although, there were group differences between OFC grey matter and these skills, at the individual level these two variables were not correlated. No other measures of face recognition correlated with OFC grey matter in any of the groups.

Finally, the hypothesis was tested that Performance IQ would be correlated with indices of right occipito-parietal cortex grey matter. This was found to be true when all participants were considered as a whole, with a positive correlation indicating that more grey matter in the voxel of maximum difference within the right occipito-parietal cortex was associated with higher Performance IQ scores. However, when these data were plotted out it became evident that there was not a straightforward linear relationship (at the individual level) between these two variables. Rather two somewhat distinct clusters were producing this correlation, with TS females clustering with low PIQ scores and smaller indices of occipito-parietal cortex grey matter and control females clustering at the upper end with higher PIQ’s and larger indices of occipito-parietal cortex grey matter. Therefore, at an individual level no direct correlation is seen between these two variables once group is taken into account. Grey matter within voxel 18,-61.5,25.5 of the occipito-parietal cortex failed to correlate with a single measure of face processing accuracy in any of the groups.
7.4.2 Mechanisms

Whether or not abnormalities of the amygdala contribute to face and emotion recognition anomalies in TS, what could be the mechanism by which the structural integrity of certain brain systems are compromised possibly leading to face-processing deficits?

As was discussed in Chapter One, the lack of an X-chromosome could influence brain development and cognition by three different mechanisms. These are lack of endogenous oestrogen, haploinsufficiency for X-linked genes and imprinted genes on the X-chromosome.

7.4.2.1 Oestrogen

All the TS women in the current study were receiving oestrogen replacement therapy. Therefore, it is unlikely that the activational influence of oestrogen on the brain is sufficient for normal face recognition skills. However, the possibility remains that the levels of circulating oestrogen in Turner syndrome may be significantly lower than in the control females, which in itself may have an impact on face recognition abilities.

Furthermore, women with Turner syndrome are typically not given exogenous oestrogen until late childhood or early adolescence, while it is likely that typically developing females will have small amounts of the hormone present throughout development. If the presence of oestrogen is important for the maturation of brain regions involved in face recognition, the effects of early
deficiency may not be reversible by subsequent administration of these hormones.

With the information available, one option to explore the effects of oestrogen on face recognition in TS is to assess whether the age at which oestrogen replacement commenced (which varies from case to case) bears any relationship to face recognition abilities. In this study it did not. The age of commencement of oestrogen therapy failed to correlate with performance on any of the cognitive measures. Age of commencement also failed to correlate with estimated regional brain volumes, except for grey matter within the amygdala in 45,X°TS females, which needs to be further explored. This would suggest that if oestrogen deficiency were in any way contributing to structural brain anomalies or face-processing difficulties in TS, it would be doing so in one of two ways. Either by the deficiency existing in a critical window of development relatively early on in life, OR from a relative deficiency in adulthood such that sub-optimal levels of oestrogen are administered. However, there was a significant trend, in 45,X° women, for earlier treatment to be associated with indices of increased grey matter in the left amygdala. Since increased grey matter in the left amygdala in these women may be associated with better fear recognition abilities, it would be interesting to study the possible therapeutic influence of oestrogen further in a larger sample.

One reason why it may be important not to dismiss the role of oestrogen out-of-hand, is that oestrogen receptors are widely expressed in the forebrain, particularly in the amygdala and certain hypothalamic nuclei in both primates and humans (Osterlund & Hurd, 2001). Animal models have demonstrated
that oestrogen may be directly involved in the development and maturation of many brain regions including the amygdala (Keefer & Holderegger, 1985; Nishizuka & Arai, 1981; Zhou, Cohen, & Pandey, 2001; Keefer et al., 1985; Zhou et al., 2001).

One method of further assessing the role of oestrogen deficiency in the development of face processing problems in TS would be to assess the women with the condition who have normal menstruation and therefore more typical levels of circulating female hormones. It is not known why some women with TS may not have abnormal ovarian development but they may provide an important way to study the effects of a single X-chromosome in isolation from the effects of a lack of oestrogen. One could also study women who have primary ovarian failure, and consequently a lack of endogenous oestrogen, but who do not have X-chromosome anomalies.

In a recent study we have looked at face processing abilities in women whom have varying sized deletions of their X-chromosome. Those women who had normal ovarian function but who had deleted beyond a critical region of the X-chromosome were found to have face processing deficits equivalent to those seen in Turner syndrome (Good et al., 2001a). This suggests that a gene dosage deficiency, rather than oestrogen deficiency, is critical in producing the observed TS phenotype.

### 7.4.2.2 Genetic mechanisms

#### 7.4.2.2.1 Haploinsufficiency for non-inactivated genes
Face processing abilities were impaired in women with Turner syndrome, irrespective of whether their single X-chromosome was maternally or paternally derived. In addition, structural brain anomalies within the amygdalae, orbito-frontal cortices and occipito-parietal cortex were found, regardless of the parental origin of the intact X-chromosome. This suggests that the deficits are the result of the insufficient product of a gene(s) on the X-chromosome that escapes X-inactivation. This gene(s) would appear to be expressed from both maternally and paternally derived X-chromosomes, since face-processing deficits and brain anomalies are detectable if either of these is missing.

Is there any other evidence that dosage of X-linked genes influences amygdala development? A number of independent neuro-imaging studies have suggested the amygdala may differ in size between females (with two X-chromosomes) and males (with just a single X). Amygdala volume is relatively larger in men than women (Goldstein et al., 2001; Good et al., 2001b; Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Goldstein et al., 2001). A suggestion that this is a direct result of dosage on non-inactivated X-linked genes that do not have Y-homologues, rather than hormonal influences, comes from a study that explored the impact of duplication of X-chromosomes on brain structure. 47,XXY males have amygdalae of similar volume to 46,XX females, whereas the amygdalae of 47,XXX females are significantly smaller than either group (Patwardhan et al., 2002). Together, with the current findings, of increased grey matter of the amygdalae in individuals with Turner syndrome (45,X), these results are strongly suggestive that amygdalae volume decreases as the number of X-chromosomes increases.
No evidence exists to suggest that the volume of the orbito-frontal cortices or indeed the parietal lobes bear this same relationship to number of X-chromosomes. It is therefore probable that the mechanisms, genetic or hormonal, that influence the development of these brain regions in TS would be different to those that influence amygdala development.

7.4.2.2.2 Imprinting

Despite the fact that face-processing difficulties were evident regardless of the parental origin of the X-chromosome, Study Two produced some evidence that imprinted genes may influence face-processing at a functional level. An unusual pattern of correlations was found for TS women, which differed according to the parental origin of the single X-chromosome. The first study found that fear recognition and face memory abilities were highly correlated in female control participants but not in females with TS (45,X^m). Study Two replicated the lack of association between these abilities in TS women with a maternal X-chromosome (45,X^m). However, women with a paternally inherited X (45,X^p), despite having sub-optimal face recognition and fear recognition abilities, showed the normal female association between performance on these two tasks.

In addition to the interaction between correlation and group seen in women with a paternal or maternal X-chromosome, there may be some subtle differences in task performance, with the women with a single paternal X being less impaired. The individuals with a paternal X-chromosome failed to differ significantly from those with a maternal X on any measures of face
recognition. However, when the 45,X^p women were compared with the control females from Study One they showed less impairment than the 45,X^m group. For example, on the Benton test of face recognition, and recognition of angry facial expressions, the women with a paternal X were not achieving significantly lower scores than the control group. This could imply that although the deficits seen in both groups of TS women are similar in nature, they may be less severe in those women with a paternal X. If this is the case then it might indicate the presence of an X-linked gene that is only expressed when it is paternally inherited. Such a conclusion would be consistent with the observation that girls with Turner syndrome with a single paternal X-chromosome have significantly better social adjustment than those with a maternal X (Skuse et al., 1997). However, a larger sample of women with this rare karyotype would need to be tested to draw any firm conclusions. The influence of the parental origin of the single X-chromosome is discussed more fully in Chapter Eight, where it is considered further what these differential correlations might mean.

At a structural level, there is also limited evidence of a subtle difference between those TS women with a paternally inherited, and those with a maternally inherited, X-chromosome. Again, the evidence comes from differing correlations between the two groups of women. In women with a single paternally inherited X-chromosome, indices of left amygdala grey matter correlated positively with fear recognition ability. This was not the case for women with a maternally derived X-chromosome or the control participants. However, as suggested previously, the correlation for 45,X^m women was similar to that for 45,X^p women. With more power (just ten
participants were assessed) a correlation may be detectable for women with a single maternal X too. It is not clear what these different correlations may mean. However, they suggest the possibility of functional differences in the way the amygdalae process faces in these two groups of women. This could be further explored using functional imaging techniques.

7.5 CHAPTER SUMMARY

From Studies One and Two, it was hypothesised that women with TS would have structural anomalies in their amygdalae and/or related neural structures. This was tested using high-resolution volumetric Magnetic Resonance Imaging. Individuals with TS were compared to a group of female controls matched for age and Verbal IQ. The images were analysed by Dr. Tina Good using Voxel Based Morphometry (VBM). As predicted structural differences between TS and control females were detected within the amygdalae bilaterally. Bilateral orbito-frontal cortex also had increased grey matter in women with TS compared to control women. These structures are implicated in the processing of socially and emotionally relevant stimuli and both are suggested to play a direct role in face and emotion recognition (Bernstein, Beig, Siegenthaler, & Grady, 2002; Morris et al., 1996; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998; Wiser et al., 2000; Wiser et al., 2000; Morris et al., 1996; Sprengelmeyer et al., 1998).

The analysis also replicated the finding of a reduction of grey matter in occipito-parietal cortex, which is in line with the reduced Performance IQ’s of these women and their difficulties with visuo-spatial functioning. The structural
differences were consistent across both groups of TS women, suggesting that they are primarily the result of either haploinsufficiency for X-linked genes or hormonal influences rather than the product of genetic imprinting.

It was necessary to compute indices of individual participant’s regional grey matter in order to assess the degree to which regional grey matter correlated with behavioural measures. These indices were derived from the amount (mm$^3$) of grey matter within a single voxel and replicated group differences in the brain regions considered.

These indices of grey matter were then correlated with various behavioural measures. The single significant correlation was for TS women with a single paternal X-chromosome. For these women, there was a positive correlation between estimated left amygdala volume and fear recognition.
8 CHAPTER EIGHT – SEXUAL DIMORPHISM?

8.1 TESTING FOR SEXUAL DIMORPHISM

In Study One, it emerged that individuals with Turner syndrome who had inherited their single X-chromosome from their mother (45,X<sub>m</sub>) performed more poorly than a control group on various tasks of face recognition. In Study Two, it emerged that these difficulties extended to women with TS who had inherited their single X-chromosome from their father (45,X<sub>p</sub>).

Impaired performance on various face processing tasks for 45,X TS generally is suggestive of a gene(s) on the X-chromosome that contributes to the typical development of these abilities, either directly or indirectly. Since males too are in possession of just a single X-chromosome throughout development, if these gene(s) do not have homologues on the Y-chromosome then males should look like women with Turner syndrome. Males should perform more poorly on tests of face and emotion recognition than a comparable group of females. Alternatively, these genes may have homologues on the Y-chromosome, meaning both males and females would have two functional
copies of the genes. If this were the case, the prediction would be that there
would be no differences in face processing abilities as assessed by our
measures. The twelfth hypothesis tested was:

12 Males would perform more poorly than females at tests of face
processing.

8.2 GENDER DIFFERENCES IN FACE PROCESSING AND SOCIAL
ADJUSTMENT

There is no consistent picture in the literature concerning the possibility of sex
differences in face processing abilities. Gender differences are not widely
reported, although some scattered indications exist to suggest that there may
be a female superiority for certain tasks. Herlitz and Yonker found that
females performed better on a task of face recognition (Herlitz & Yonker,
2002). Furthermore they report that face recognition ability is unrelated to IQ
in females but that in males the two scores are correlated. This may indicate
that for males, face recognition is more dependent on general intelligence.

Both sexes would appear to be competent at recognising non-verbal cues
including facial displays of emotion, with many studies finding that males and
females perform at equivalent levels on a wide variety of tests of face and
emotion recognition. However, where differences are reported they typically
show a female advantage, with women being more accurate decoders than
men (Hall, Gaul, & Kent, 1999; Hall, 1978). One study for example, found that
females had a higher rate of correct classification, with males being more likely to have difficulty distinguishing one emotion from the other (Thayer & Johnsen, 2000). This finding holds both for basic emotional expressions such as fear and happiness (Kilgore, 2000) and also for more complex emotional and mental states (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997).

Women have also been noted to be more emotionally expressive in naturally occurring facial expressions (Wagner, Buck, & Winterbotham, 1993) and may be more responsive to distress in others, even from a very young age (Hoffman, 1977). It is also reported that females have a higher degree of facial muscle reactivity when viewing facial expressions in others, to the extent that they mimic the expression themselves (Dimberg & Lundquist, 1990). Right from the very first days of life it is thought that females pay more attention to faces, with female neonates looking for longer at faces, and males spending more time looking at inanimate objects (Connellan & et al., 2001).

Brain imaging studies of developmental changes in responses to facial expressions of fear showed activation of the amygdala to be moderated by age and sex of the respondent (Kesler-West et al., 2001; Kilgore, Oki, & Yergelin-Todd, 2001; Thomas et al., 2001). Assessing electrophysiological responses to facial expressions, Orozco & Ehlers (1998) discovered that females generated significantly longer latency and higher amplitude P450 components than males to both happy and sad faces.
Evidence to suggest that functional asymmetry may play a role in this dimorphism is provided by Harrison, Goreliczenko, & Cook (1990). Here males and females had similar reaction times to emotional expressions presented to the left hemisphere (right visual field) but males were faster to respond to facial expressions that were presented to the right hemisphere (left visual field). Do males have a right hemisphere advantage in emotion recognition?

Kilgore and colleagues (Kilgore et al., 2001) also suggest that hemispheric lateralisation may play a role in gender differences in emotion recognition. Using fMRI technology in a group of adolescents, they discovered that while right amygdala activation to fearful faces appeared to be unrelated to age, left amygdala activation decreased significantly for females (but not males) during adolescence. This was coupled with an increase in prefrontal activation, perhaps implying greater modulation of amygdala activation by pre-frontal cortex for females with increasing age. Adolescent maturation may involve sexually dimorphic development of the pre-frontal cortex and amygdala circuits involved in affective processing.

Neuro-imaging studies suggest that the amygdala is also differentially activated in response to emotionally influenced memory storage. In males, enhanced activity in the right amygdala is related to enhanced memory for emotional films, while for women left amygdala activation is associated with subsequent memory (Cahill et al., 2001b). With specific regard to memory for faces, similar lateralisation differences have been demonstrated. Measuring ERP responses during a face-recognition memory task in a group of pre-
pubertal children, one group found that the boys had greater right hemisphere amplitude, while girls had greater left hemisphere amplitude (Everhart, Shucard, Quatrin, & Shuchard, 2001).

At a structural level, neuroimaging studies demonstrate differences in one of the neural regions involved in social cognition and the processing of facial expressions of emotion. Amygdala volume is relatively larger in men than women (Giedd et al., 1997; Goldstein et al., 2001; Good et al., 2001b). The size of the corpus callosum is also reported to differ according to gender, with females generally having a greater volume in this area (Allen, Richey, Chai, & Gorski, 1991). This structure, which allows information to pass between the left and right hemispheres, may play a role in allowing us to verbally encode emotional information. Both anecdotal evidence and research suggests that women's conversation involves much more talk about feelings, whereas men's conversation tends to be more object or activity focused (Morrow, 1990).

With regard to social competence more generally, it would seem that girls may acquire a Theory of Mind and False-belief understanding slightly earlier than boys (Charman, Ruffman, & Clements, 2002; Happe, 1995). Girls, it would seem, may also be more successful than boys at understanding the feelings of others (Dunn, Brown, Slomkowski, Tesla, & Youngblade, 1991). Disorders of social adjustment such as autism and psychopathy are far more common among males, and these disorders tend to be associated with abnormalities in facial emotion recognition (Hobson, Ouston, & Lee, 1989;
Stevens, Charman, & Blair, 2000). In turn, Autistic and Psychopathic behaviours have both been linked to compromised integrity of neural structures involved in social cognition such as the amygdala and the orbito-frontal cortex (Baron-Cohen et al., 1994; Blair, Jones, Clark, & Smith, 1997; Howard et al., 2000). Simon Baron-Cohen has suggested that autism can be conceptualised as an extreme form of the male brain (Baron-Cohen, 2002) – would difficulties evident in individuals with autism, such as poor emotion recognition skills, be reflected in sex-differences in the normal population?

8.3 AIM

Study Three sought to test the hypothesis that males would have relatively poor face processing abilities compared to females.

8.4 METHODOLOGY

8.4.1 Sample recruitment

Forty control participants (20 male and 20 female) were recruited from in and around the University of London and Great Ormond Street Hospital, by means of recruitment posters. The posters advertised the study as involving taking part in some ‘fun psychological tests’ and informed participants that they would be paid £15 for their participation. Participants were invited to take part if they were between 18 and 36 years of age and had been resident in the UK.
for more than three years. Volunteers were excluded if they had lived in the UK for less than three years, if they had known psychiatric or neurological disease, or a Verbal IQ of less than 70. One male was excluded after testing because a Wecshler Adult Intelligence Scale (WAIS) revealed an estimated Verbal IQ of less than 70 points.

8.4.2 Sample characteristics

8.4.2.1 Age

The participants used in this study were young adults, all between the ages of 16 – 39 years. Age characteristics are shown in table 8.1. The males and females were of equivalent ages according to an Independent Samples T-Test (t (1,37) = -7.38, p=.47).

Table 8.1: Age in years of study participants.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XX (females)</td>
<td>20</td>
<td>21.85</td>
<td>5.26</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>46,XY (males)</td>
<td>19</td>
<td>23.00</td>
<td>4.41</td>
<td>16</td>
<td>36</td>
</tr>
</tbody>
</table>
8.4.2.2 Ethnicity

Participants were asked to indicate their ethnicity as being one of the following: White, Indian/Pakistani, Asian, African/Caribbean or other. Seventeen of the male and seventeen of the female participants described themselves as 'White', with one participant from each group being 'Indian/Pakistani'. The remaining male classified himself as Asian with the remaining two female participants classifying themselves as African/Caribbean and Other.

8.4.2.3 Educational level

Participants indicated the highest educational level that they had attained out of the following options: No exam qualifications, GCSE/O-Level, Secretarial or technical, A-Level, Professional qualification without University degree (e.g. SRN, teaching diploma, HNC, TEC), University degree (or equivalent). Proportions for each educational level were similar across the groups as can be seen in table 8.2 and the mean ranks of the groups were not significantly different according to Mann-Whitney test statistics (females 46,XX = 17.75, males 46,XY = 22.37, U=145, p=.19).
Table 8.2: Maximum level of educational qualification achieved

<table>
<thead>
<tr>
<th>Educational qualifications</th>
<th>46,XX (females)</th>
<th>46,XY (males)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=19</td>
</tr>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GCSE/O-Level</td>
<td>3 15.0</td>
<td>2 10.5</td>
</tr>
<tr>
<td>Secretarial/Technical</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A-Level</td>
<td>10 50.0</td>
<td>4 21.1</td>
</tr>
<tr>
<td>Professional qualification</td>
<td>1 5.0</td>
<td>6 31.6</td>
</tr>
<tr>
<td>University degree</td>
<td>6 30.0</td>
<td>7 36.8</td>
</tr>
</tbody>
</table>

8.4.2.4 Social class

Participants occupations were classified according to the Standard Occupational Classification 2000 (Office of National Statistics, 2000). The classification included nine groupings: 1. Managers/Senior officials, 2. Professional occupations, 3. Associate professional and technical occupations, 4. Administrative/secretarial occupations, 5. Skilled trades, 6. Personal service occupations, 7. Sales/Customer service occupations, 8. Process/plant/machine occupations, 9. Elementary occupations (see table 8.3). None of the participants were classified as belonging to groups 1, 6, or 7. One woman described her occupation as a house/wife and one male described his as unemployed with no indication of previous employment type.
These descriptions cannot be classified according to the criteria. The mean rank of the participants is not significantly different according to gender (Females 46,XX =18.68, males 46,XY = 19.33, U=165, p=.82).

Table 8.3: Social group classification

<table>
<thead>
<tr>
<th>Occupation</th>
<th>46,XX (females)</th>
<th>46,XY (males)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=19</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Unemployed (not classified)</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>1. Managers/Senior officials</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Professional occupations</td>
<td>14</td>
<td>73.7</td>
</tr>
<tr>
<td>3. Associate professional &amp; technical</td>
<td>4</td>
<td>21.1</td>
</tr>
<tr>
<td>4. Administrative &amp; secretarial</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5. Skilled trades</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6. Personal Service</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7. Sales/Customer service</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8. Elementary</td>
<td>1</td>
<td>5.3</td>
</tr>
</tbody>
</table>
As with Study One, participants were excluded if their Verbal IQ was below 70. One of the male participants had a Verbal IQ within this range and was therefore excluded from analyses. Groups were matched in terms of both Verbal and Performance IQ and consequently were matched for full scale IQ. The IQ distributions of the groups can be seen in table 8.4.

<table>
<thead>
<tr>
<th></th>
<th>46,XX (female)</th>
<th>46,XY (male)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=19</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>100.35</td>
<td>106.37</td>
<td>.082</td>
</tr>
<tr>
<td>sd</td>
<td>11.35</td>
<td>9.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>111.70</td>
<td>107.95</td>
<td>.393</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>14.33</td>
<td>12.67</td>
<td></td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>105.50</td>
<td>107.58</td>
<td>.587</td>
</tr>
<tr>
<td></td>
<td>12.38</td>
<td>11.25</td>
<td></td>
</tr>
</tbody>
</table>

8.4.3 Statistical procedures

The groups did not differ significantly on any of the background variables considered and therefore none were entered as covariates in the following analyses. For all variables (separately for each group), the assumption of normality of distributions was tested using one-sample Kolmogorov-Smirnov tests. For one variable (Ekman-Friesen recognition of happy faces), all
participants achieved the maximum score of ten. With no variance, it is not possible to perform a test for normality. All other test results were found to be normally distributed for both males and females.

8.5 RESULTS

8.5.1 Tests of face recognition

As can be seen from table 8.5, performance on none of the face recognition tasks varied according to gender. The males performed at the same level as the females on all accuracy measures. They were as accurate as females at matching faces for the Benton test of face recognition. They were as accurate as females at learning new faces (The Warrington face recognition memory test) and they were as good at recognising familiar (famous) faces.
Table 8.5: Group comparisons for tests of face recognition accuracy

<table>
<thead>
<tr>
<th>Variable</th>
<th>46,XX (females)</th>
<th>45,XY (males)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Benton face recognition</td>
<td>20</td>
<td>46.30</td>
<td>3.64</td>
</tr>
<tr>
<td>Warrington recognition memory (faces)</td>
<td>20</td>
<td>42.20</td>
<td>4.81</td>
</tr>
<tr>
<td>Warrington recognition memory (words)</td>
<td>20</td>
<td>49.10</td>
<td>1.12</td>
</tr>
<tr>
<td>Famous faces (cropped)</td>
<td>20</td>
<td>82.96</td>
<td>15.48</td>
</tr>
<tr>
<td>Famous faces (uncropped)</td>
<td>20</td>
<td>88.81</td>
<td>9.72</td>
</tr>
<tr>
<td>Famous faces (total)</td>
<td>20</td>
<td>85.78</td>
<td>11.79</td>
</tr>
</tbody>
</table>
8.5.2 Tests of configural face processing

8.5.2.1 Mooney face recognition

An independent samples T-test was applied to examine the effect of group (males vs. females) on adjusted Pr' scores derived from performance on this task. There was no difference between the groups in their accuracy for this task (df=37, t=.057, p=.96). Accuracy for judgements about the age and gender of the faces were also similar for male and female participants (age: df=37, t=.50, p=.57, gender: df=37, t=.58, p=.62).

Table 8.6: Mooney face recognition

<table>
<thead>
<tr>
<th></th>
<th>46,XX (female)</th>
<th>46,XY (male)</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>.438</td>
<td>.436</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sd</td>
<td>.17</td>
<td>.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr' prime score (for accuracy and false hits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.438</td>
<td>.436</td>
<td>.057</td>
<td>.96</td>
</tr>
</tbody>
</table>

Accuracy for age judgements (%)

<table>
<thead>
<tr>
<th></th>
<th>75.86</th>
<th>73.05</th>
<th>.498</th>
<th>.62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.67</td>
<td>19.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Accuracy for gender judgements (%)

<table>
<thead>
<tr>
<th></th>
<th>86.07</th>
<th>83.20</th>
<th>.576</th>
<th>.57</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.17</td>
<td>13.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### 8.5.2.2 Facial inversion test

Accuracy in matching upright and inverted faces was examined by ANOVA. The dependent variable was orientation (upright or inverted), the group factor was gender (male or female). There was a main effect of orientation, in favour of upright faces ($F(1,37) = 15.39, p > .0001$) but no effect of group ($F(1,37) = .027, p = .87$) and no interaction between group and orientation ($F(1,37) = .39, p = .53$). Both males and females were more accurate at matching upright than inverted faces (see figure 8.1).

![Upright and inverted face matching](image)

**Figure 8.1:** Matching of upright and inverted faces. Bars show mean. Error bars show standard error.
8.5.2.3 Whole/part face matching

Accuracy measures for the whole face, upper face, and lower face matching were entered into ANOVA as three levels of a single dependent variable (part-of-face). The group factor was gender (male or female). There was a main effect of part-of-face with whole faces being more accurately matched \((F(1,36) = 5.24, p=.01)\). There was no effect of group \((F(1,36) = .051, p=.82)\). There was a non-significant trend for an interaction between group and condition \((F(1,36) = 3.65, p=.06)\) (see figure 8.2). Females were more accurate for whole face and upper face stimuli while males out-performed females on lower faces.

![Figure 8.2: Accuracy for matching whole, upper and lower face parts. Bars show mean. Error bars show standard error.](image)

Gender
- Females (46,XX)
- Males (46,XY)

upper face  whole face  lower face

Accuracy (%) 100.00 90.00 80.00 70.00 60.00 50.00

Figure 8.2: Accuracy for matching whole, upper and lower face parts. Bars show mean. Error bars show standard error.
8.5.3 Facial expression classification

Accuracy (raw scores) for each facial expression category were entered into a MANOVA. Happiness scores were omitted as both groups scored at ceiling for this measure. Figure 8.3 shows the distribution of accuracy scores and demonstrates that the male and female participants were recognising equivalent proportions of each facial expression. Scores failed to differ between male and female participants (F (1,33) = .706, p = .62). None of the emotions had significantly different rates of accuracy according to gender. The groups also failed to differ with regard to total score for emotion recognition accuracy (XX mean = 52.9 (sd 4.3), XY mean 51.6 (sd 3.9).

Expression classification accuracy

Figure 8.3: Emotion recognition accuracy for six basic emotions. Bars show mean. Error bars show standard error.
8.5.4 Correlational analyses

In Studies One and Two it was found that fear recognition and face memory abilities were correlated in typically developing women and individuals with TS with a paternally inherited X-chromosome (45,X\(^{p}\)) but not in TS women with a maternal X-chromosome (45,X\(^{m}\)). The correlation patterns were explored separately for the male and female groups in this study. First, the female group was examined to see if the correlations reported in Study One would be replicable.

Bivariate correlations (Pearson’s test) were calculated for individual expression scores below ceiling level (surprise, fear, sadness, anger and disgust, but not happiness) with face recognition scores.

As was the case in Study One, the correlations between the face recognition and fear recognition variables were significant for the female participants as can be seen in figures 8.4 and 8.5. Pearson correlation coefficients were similar to those obtained in Study One for the fear and Warrington face recognition correlations (Pearson correlation coefficient Study One females = .735, p < .0001) and the fear and Famous face recognition correlation (Pearson correlation coefficient Study Two females = .564, p = .005). In addition to the correlations found in Study One, two other negative emotions (anger and disgust) were also found to be correlated with face recognition accuracy on the Warrington and famous face recognition tasks (see table 8.7). In addition, Benton face recognition was significantly correlated with recognition...
of the facial expression of disgust. Total emotion recognition score was also significantly correlated with Benton face recognition (Pearson correlation coefficient .481, p=.03), Warrington face recognition (Pearson correlation coefficient .675, p=.001) and famous face recognition (Pearson correlation coefficient .674, p=.001) in females.
Table 8.7: Correlations between emotion recognition scores and face recognition and configural processing measures - 46,XX females.

<table>
<thead>
<tr>
<th></th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton</td>
<td>.006</td>
<td>.326*</td>
<td>-.363</td>
<td>.521*</td>
<td>.373</td>
</tr>
<tr>
<td>face recognition</td>
<td>-226</td>
<td>.690***</td>
<td>.215</td>
<td>.502*</td>
<td>.531**</td>
</tr>
<tr>
<td>Warrington</td>
<td>-165</td>
<td>.585**</td>
<td>-.099</td>
<td>.640**</td>
<td>.783***</td>
</tr>
<tr>
<td>Famous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mooney</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition (sensitivity to 1st order relations)</td>
<td>-.392</td>
<td>.421</td>
<td>.284</td>
<td>.147</td>
<td>.564*</td>
</tr>
<tr>
<td>Whole-part</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>face recognition (holistic processing)</td>
<td>.211</td>
<td>-.330</td>
<td>-.327</td>
<td>.010</td>
<td>-.226</td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2nd order relations)</td>
<td>-.152</td>
<td>.295</td>
<td>.400</td>
<td>-.148</td>
<td>.349</td>
</tr>
</tbody>
</table>

* p<.05 (two-tailed)
** p<.01 (two-tailed)
*** p<.001 (two-tailed)

no longer remain significant after Bonferroni corrections for multiple comparisons.
Figure 8.4: Scatter plot showing the correlation between fear recognition and Warrington recognition memory for faces in females, with line of best-fit and 95% confidence intervals displayed.
Fear recognition

Figure 8.5: Scatter plot showing the correlation between fear recognition and famous face recognition in females, with line of best-fit and 95% confidence intervals displayed.

Bivariate correlations were performed separately for the male participants with the same variables. As can be seen from table 8.8, the correlations between fear recognition and the face recognition memory variables failed to approach significance in these participants. In fact, the only correlations to reach significance for male participants were the positive correlations between Benton face recognition and the recognition of facial expressions of fear and anger. Figures 8.6 and 8.7 demonstrate the lack of association between fear recognition scores and face recognition memory ability.
Table 8.8: Correlations between emotion recognition scores and face recognition and configural processing measures – 46,XY (males)

<table>
<thead>
<tr>
<th></th>
<th>N=19</th>
<th>Surprise recognition</th>
<th>Fear recognition</th>
<th>Sadness recognition</th>
<th>Disgust recognition</th>
<th>Anger recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton face recognition</td>
<td>-.011</td>
<td>.690***</td>
<td>-.219</td>
<td>.303</td>
<td>.514*</td>
<td></td>
</tr>
<tr>
<td>Warrington face recognition</td>
<td>.012</td>
<td>.123</td>
<td>-.176</td>
<td>.263</td>
<td>.168</td>
<td></td>
</tr>
<tr>
<td>Famous face recognition</td>
<td>-.187</td>
<td>-.104</td>
<td>.129</td>
<td>.225</td>
<td>-.117</td>
<td></td>
</tr>
<tr>
<td>Mooney face recognition (sensitivity to 1st order relations)</td>
<td>-.266</td>
<td>.402</td>
<td>-.153</td>
<td>-.010</td>
<td>.236</td>
<td></td>
</tr>
<tr>
<td>Whole-part face recognition (holistic processing)</td>
<td>-.230</td>
<td>-.214</td>
<td>.000</td>
<td>.418</td>
<td>-.074</td>
<td></td>
</tr>
<tr>
<td>Upright-inverted Face recognition (sensitivity to 2nd order relations)</td>
<td>-.014</td>
<td>.311</td>
<td>-1.67</td>
<td>.020</td>
<td>-.060</td>
<td></td>
</tr>
</tbody>
</table>

*p<.05 (two-tailed)  
**p<.01 (two-tailed)  
***p<.001 (two-tailed)  

no longer remain significant after Bonferroni corrections for multiple comparisons
The hyperstat method (as described in study one) was applied to test for a difference in the magnitudes of the correlations for the male and female participants. Fear recognition and Warrington face recognition were correlated to a significantly greater degree in females than in males (z=2.07, p=.02). Fear recognition and Famous face recognition were also significantly more correlated in females than in males (z=2.21, p=.01).
Figure 8.7: Scatterplot showing the lack of correlation between fear recognition and famous face recognition in the male participants, with line of best-fit and 95% confidence intervals displayed.

In male participants, unlike the females, total emotion recognition accuracy failed to correlate with any measure of face recognition.

8.6 DISCUSSION

Numerous studies are suggestive of possible gender differences in recognition of faces and facial expressions of emotion (Herlitz et al., 2002; Thayer et al., 2000). However, in this study, males and females performed at equivalent levels on all tasks of face and emotion recognition. There were no significant gender differences for any of the measures reported.
The hypothesis was that men, like women with Turner syndrome, have just one X-chromosome and would therefore also perform at a lower level than females (with two X-chromosomes) on tasks of face and emotion recognition. There are at least two plausible explanations (at a genetic level) for why males do not differ to normal females despite just having a single X-chromosome. The first is that the gene(s) important for the development of normal face processing abilities that are located on the X-chromosome may have Y-homologues. That is the genes important for face recognition on the X-chromosome have equivalent counterparts on the Y-chromosome, meaning that males and females would both have two functioning copies of these genes.

The second possibility is that the Y-chromosome does not have a homologue of the gene(s) but its presence serves to up-regulate expression from the single maternal X-chromosome (Graves, Distecho, & Toder, 1998). So that although males (like women with TS) would have just one functioning copy of the gene(s), their expression of this gene would be similar to the levels of females with two X’s as the level of expression from this single gene(s) would be greater.

The correlation differences between males and females, however, support the suggestion that imprinted genes may play an important role in the functional specialisation of neural systems involved in face and emotion processing. For typically developing females (who inherit an X from both their mother and their father), fear recognition and face recognition were highly correlated, whilst in
males (whose single X always comes from their mother) there was no
correlation between these abilities. These results are of interest taken
alongside the observation (reported in Chapter Five) of differing correlations in
women with TS according to the parental origin of their intact X-chromosome.
Fear and face recognition abilities were correlated in females with TS and a
single paternally derived X-chromosome but showed no association when the
single X was maternally derived.

The possession of a paternally derived X chromosome (46 XX and 45 X^p)
characterises those women who show a strong correlation between fear
recognition and face recognition memory, suggesting a common factor
underlying performance on these tasks. If a paternally derived chromosome
is not present (46,XY males and 45X^m), there is no correlation suggesting the
lack of a common factor underlying performance on the two tasks. Whatever
this factor may be, I hypothesise that it will be evident in specific patterns of
brain activation.

One hypothesis, testable using fMRI, is that activity within the amygdalae of
the right and left hemisphere is differentially associated with face recognition
memory and fearful face recognition depending on the presence of a
paternally derived X-chromosome.

Memory for arousing events is associated with enhanced amygdala activity,
possibly via interactions with endogenous stress hormones (Cahill, 2000;
Cahill & McGaugh, 1998). In Chapters Two and Six the novel suggestion was
made that since faces are arousing stimuli, memory for faces may also be enhanced by amygdala activity. Gender-related lateralisation of amygdala involvement in emotionally influenced memory has been reported (Cahill et al., 2001). Amygdala activity during the viewing of emotional films was correlated with subsequent recall of these films up to four weeks later. In males, activity within the right amygdala, in particular the basolateral nuclei, correlated with subsequent recall. However, in females, recall was correlated with activity within the left amygdala, particularly regions encompassing the central and medial nuclei.

If this sex-specific pattern of lateralisation of amygdala extended to explicit memory for faces, then face recognition may be associated with right amygdala activity in males but left amygdala activity in females. I am not aware that any neuro-imaging studies of face recognition have explicitly compared neural activity in males and females for a face recognition task. One study which has some data to address this point is a study that looked at the effect of encoding strategy on neural correlates of memory for faces (Bernstein, Beig, et al. 2002 3097 /id). In two of the face encoding conditions employed in this Positron Emission Tomography (PET) study, good recognition for the faces presented was correlated with activity in a number of regions, including cerebellum, fusiform, hippocampus and inferior temporal regions. Most importantly, at both encoding and recognition, bilateral amygdala activity predicted face recognition ability. Since the study participants were a mixture of both males and females, six of each, and no comparisons were made, it is not possible to assess the extent to which each
group is contributing to this overall finding. Based on my prediction, it could be
the case that for males, right amygdala activity correlates with face memory
while for females left amygdala activity would correlate, meaning that
considering both sexes together would mask any laterality effects.

How could such (predicted) face-recognition sex-differences in lateralisation
be associated with fear-labelling differences? Alongside the general
observation that amygdala activity is associated with the recognition of fearful
faces (for a review see (Phan, Wager, Taylor, & Liberzon, 2002)), several
neuroimaging studies have reported left lateralisation of this response in both
male and female participants (Breiter et al., 1996; Morris et al., 1996; Thomas
et al., 2001). There is preliminary evidence from our own work that a
correlation exists for females between the response of the left amygdala, and
associated cortical face processing systems, and accuracy of naming fear
specifically, in an emotion recognition task.

If, as suggested above, females may also recruit the left amygdala for face
memory, then overlapping neural systems, focussed on the left amygdala,
may be engaged for both fear recognition and face recognition memory.
However, for males it was predicted that neural activity within the right
amygdala may characterise face recognition. Since explicit naming of fearful
facial expressions engages the left amygdala, the neural networks dealing
with each of these tasks would be at least partially distinct in men, compared
with women.
To summarise: in females, explicit recognition of fear in faces and of facial identities may correlate because they both engage left amygdala and therefore rely on some common neural circuitry. However, in males, where these abilities fail to correlate, the tasks may be engaging at least partially distinct neural substrates, which may account for the lack of association at a behavioural level.

This reasoning can be extended to the interpretation of the group differences in correlations for women with TS who have a paternally derived, and those who have a maternally derived X-chromosome. Like males (who have a single maternal X-chromosome) women with TS and a single maternally derived X-chromosome show no evidence of association between their fear recognition and face recognition memory abilities.

The cortical activation hypothesis would therefore be that for these women (as for men) face recognition memory would be associated with neural activity within the right amygdala, whilst explicit fear recognition would largely recruit the left amygdala. Where fear recognition and face recognition memory are highly correlated (45X_p TS and typically developing females), it would be predicted that left amygdala activity would be associated with both face recognition and fear recognition abilities.

In conclusion, the hypotheses to test during future fMRI experiments would be:
1. In individuals with a paternally derived X-chromosome (typically developing females and individuals with TS with the 45,X^P karyotype) left amygdala activity would be associated with face recognition and fear recognition.

2. In individuals who do not possess a paternally derived X-chromosome (typically developing males and individuals with TS with the 45,X^m karyotype) right amygdala activity would be associated with face recognition memory, whilst left amygdala activity would be associated with fear recognition abilities.

Both the Ekman-Friesen affect recognition task and the Warrington recognition memory task could be administered as components of a functional neuroimaging study. The Ekman stimuli have been used frequently in such experiments {Morris, Frith, et al. 1996 281 /id}{Phillips, Young, et al. 1997 251 /id} and tasks similar to the Warrington have also been administered under such conditions {Bernstein, Beig, et al. 2002 3097 /id}.

It would then need to be considered HOW the imprinted gene would influence brain function and also WHY, from an evolutionary perspective, this gene would have been preserved given that it would contribute to gender differences in behaviour.

Cahill and colleagues (Cahill et al., 2001) suggest that for women memory-related processing of emotional stimuli may be viscerally mediated. In addition to the laterality differentiation of amygdala activation in males and females, it
was found that the region of the amygdala activated in females was more medial. The medial amygdala nuclei have well-established connectivity to hypothalamic and brain stem regions \cite{Petrovich, Caneras, et al. 2001} that are involved in the regulation of the autonomic nervous system. For males, right amygdala activation primarily involved the basolateral nuclei, which connect strongly to striatal and cortical regions \cite{Swanson & Petrovich, 1998}. Cahill and colleagues therefore suggest that, for males, memory related processing for emotional stimuli might be mediated more by cognitive cortical-related circuitry and in females by autonomic-related circuitry. Could imprinting of X-linked genes, rather than any hormonal influences, influence these different functional correlates of emotional memory processing for males and females? Moreover, could this sexually dimorphic epigenetic modification of gene activity be evolutionary advantageous to both males and females?
8.7 CHAPTER SUMMARY

This study sought to test two hypotheses. The first was that males would perform more poorly than females on tests of face and emotion recognition. This was based on the premise that, like individuals with TS, males also have just a single X-chromosome. However, on all the cognitive tasks males and females performed at equivalent levels. There was no sexual dimorphism in terms of face and emotion recognition abilities.

The second hypothesis was that males would not show the typical female correlation between face recognition memory and fearful face recognition. This was based on the premise that individuals with TS and a single paternal X show the normal female association while those with a single maternal X do not. As males always inherit their X-chromosome from their mother, if the association is a result of the presence of a paternally inherited X-chromosome, males should not show the correlation. This was indeed the case. The highly significant correlation between face memory and fear recognition skills was replicated in an independent group of females, but no evidence of a correlation was seen in the male participants.

The results were then discussed in terms of the possible differential lateralisation of neural activity, centred on the amygdala, that may underlie task performance in males and females and additionally in 45,X<sup>m</sup> and 45,X<sup>p</sup> TS females.
9 CHAPTER NINE – GENERAL DISCUSSION

9.1.1 OVERVIEW

Turner syndrome is a rare genetic condition, where females have just one (instead of two) X-chromosomes. Studying this condition is not only useful to our understanding of the condition itself but can also inform our knowledge of the importance of X-linked genes in normal development.

Individuals with TS are reported to experience social adjustment difficulties, although there is a limited understanding of the exact nature or underlying causes of these difficulties. Face processing abilities for recognition of identity and emotion are important in social development. This Thesis tested the hypothesis that women with Turner syndrome would have sub-optimal face and emotion recognition abilities. It also sought to investigate the possible genetic mechanisms that may underlie these abilities.

Women with TS had significant face and emotion recognition deficits regardless of whether their single X-chromosome was maternally or paternally derived. These face-processing difficulties were found despite the fact that the women were able to process faces in a typical configural manner. It was suggested that dysfunctional socio-emotional processing was the best
explanation for the specific combination of deficits observed. The pattern of
deficits were reminiscent of those experienced by patients with bilateral
amygdala damage and were consistent with our knowledge of the roles of this
region from functional neuroimaging studies. It was therefore predicted, and
confirmed using structural magnetic resonance imaging, that these women
would have structural differences in their amygdalae compared to a group of
control females. However, rather than having reduced grey matter of the
amygdalae, the women had increased grey matter relative to a control group
of females. The orbito-frontal cortices also had increased grey matter in these
women, suggesting a possible link between the development of parts of this
neural circuit involved in socio-affective processing and face processing
abilities in Turner syndrome. Reduced grey matter was identified within right
occipito-parietal cortex. This region has also been reported to play a key role
in emotion recognition from faces (Adolphs et al, 1996). However, given the
specificity of the emotion recognition problems in TS and the other associated
face recognition problems in this population, the amygdala would appear to
appear a better candidate for playing a causal role in the development of
difficulties. The abnormal structure of the occipital parietal cortex, however,
may also be important in contributing to these anomalies and functional
imaging work could perhaps elucidate this further.

A correlation in an un-predicted direction was observed between fear
recognition ability and amygdala size, such that in women with TS, the higher
the grey matter index for amygdala grey matter (suggesting increased grey
matter), the better the fear recognition ability. From this it was argued that
hypertrophy in the amygdalae in TS may in part reflect a compensatory response to anomalous function of this region and possibly other related circuitry.

Women with TS with a single paternal X-chromosome showed the normal female association between fear recognition and face recognition memory abilities, while women with a single maternal X-chromosome did not. If this difference was related to gene(s) that are expressed from a paternally inherited X but not from a maternally inherited X and had no Y-homologue, it was hypothesised that males would (like 45, X0 TS women) show no correlation between fear and face recognition abilities. Although males performed as well as normal females on all tasks of face processing they did, as predicted, fail to show any association between fear recognition and face recognition memory. It was suggested that these correlation differences may relate to differential lateralisation of face memory processing, according to the presence of an imprinted gene expressed only from the paternally derived X-chromosome.

These results suggest that at least two genetic mechanisms may come into play in influencing the emerging TS phenotype. The first of these is haploinsufficiency for non-inactivated genes on the X-chromosome, whereby women with Turner syndrome have half the gene expression of typically developing women. This mechanism may contribute to the relative deficit in face processing abilities described in these women. The second mechanism would appear to relate to an imprinted genetic locus that is expressed from
the paternally inherited X-chromosome but silenced on the maternally inherited X chromosome. This mechanism does not influence level of face processing ability (at least not on tasks considered here) but may serve to influence the way that these tasks are performed functionally.

9.2 IMPLICATIONS

What do these results contribute to our understanding of face processing more generally?

Current interest in face processing arose largely from the observation that the ability could be impaired relatively selectively in patients with brain damage e.g. (Bodamer, 1947). A great deal is now known about how faces are processed in the typically developing brain. This is just beginning to be enriched, in turn, by the consideration of face processing abilities in individuals with developmental anomalies (Deruelle, Mancini, Livet, Cassse-Perrot, & de Schonen, 1999; Howard et al., 2000).

In autism, where face-processing abilities are compromised, configural face processing abilities also appear to be anomalous. Individuals with this condition do not show the normal sensitivity to manipulations of the face image that disproportionately effect this type of processing (Hobson, Ouston, & Lee, 1988; Teunisse & de Gelder, 1994). However, in William's syndrome, where configural face processing is also compromised, face recognition
appears to be a relative strength (Deruelle et al., 1999; Karmiloff-Smith, 1997). The results presented in this thesis suggest that the remaining combination of these abilities is present in TS, where poor face recognition abilities are seen alongside normal configurational face processing. Taken together these results imply that configurational face processing is neither necessary, nor sufficient for face recognition abilities to develop. That is not to say that in typical development these abilities are not highly inter-related but that other influences must also come to bear upon the development of face recognition abilities.

In this thesis, it is suggested that one of these other influences might be the ability to respond to the affective significance of faces. There is no doubt that faces hold a supreme significance to humans throughout development, with even young babies paying more attention to faces than to various other stimuli (Johnson, Dziurawiec, Ellis, & Morton, 1991). A failure to respond to the emotional significance of faces may be at the route of face processing anomalies in particular neurodevelopmental disorders. This anomalous responsiveness to faces may be mediated by sub-optimal development of neural circuits implicated in social cognition, including the amygdalae and orbito-frontal-cortices.

With regard to autism, Grelotti and colleagues also highlight the importance of normal emotional responsiveness to faces in the development of typical face recognition skills (Grelotti, Gauthier, & Schultz, 2002). In autism, anomalous amygdala structure and function accompany poor face and emotion
recognition abilities. Grelotti and colleagues suggest that this points to the fact that face expertise fails to develop in these individuals due to the abnormal social significance of faces for them. Although, in Turner syndrome there are no configurai face processing abnormalities, many of the other deficits identified within this thesis bear a striking resemblance to those that have been noted for individuals with autistic spectrum disorders. Poor face recognition memory abilities and poor facial emotion recognition abilities, in particular for fearful faces, have been observed in autism (Boucher & Lewis, 1992; Howard et al., 2000).

Can the genetic anomaly in TS inform our understanding of the appearance of these same characteristics in autism? Just because the same behavioural difficulties, possibly accompanied by abnormalities in a similar underlying neurocognitive system, occur in two conditions does not in itself imply that the aetiology of the difficulties would be the same in each. Furthermore, the fact that face-processing anomalies are accompanied by amygdala anomalies in these two conditions does not mean that the brain anomaly and behaviour are necessarily related or in which direction, if any, causality may apply. Abnormal function of this structure could conceivably elicit the difficulties identified (as evidenced by a case of developmental damage to this region (Tranel & Hyman, 1990)). However, it is not inconceivable that abnormal developmental experience with faces, for some other reason, could influence the structural development of this brain region. Therefore great caution needs to be exercised in inferring causality and it is important to be mindful of the role development itself may play in the neuro-cognitive patterns evident in
adulthood (see for example (Karmiloff-Smith, 1997)). Causality aside, the co-occurrence of this neuro-cognitive phenotype in TS and in autism may be informative to our understanding of the genetic underpinnings of autism. Especially as females with TS are much more likely than normal females to be autistic and show autistic traits of behaviour (Creswell & Skuse, 2000).

It is widely understood that autism is a highly heritable condition, and most cases of autism are caused by genetic factors. Epidemiological studies typically demonstrate a much higher prevalence in siblings, with a recurrence that is 50 to 100 times greater compared to the incidence in the general population (Fombonne, 1998). Twin studies suggest a genetic mechanism. Monozygotic twins are more likely to be concordant for autism (up to 60% concordance) than dizygotic twins (Bailey et al., 1995). However, little progress has been made by linkage studies seeking to identify which genes might be responsible for the condition. Males are at least four times more likely to suffer from autism than females (Lord, Rutter, & LeCouteur, 1994; McLennan, Lord, & Schopler, 1993; Szatmari, Jones, Zwaigenbaum, & MacLean, 1998; Volkmar, Szatmari, & Sparrow, 1993). Could the fact that males have just a single X-chromosome, like our females with Turner syndrome, be of significance?

There is an increased incidence of autism in Turner syndrome (Creswell et al., 2000). Maybe the second X-chromosome in normal females acts in some way as a protective factor against the development of autism. If the development of the face recognition abilities is functionally dimorphic in males and females,
as suggested in Chapter Eight, anything that influences the development of these abilities will be likely to have sexually dimorphic consequences.

9.3 FUTURE DIRECTIONS

As with most research, particularly within the realms of cognitive neuroscience, this thesis raises many more questions than it answers. It has served as the basis for a wider investigation into the influence of X-linked genes on face processing skills and social cognitive development.

There are many hypotheses that can be generated from the studies reported and I will now close this thesis by considering some further investigations that could be undertaken to enhance our knowledge of the theoretical issues that have been discussed. For some of the suggestions, further investigation is already underway.

9.3.1 Identifying a candidate gene

Studies One and Two of this thesis demonstrated the importance of X-linked genes in the development of face processing abilities. There are known to be in excess of 1,000 genes on the human X-chromosome (Wellcome Trust, 2001), of which a significant proportion escape X-inactivation. These genes are needed in two copies in normal females, and are therefore regarded as being dosage sensitive. In order to understand the mechanisms that may mediate the link between genotype and the development of face processing
abilities, it is our ultimate aim to identify which of these dosage-sensitive
genes are critical. Assessing individuals who have naturally occurring
deletions of one of their X-chromosomes is one type of methodology that can
be employed to explore this question.

We have identified a number of such females who have deleted varying sized
portions of the short arm of their X-chromosome (see (James et al., 1998)).
Our preliminary investigations suggest that a region between 36.6 and 42.6
Megabases from the telomere is likely to contain genes that influence face-
processing abilities and amygdala development (Good et al., 2001).
Individuals with deletions of the X-chromosome that do not extend into this
region, have apparently normal face processing abilities and structurally
normal amygdalae, despite being symptomatic for other features of Turner
syndrome. However, women with deletions that encompass this critical region
show face processing deficits and amygdala anomalies associated with a
complete deletion of the X-chromosome (Turner syndrome).

There are twenty-five known genes within this 6 megabase region. Only those
genes (up to twenty) that escape X-inactivation are potential candidates.
Because these genes exist in just a single copy in females with deletions of
the critical region, any phenotypic features must be due to insufficient dosage
of their gene product. Two genes, that may escape X-inactivation, stand out
as being potentially very interesting to investigate. The Monoamine Oxidase A
(MAOA) and Monoamine Oxidase B (MAOB) genes are both found within this
critical region. These genes are involved in the degradation of biogenic
amines including dopamine, serotonin and norepinephrine, all of which are known to play a role in emotion regulation (Shih, Grimsby, Chen, & Zhu, 1993).

A recent study suggests that at least one of these neurotransmitters, serotonin (5-HT), is functionally important to the response of the human amygdala to fearful faces (Hariri et al., 2002). In humans the short allele of the serotonin transporter gene (SLC6A4) is associated with reduced serotonin expression and function. Hariri and colleagues report that individuals with one or two copies of this gene exhibit greater neuronal activity in response to fearful faces, than do individuals who are homozygous for the long (more efficient) allele. It would seem that serotonin has a direct impact on the function of neural circuits including the amygdala that are part of a network that responds to fearful stimuli. Any gene involved in the degradation of serotonin (for example MAOA and MAOB) may therefore also be implicated in the optimal functioning of this circuitry. It may be important to clarify whether either of these genes play a role in the development of face-processing, in particular fear recognition. One way of exploring this would be to investigate these abilities, together with brain structure and function, in individuals with mutations or functional variants of MAOA or MAOB.

9.3.2 Imprinted genes, emotion processing and memory

The studies reported within this thesis found that fear recognition and face recognition memory were highly correlated in females and TS women with a
paternally-derived X-chromosome but not in males or TS women with a maternally derived X-chromosome. Of course, males always have a maternally-derived X-chromosome too. From this observation, it was suggested that the role of the amygdala in regulating brain activity in pathways and regions recruited by these tasks may differ with respect to whether an individual possesses a paternally derived X-chromosome.

Based on the work of Cahill and colleagues (Cahill et al., 2001), it was suggested, in Chapter Eight, that amygdala influences on face memory may be lateralised differently in males and females. The proposition was that in females, left amygdala activity during the presentation of a series of faces might predict subsequent memory for these faces, however in males, memory may be better predicted by right amygdala activity. Furthermore, it was hypothesised that females with TS and a paternally derived X-chromosome would resemble normal females whilst women with TS and a maternally derived X-chromosome would resemble males.

Both the Ekman-Friesen affect recognition task and the Warrington face recognition memory task could be administered as a component of a functional neuroimaging study. One would need to assess typically developing males and females, and women with TS with a single X that is either maternally or paternally derived. We could assess the extent to which the presence or absence of a paternally derived X-chromosome influences functional laterality of the amygdala response to faces and its relationship to face memory.
9.3.3 Other aspects of face processing

This thesis explored face processing in TS as a way of trying to understand the social cognitive difficulties of women with this syndrome. Some aspects of face processing (for example eye gaze discrimination) were not considered within the scope of these studies. These might also be critical to optimal social adjustment and the possibility for future investigations, looking at other aspects of face processing, are discussed below.

9.3.3.1 Monitoring of eye gaze

In Chapter Two, I alluded to the social importance of understanding and interpreting eye gaze. Being able to identify where an individual is looking is important for social interactions. Monitoring eye gaze, like the face processing tasks considered within this thesis, also calls on a network of neural structures involved in social cognition, including the amygdala (Kawashima et al., 1999), orbito-frontal cortex (Calder et al., 2002) and Superior Temporal Sulcus (Campbell, Heywood, Cowey, Regard, & Landis, 1990).

Based on the studies reported within this thesis it was predicted that women with TS would also be poor at gaze monitoring. We have recently assessed ability to detect line of sight in individuals with TS. It was found that women with TS were poor at judging whether a person (an actor displayed on a computer screen) was looking at them or not. They were also less accurate
than controls at judging where an individual was looking, when gaze was averted from the viewer (Elgar, Campbell, & Skuse, 2002). Furthermore, the individuals with TS appeared to be tackling the task in a different manner to typically developing females, placing more reliance on head direction than eye direction as a cue to where someone was looking.

However, on a task of attentional cueing, using eye gaze as a cue to location, women with Turner syndrome did not differ from control females (Elgar et al., 2002). Like control females, the women with TS were unable to ignore the direction of a pair of eyes even when this had no predictive value with regard to where the after-coming target would appear. When the eyes were directed to the target location, individuals with and without TS were quicker to respond to the target than when the eyes were directed away from this location. This would suggest that women with Turner syndrome may be responding implicitly (non-consciously) to eye gaze, despite performing poorly on explicit tests of eye gaze judgements. More investigations are required to help establish whether the differential performance of women with TS on implicit and explicit tasks relates to this dimension or whether other characteristics that differ between the tasks may be mediating the effects.

9.3.3.2 Implicit processing of faces

The studies reported within this thesis all explored explicit (conscious) aspects of face-processing. As was pointed out in Chapter Seven, explicit
performance on such tasks can not always predict how individuals will respond implicitly (without awareness) to the same stimuli.

Implicit responses to faces in females with TS are currently being explored in collaboration with Dr. John Morris using functional magnetic resonance imaging (fMRI). Morris has written extensively on the role of the amygdala in both the explicit and implicit processing of fear (Morris et al., 1996; Morris, Buchel, & Dolan, 2001). Individuals with Turner syndrome and a group of typically developing female control subjects are being scanned. The task is to view a random sequence of fearful and neutral faces and to make judgements about the gender of these faces. The activity associated with fearful faces will be subtracted from the activity associated with neutral faces in order to determine neural regions that may be differentially involved in the processing of fearful faces. We know that, at an explicit level, women with TS are poor at recognising fearful faces. This study will enable us to ascertain whether they are implicitly responding to these fearful faces in any way or if there is a lack of neural differentiation between fearful and neutral faces.

It is also possible to investigate patterns of functional connectivity using fMRI. In typically developing individuals, amygdala activity in response to fearful faces, predicts expression-specific activity in extrastriate cortex (Morris et al., 1998). Morris and colleagues suggest that the amygdala may modulate activity to fearful faces in these early perception sites. By analysing the psychophysiological interaction between these brain regions in TS, we can learn not just whether the amygdalae are responsive to fearful faces, but also whether the functional connectivity to other brain regions is typical.
9.3.4 Understanding developmental aspects of emotion recognition

This thesis explored face processing and brain structure in adult women with TS. TS is a developmental syndrome and a full understanding of the manifestation of the behavioural phenotype cannot be gained without considering infants and children with the syndrome. I would like to propose two suggestions for further work that would be important to advancing our understanding of the development of face processing abilities. The first of these would be to assess face-processing abilities, alongside brain function in infants, children and adolescents with Turner syndrome. This would involve adapting the methodology employed within this thesis to make it suitable for these populations. The second avenue for further work that is suggested is one that relates to typically developing children and is explored in more detail below.

It is understood that face identity recognition improves considerably with age and would seem to undergo qualitative as well as quantitative changes. However, very little is known about the development of emotion recognition abilities throughout childhood. There are several reports of the ability of infants to discriminate facial expressions (Nelson, 1987). Interestingly, one study has reported that 7 month old infants show a persistent interest in looking at fearful expressions (Kotsoni, de Haan, & Johnson, 2001), suggesting that they can implicitly discriminate this facial expression.
However, fear may be an emotion that children have particular difficulty explicitly naming. Lenti and colleagues studied facial emotion recognition in 8-16 year old children and found that some emotions were recognised accurately whilst others were frequently misnamed (Lenti, Lenti-Boero, & Giacobbe, 1999). Happiness and disgust were correctly recognised on 99% and 94% of trials respectively, while fear was correctly recognised on just 55% of trials. Baird and colleagues, looking solely at adolescents, found that they too were poor at explicitly recognising facial expressions of fear. This was despite strong implicit bilateral amygdala responses to fearful faces (Baird et al., 1999).

So perhaps, despite being able to implicitly discriminate fear from an early age, our ability to explicitly name this emotion is one that emerges relatively late in development. The recognition of fear from facial expressions is particularly sensitive to selective impairment. Understanding more about the typical developmental emergence of this ability could inform why this might be the case. Studying developmental factors related to the recognition of fear may also help us to understand more fully, why this emotion would appear to be so 'special'. A study is currently being planned to investigate facial expression recognition alongside other aspects of face processing in children and adolescents aged between five and sixteen years.
9.3.5 How do we explain behavioural variability within Turner Syndrome?

Finally, there is a need to consider an issue that is frequently ignored in the study of genetic syndromes. How is it that there is such population variance within individuals all with an apparently identical genetic anomaly? Some of the women with TS recognised just one of the ten facial expressions of fear, whilst others recognised all ten such faces presented in the context of the Ekman task (Ekman & Friesen, 1976). Similarly, recognition memory for faces, assessed using the Warrington task (Warrington, 1984), was generally poor, with many of the women performing at chance level (26/50) but with a few being highly accurate (47/50). There was a striking amount of concordance between the low and high scorers on these tasks. Individuals who were poor at recognising fearful faces also tended to have difficulties recognising faces in the face memory test, whilst those that were accurate at recognising fear were typically good at recognising faces too.

If, as has been proposed within this thesis, women with Turner syndrome are all haploinsufficient for a gene(s) on the X-chromosome that contributes to the development of face processing abilities, why should there be such variability in their behavioural profiles?

Firstly, environmental influences may play a role in the development of face recognition abilities. We know, for example, that children who have cataracts at birth that are removed shortly after, can experience subtle difficulties
processing faces despite normal vision (Le Grand, Mondloch, Maurer, & Brent, 2001). The absence of a particular type of environmental experience at a critical period in development can therefore lead to deficits in face processing abilities that are detectable many years later. Secondly, it is not the purpose of this thesis to suggest that the only genes influencing the development of the face processing abilities or the brain regions that support them, would be situated on the X-chromosome. Indeed, it is likely that many genes operate interactively to influence the development of these abilities, and functional variants of these other genes may serve to explain some of the variance within the TS population. Thirdly, allelic variants of genes on the intact X-chromosome may influence the outcome in TS and in typically developing individuals. This third explanation is interesting to explore because it suggests some interesting avenues for further study. It is considered in more detail below.

If variant alleles of the gene(s) on the X-chromosome influencing face processing skills do exist, then one might predict that they would impact upon these skills in typically developing individuals as well as in individuals with Turner syndrome. If we presume that more than one allele exists with reasonable frequency in the general population, one predisposing to good face processing skills and the other not, then XX females could be either heterozygous or homozygous for either allele whilst women with TS (X0) and XY males would have only a single copy. Genotype at this particular locus may predict face-processing skills.
Following from this, it may be the case that the women with TS who are particularly good at recognising faces and fearful facial expressions may possess an allele that predisposes to the development of good face processing skills. Although they possess just a single dosage of this gene, it may be sufficient for relatively normal development of face processing abilities. Correspondingly, the women with TS who have particular difficulties at these tasks may have an allele that is disadvantageous to the development of these abilities. In Turner syndrome, the observed face processing phenotype may therefore be influenced both by gene dosage effects (they have one half the expression of typical females) and by the allelic variant of the single gene they possess.

Given that these allelic variants may exist with reasonable frequency in the general population, one might also predict that they could account for some of the variance in face processing skills in the general population. Since normal females would be heterozygous for these genes, the effect of a single inefficient allele will be moderated by the variant of the second copy of this gene. If it was paired with the allelic variant that predisposed to good face processing abilities, the detrimental impact of the inefficient gene may be much less severe than in TS where there is just a single copy. However, some females in the normal population also encounter difficulties on these tasks. It would be interesting to look at whether these females might possess two copies of the allelic variants that predispose to sub-optimal development of face processing abilities.
Given that XY males, like women with Turner syndrome, will have just a single copy of any non-inactivated X-linked genes, one might predict that they would look like females with TS with regard to their face processing abilities. However, in Chapter Eight of this thesis, I reported that males and females did not differ in their accuracy for fear recognition or face recognition memory. It was suggested that the presence of a Y-chromosome in males may serve to upregulate the expression of the single copy of the gene which they possess (Graves, Disteche, & Toder, 1998). If this were the case, we might still be able to detect phenotypic variations according to the allelic variant of the single gene that they possess.

Since males would have just one copy of any X-linked gene, an inefficient allele would have an increased chance of having a severe impact on the development of face processing abilities than in females who would have two copies. Even if the presence of a Y-chromosome serves to upregulate the expression of the single allele, if the allele is one that predisposes to sub-optimal development of face processing abilities this would be unlikely to produce any beneficial affect. However, for females there is a chance that the second copy of the gene will be an efficient allelic variant, which may serve to minimise the impact of the inefficient gene. From this, it could be predicted that males would be more susceptible to face processing difficulties than females but that overall the average performance of males would not be dissimilar to females.
We have recently begun preliminary testing to explore this hypothesis. In a sample of 56 males and 127 females there was no difference in mean scores for fear recognition according to the sex of the participants. However, twice the number of males compared to females were represented in the clinically impaired range. There was a clear sex difference and bimodality of the distributions with 12.5% of males (7/56) and 6.3% of females (8/127) obtaining scores less than or equal to 4/10 on this task. Such gender differentiation or bimodality was not found for the five other emotions in the Ekman test.

To us this suggests that allelic variants of genes on the X-chromosome may be influencing the development of face processing abilities in the normal population. This in turn might contribute to sex differences in the proportion of individuals that have difficulties in these domains. The next step is to explore whether this can in any way inform the identification of a genetic cause for male susceptibility to autism, a condition in which both fear and face recognition are sub-optimal, and which is much more common amongst males than females.
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