Characteristics of Visual Function in Asperger's Syndrome and the Autism Spectrum

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Summary

Autism is a pervasive developmental disorder and Asperger's syndrome is part of the spectrum of autism disorders. This thesis aims to:

- Review and investigate current theories concerning visual function in individuals with Asperger's syndrome and high functioning autism spectrum disorder and to translate the findings into clinical practice by developing a specific protocol for the eye examination of individuals of this population.
- Investigate whether those with Asperger's syndrome are more likely to suffer from Meares-Irlen syndrome and/or dyslexia.
- Assess the integrity of the M-cell pathway in Asperger's syndrome using perimetric tests available in optometric practice to investigate and also to describe the nature of any defects.
- Evaluate eye movement strategies in Asperger's whilst viewing both text and images. Also to evaluate the most appropriate methodology for investigating eye movements; namely optical digital eye tracking and electrophysiology methodologies.

Findings of the investigations include

- Eye examinations for individuals with Asperger's syndrome should contain the same testing methods as for the general population, with special consideration for clear communication.
- There is a depression of M-pathway visual field sensitivity in 57% (8/14) of people with Asperger's syndrome, supporting previous evidence for an M-cell deficit in some individuals.
- There is a raised prevalence of dyslexia in Asperger's syndrome (26% of a sample of 31) but not necessarily of Meares-Irlen syndrome.
- Gaze strategies are abnormal in Asperger's syndrome, for both reading and viewing of images. With increased saccadic movement and decreased viewing of faces in comparison to background detail.

Key words: Asperger's syndrome, Autism, eye movements, Meares-Irlen syndrome, Magnocellular pathway.

To Mum and Rob for helping me believe I could

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Introduction to Vision and The Autism Spectrum

1.1. History of Autism and The Autism Spectrum

Autism is a complex developmental disorder and was first described by Leo Kanner in 1943, when he defined a pattern of behaviour which he named "early infantile autism" (Kanner, 1943) . At around the same time (1944) in Germany Hans Asperger wrote a paper describing what he termed "autistic psychopathy", which is now known as Asperger's syndrome. At this point and for the years that followed, childhood autism was considered to be a very rare condition. This view continued until the 1980's, since when studies have shown much higher rates of prevalence (see section 1.3 epidemiology). Initially in America Kanner felt that infantile autism was a genetic disorder but owing to the climate of the times, wherein psychoanalytical theories were popular, it was believed that, in fact the children's behaviours were an emotional disorder caused by their upbringing and without any neurological basis. It wasn't until the 1960's that opinion began to change following action from parents groups and scientific investigations into the biology of autism. Autism is now recognised as one of the Pervasive Developmental Disorders (PDD) along with Rett syndrome, childhood disintegrative disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS also known as atypical autism).

The idea of an autism spectrum (figure 1.1) was described firstly by Wing and Gould in the late 1970's, in order to reflect the wide range of ways in which an individual may be affected by the disorder. A person who is diagnosed with an Autistic Spectrum Disorder (ASD) may by very profoundly affected or relatively subtly but all will share certain characteristics discussed below.

Conditions included in the term autistic spectrum disorder

- **Autistic disorder-** A type of Pervasive Developmental Disorder that is defined by: (a) the presence of abnormal or impaired development and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behaviour. In addition to these specific diagnostic features, a range of other non specific problems are common, such as phobias, sleeping and eating disturbances, temper tantrums, and (self-directed) aggression (WHO, 1994).

- **Asperger's disorder**- Is characterized by the same type of qualitative abnormalities of reciprocal social interaction that typify autism, together with a restricted, stereotyped, repetitive repertoire of interests and activities. It differs from autism primarily in the fact that there is no general delay or retardation in language or in cognitive development. This disorder is often associated with marked clumsiness (WHO, 1994).

- **Atypical Autism and Pervasive Development Disorder Not Otherwise Specified (PDD-NOS) -** Disorders characterized by qualitative abnormalities in reciprocal social interactions, in patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative abnormalities are a pervasive feature of the individual's functioning in all situations (WHO, 1994). Essentially atypical autism and PDD-NOS are terms used when there is significant impairment in the three areas stated in the diagnostic criteria, but the specificities of criteria cannot be met.

Figure 1.1 Terms included under the umbrella term of autism spectrum disorder.

1.2. Definition and Diagnosis

A diagnosis of autism is based on a "triad of impairments", which put the individual on the autism spectrum first described by Wing and Gould (Wing, 1996b; WING L, 1979; Wing and Gould, 1979), The triad is described below.

- **Social –**Impaired, deviant and/or extremely delayed social development, especially of interpersonal development. Variation from autistic aloofness to active but odd characteristics.

- **Language and communication-** Impaired and deviant language and communication, both verbal and non verbal. Deviant semantic and pragmatic aspects of language.

- **Thought and behaviour-** Rigidity of thought and behaviour with poor social imagination. Ritualistic behaviour, reliance on routines and extreme delay or absence of "pretend play".

This triad of impairments forms the basis of the main world classification systems for Autism, found in diagnostic handbooks, such as ICD-10 (International Classification of Disease, World Health Organisation) and Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association 1994). More recent additions to these are used to support separation of certain diagnostic categories such as Asperger's syndrome from the rest of the spectrum (DSM IV- APA 1994 and ICD-10 WHO 1993). There is a debate as to whether these subdivisions are justified (see Asperger's syndrome below).

1.2.1. Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV)

DSM IV was published by the American Psychiatric organisation (A.P.A and Association), June 2000; Klin et al., 2000). The manual states that individuals must have abnormal functioning in at least one of the following areas, with onset before 3 years of age. **1)** Social interaction. **2)** Language as used in social communication, **3)** symbolic or imaginative play. Diagnosis also requires six or more items from **(1), (2)** and **(3)** with at least 2 from **(1)** and one each from **(2)** and **(3):**

1. **Impairment in social interaction**, as manifested by at least 2 of the following:
    - marked impairment in the use of multiple nonverbal behaviours such as eye to eye gaze, facial expression, body postures and gestures to regulate social function;
    - failure to develop peer relationships appropriate to developmental level;
    - a lack of spontaneous seeking to share enjoyment, interests or achievements with other people (e.g. lack of showing, bringing, pointing out of objects)
    - Lack of social or emotional reciprocity.

2. **Impairment in communication**:
    - Delay in or lack of development of spoken language.
    - In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others.
    - Stereotyped and repetitive use of language or idiosyncratic language.
    - Lacks of varied, spontaneous make believe play or social imitative play appropriate to developmental level.

3. **Repetitive behaviours and stereotyped behaviour patterns**:
    - Encompassing preoccupation with one or more stereotyped and restricted patterns of interest, that is abnormal either in intensity or focus.
    - Apparently inflexible adherence to specific, non-functional routines or rituals.
    - Stereotyped and repetitive motor mannerisms
    - Persistent preoccupation with parts of objects

1.2.2. International Classification Disease (ICD)- 10

The other main system for the classification of autistic disorders is the International Classification of Disease ICD-10 system published by the world health organisation it is available online at http://www.who.int/classifications/apps/icd/icd10online/ or in print (WHO, 1994).

A. Abnormal or impaired development is evident before the age of three years in at least one of the following areas:

1. Receptive or expressive language as used in social communication:
2. The development of selective social attachments or of reciprocal social interaction:
3. Functional or symbolic play.

B. A total of at least six symptoms form 1, 2 and 3 must be present, with at least two from 1 and at least one from each 2 and 3:

1. Qualitative abnormalities in reciprocal social interaction are manifest in at least two of the following areas:
   (a) Failure adequately to use eye to eye gaze, facial expression, body posture and gesture to regulate social interaction:
   (b) Failure to develop (in a manner appropriate to mental age and despite ample opportunity) peer relationships that involve a mutual sharing of interests: activities and emotions:
   (c) Lack of socioemotional reciprocity as shown by a lack of modulation of behaviour according to social context: or a weak integration of social emotional and communicative behaviours:
   (d) Lack of spontaneous seeking to share enjoyment, interest or achievements with other people (eg. A lack of showing, bringing or pointing out to other people objects of interest to the individual).

2. Qualitative abnormalities in communication are manifest in at least one of the following areas:
   (a) a delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate trough the use of gesture or mime as an alternative mode of communication (often preceded by a lack of communicative babbling):
   (b) relative failure to initiate or sustain conversational interchange (at whatever level of language skills is present), in which there is a reciprocal responsiveness to the communications of the other person:
   (c) stereotyped and repetitive use of language or idiosyncratic use of words or phrases:
   (d) Lack of varied spontaneous make believe or (when young) social imitative play.

3. Restricted, repetitive and stereotyped patterns of behaviour, interests and activities are manifest in at least one of the following areas:
   (a) An encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature through not in content or focus:
   (b) Apparently compulsive adherence to specific, non-functional routines or rituals;
   (c) Stereotyped and repetitive motor mannerisms that involve either hand or finger twisting, or complex whole body movements;
   (d) Preoccupations with part objects or non-functional elements of play materials (such as their colour, feel of surface, noise or vibrations generated).

C. This clinical picture is not attributable to the other varieties of pervasive developmental disorder (PDD): specific developmental disorder of receptive language with secondary socioemotional problems; reactive attachment disorder or disinherited attachment disorder; mental retardation with some associated emotional or behavioural disorder; schizophrenia of early onset; and Rett's syndrome.

1.2.3. Other characteristics of Autism

Other characteristics which are commonly found in autism spectrum disorders but are not diagnostic criteria.

Communication

- Loss of speech development previously demonstrated.
- Apparently adequate speech and language but poor or no ability to engage in sustained conversation.
- "Echolalia" this is the repetition of what someone else has said either immediately after them (immediate echolalia) or after a period of time (delayed echolalia).
- Monotone or limited variability in vocal inflection.
- Poor or limited nonverbal communication (e. g., pointing, gesturing).
- Poor or limited understanding of language beyond its concrete meaning (e.g. difficulty with humour, figurative language, metaphor).

Social Interaction

- Limited development in the typical expansion upon play themes.
- Sensory impairments (e. g., auditory, tactile) that interfere with the ability to respond and participate in social exchanges and play.

Behaviour

- Self-stimulating behaviours may be verbal (repeating sounds/ phrases) or motor (rocking, spinning, pacing, hand flapping).

1.2.4. Asperger's Syndrome

Asperger's syndrome is essentially an extension of the Autism spectrum, and it can be argued that Asperger's syndrome is the same as high ability autism. Around 25% of people with an ASD have average or above intelligence (Coleman, 2005; Volkmar and Pauls, 2003) although this figure has been found to be between 15 and 30% by different studies (Bryson et al., 1988; Gillberg, 1984; Ritvo et al., 1989b; Steffenburg and Gillberg, 1986a; Wing, 1979; Wing, 1993). This variability may be due to the studies using slightly differing criteria for inclusion, differing locations and also using differing IQ testing methods (Wing, 1993). This has led to some authors questioning the need to separately label this group of individuals (Ritvo et al., 2008; Volkmar, 1998). However it is a widely used and generally accepted term found useful in clinical practice involving this group (Kugler, 1998), mainly because clinical practitioners find it more acceptable to the individual and their family to separate this condition from the negative stereotypes of classical autism.

Diagnosis of Asperger's disorder as found in DSM IV
(American_Psychiatric_Association, June 2000) is as follows.
Individuals must fulfil criteria **A** and **B** BUT *lack any clinically significant delay in language or cognitive development.* Criteria **A** is the same as DSM IV criteria for autism section **1** and **B** is the same as section **3**.

ICD-10 diagnostic criteria for Asperger's syndrome are as follows (WHO, 1994):

- There is no clinically significant general delay in spoken or receptive language or cognitive development. Diagnosis requires that single words should have developed by two years of age or earlier and that communicative phrases be used by three years of age or earlier. Self help skills adaptive behaviour and curiosity about the environment during the first three years should be at a level consistent with normal intellectual development. However motor milestones may be somewhat delayed and motor clumsiness is common, but are not require for diagnosis.

- There are qualitative abnormalities in reciprocal interaction (criteria as for autism).

- The individual exhibits an unusually intense, circumscribed interest or restricted, repetitive and stereotyped patterns of behaviour, interests and activities (criteria as for autism: however it would be less usual for these to include either motor mannerisms or preoccupations with part-objects or non-functional elements of play materials).

- The disorder is not attributable to the other varieties of PDD; schizophrenia, Obsessive Compulsive Disorder (OCD), personality disorder or reactive and disinhibited attachment disorders of childhood.

1.3. Epidemiology

The currently stated value for prevalence of autism in the UK by the national autistic society is 1% (NAS); there has however been a great deal of variation in the figures quoted for the prevalence of autism. Figures range from 3-16 per 10,000 (Bryson et al., 1988) to 58 in 10,000 (Wing, 1996a). This variation may be due to differences in the inclusion criteria used; different studies have included or not included certain groups, for example the most recent estimates of ASD's in the general population include Asperger's and PDD-NOS and find prevalence to be between 0.6-1.1percent of school age children (Gillberg, 2005). A full discussion of factors affecting the prevalence of ASDs is found by differing studies found in a paper by Williams et al "Systematic review of prevalence studies of autism spectrum disorders" (Williams et al., 2006) . The conclusions of this paper were as follows; over half of the variation among study estimates can be explained by the age of the children screened, the diagnostic criteria used and the country studied. Other important factors were whether the study was in a rural or urban location and whether cases were assessed prospectively or retrospectively. The impact of these identified factors on prevalence estimates needs to be further investigated as they may be acting as proxies for other influences on prevalence. For example, the effect of geographical location on prevalence may be due to the services available, or variation in awareness of the disorder.

1.3.1. Figures stated for prevalence by different studies.

Chakrabarti and Fombonne, reported in the Journal of the American Medical Association (Chakrabarti and Fombonne, 2001) that the prevalence of PDD in preschool children in the Staffordshire region of the UK was estimated to be 62.6 children per 10,000. 15500 children aged 2.5 to 6.5 years were screened for developmental problems and 97 children (79.4% male) were confirmed to have a PDD. The prevalence of PDDs included 16.8 per 10,000 for autistic disorder and 45.8 per 10,000 for other PDDs. A literature review of prevalence was produced in 1999 and found that early studies yielded prevalence rates of under 0.05 in 10,000 children, whereas the later ones showed a mean rate of about 0.1 in 10,000. This difference is probably due to the lower rates obtained by use of criteria strictly based on Kanner's description of his syndrome in early studies. The US studies reported atypically low rates (Gillberg and Wing, 1999).

The autism research centre in Cambridge used public records, screening instruments, and educational psychology and Special Education Coordinating Officer (SENCO) records to seek cases of diagnosed ASD in children in Cambridgeshire schools aged between 5 and 11 years in July - December 1999. The results found a prevalence of ASD in the age-group 5-11 yrs of almost 0.6% (57 per 10,000) which is 11 times higher than the rate of classic autism but in line with other recent national and international rates for the broader spectrum (Scott et al., 2002) . Half the responding mainstream primary schools had at least 1 child with an ASD. In the responding mainstream schools the prevalence was 0.33%. In the responding special needs population it was 12.5%.

Variation is also found by country (see figure 1.2 below). Above quoted figures are for the UK. The Irish Society for Autism reported an increase in their rates of Autism from 5 per 10,000 in 1996 to 15 in 10,000 in 2002.

Country	Prevalence per 10,000	Year and Diagnostic criteria used
Britain	60	2005 DSM
Ireland	15	2002 DSM
Canada	10.1	1988 DSM
Sweden	11.5	1991 DSM
Japan	13	1989 DSM
USA	66	2007 (unknown)

Figure 1.2 Table constructed based on data from (Wing, 1993; Wing, 2001) except USA (Autismsociety_of_America, 2007).

The medical research council review quotes the figure for ASD as 60 in 10,000 children, and it is estimated there are 535000 individuals in the UK with an ASD (NAS website). This is 20-100 times higher than the rates suggested 40 years ago

The figures for ASD prevalence have increased over time; this is probably due to several factors, such as better diagnostic procedures, increased public awareness and possible increase in causal factors see figure 1.3.

Reasons for the apparent increase in the prevalence rates of autism.
(Gillberg, 2005)

- ***Conceptual change***- the conceptualization of this condition has been changed several times over the last 40 years. Originally it was thought to be a discrete disease entity, but now is recognised as one of several behavioural presentations of a spectrum. This broadening of the group will obviously increase the number of individuals affected. This leads to the next point.

- ***Change in diagnostic criteria over time***- there has been large change in the diagnostic criterion over the last 25yrs. Lorna Wing rediagnosed her cases in the original Camberwell study using ICD-10 rather the Kanner criteria she originally used in the 70's (Gillberg and Wing, 1999; Wing, 1979). This actually produced a 3x increase in the rate of diagnosed autism.

- ***Better awareness of autism in the community***- it is generally agreed that knowledge about autism among lay people has increased dramatically in recent years. This would lead to more people attending clinics enquiring about the possibility that their child might have an ASD.

- ***The development of autism diagnostic services***- legislation and national guide lines for diagnosing and intervening in autism are now available (US, UK, Scandinavia, Canada). This has lead to the increase in autism prevalence because the cases are registered on file (Gillberg, 2005)

- ***Possible link with social changes***- Simon Baron Cohen suggests that the change in our social mechanisms may have meant that people who would not have formed relationships and had children may now be more socially successful.

Figure 1.3 Suggested reasons for increased stated rates of Autism.

1.3.2. Age of onset

Recent studies suggest that autism may be present from birth. Studies of neonatal blood show levels of neutrophils and neuropeptides were increased in 99% of children who went on to be diagnosed with an ASD. Although raised levels were also found in those who were later diagnosed with Downs's syndrome or Learning Disability (LD), the levels could not be used to distinguish between the groups (Nelson et al., 2001).

The average age of diagnosis varies depending partly on the nature of the ASD and is around five years for autism, around 11 years for Asperger's syndrome (Jordan, 1999; NAS). There is a significant difference in sex distribution in ASD, with males being far more often affected. Autism affects approximately three times as many males as

females (Scott et al., 2002; Steffenburg and Gillberg, 1986b) and high functioning autism (HFA) or Asperger's syndrome affects almost five times as many (Rutter and Schopler, 1987; Scott et al., 2002).

1.4. Aetiology

1.4.1. Genetics

Autism is a neurodevelopmental disorder and research indicates that there are a variety of causes, affecting brain systems and impeding development of social and communicative skills. Twin and family studies have shown that ASD's are highly hereditary. Identical (monozygotic) twins have a 92% concordance for ASD (Bailey et al., 1995). Dizygotic (non-identical twins) have a 10% concordance (Frith and Hill, 2004; Muhle et al., 2004). The higher rate of mono-zygotic concordance provides convincing evidence for the strong influence of genetics in the cause of autism.

It has been found that if a family have one child with an ASD then there is a 2-7% chance that a sibling will also have ASD (Rutter et al., 1999). The relative risk is 50-200 times higher than the general population (Volkmar and Pauls, 2003). It seems that genetic causes are complex and only a minority of cases (5-10%) are due to single gene or chromosomal disorders (Bailey et al., 1995). It was reported that a potential location of an "autism gene" had been found (Cook et al., 1997) but this was refuted by another paper shortly afterwards (Klauck et al., 1997). A prospective study undertaken by Battaglia and Carey (Battaglia and Carey, 2006) on subjects diagnosed as having a PDD (Pervasive Development Disorder), found evidence for a complex genetic predisposition to most cases of PDD. Six potential genomic susceptibility regions were identified on 7q, 2q, 16p, 17q, 6q, and 3q. Mutatins have also been found in the '*beta-neurexin gene1*', located on chromosome 11(Feng et al., 2006). The gene is involved with post-synaptic cell adhesion and sequences from it were found in 192 patients with autism. So although genes seem to be a factor it is possible that a genetic predisposition may interact with organic brain damage which leads to the development of ASD's (Jordan, 1999). Some proposed theories as to the cause of this brain damage are discussed below.

1.4.2. Pregnancy and birth complications

Difficulties in pregnancy or birth which are associated with autism include the following (Baron-Cohen, 1993).

- Mothers above 35 years old at the time of the child's birth;
- Birth order - first or fourth or later-born children may carry a slightly higher risk;
- Taking medication during pregnancy;
- Meconium (the first stools of the infant) were present in the amniotic fluid (the "waters") during labour;
- Bleeding between fourth and eight month of pregnancy.
- A "rhesus incompatibility" between the mother's and the child's blood group (Larsson et al., 2005);
- Prematurity, less than 36 weeks gestational age;
- Low birth weight.

1.4.3. Environmental factors

Environmental factors which have been suggested are prenatal exposure to, Thalidomide (Stromland et al., 1994). Valproic acid used to treat seizures (Christianson et al., 1994), cocaine (Davis et al., 1992) and alcohol abuse during pregnancy (Fombonne, 2002; Harris et al., 1995; Nanson, 1992) as well as viral infections such as rubella.

Heavy metals have also been implicated as a potential cause of ASD. Lead levels have been found to be higher in children with developmental problems including autism (Lewendon et al., 2001). However it has not been shown whether this is a causal factor or associated feature. Mercury and particularly methyl mercury have also been debated as a potential causal factor (Adams et al., 2007; Bernard et al., 2001; Mutter et al., 2005) leading to concerns about the use of Thiomersal (49% ethyl mercury) as a preservative in vaccines (Bernard et al., 2001). A report in the USA by the Institute of Medicine of the National Academies found the literature and studies on the possibilities of a link with autism and Thiomersal to be inconclusive (Statton et al.,

2001). Current evidence does not therefore support a proven link between these heavy metals and ASD.

1.4.4. Viral

"Viruses that effect the brain in young infants or in the foetus may contribute to cause of autism" (Baron-Cohen, 1993).

Viruses that have been associated with autism in childhood are herpes simplex virus encephalitis (Ghaziuddin et al., 1992) congenital rubella infection (Chess, 1971; Chess, 1977), Cytomegalovirus (Ivarsson et al., 1989) and measles virus (Singh et al., 1998). This led to suggestions of ASD being related to the Measles Mumps and Rubella (MMR) vaccinations (Chen et al., 2004; D'Souza et al., 2006), although it is disputed following a number of research studies which followed.

1.4.5. Diet

A more recent line of investigation into the causes of ASD has been to consider diet and gastrointestinal abnormalities. It has been suggested that abnormal food metabolism could lead to an altered chemical environment in the brain. This inability to metabolise specific foodstuffs, for example gluten or casein, adequately may lead to toxins entering the bloodstream via the gut wall and potentially crossing the blood brain barrier (Jordan, 1999). Anecdotal evidence has suggested that some individuals with an ASD may find improvements by using gluten free (wheat free) or casein (dairy free) free diet (Alpert, 2007). There is, though, little experimental research into this and results have proved so far inconclusive, only two placebo controlled trials have been carried out (Elder et al., 2006; Seung et al., 2007). Seung used video recordings of at-home parent-child play and analyzed these for behavioural change. Results demonstrate that double-blind clinical trials of diet intervention are feasible but results were inconclusive regarding the efficacy of diet for improving communication. This was perhaps due to the relatively short period of diet intervention used, Elder collected data on autistic symptoms and urinary peptide levels over the 12 weeks that they were on the diet. They found no statistically significant findings even though several parents reported improvement in their children.

Several studies in recent years have looked at the possible benefits of fatty acid supplements in people with ASD. The Oxford Durham study (Richardson and

Montgomery, 2005) showed improved reading and writing skills as well as behaviour in children with developmental disorders who were given omega 3 and 6 supplements. Bell (Bell, 2003) found that children with ASD and Asperger's syndrome show significantly more features of a fatty acid deficiency than neurotypical controls. It has also been suggested that ASD, dyslexia and ADHD (Attention Deficit Hyperactivity Disorder) may be related by a phospholipid disorder which could be helped by increasing the amount of essential fatty acids, such as omega 3 and 6, in the diet. Research is still being conducted in this area (Richardson, 2000b; Richardson, 2003; Richardson and Montgomery, 2005).

1.4.6. Embryogenesis errors

Autism is associated with several other conditions characterised by developmental errors in early embryogenesis (Miller et al., 1998; Miller et al., 2005).

Recent studies have reviewed the findings in five studies involving individuals manifesting the characteristic findings of ASD associated with malformations and dysfunctions known to result from early embryogenic defects (Johansson et al., 2006; Miller et al., 2005). The investigations included defects associated with: Thalomide embryopathy, Mőbius sequence with Misoprostol, most Mőbius sequence cases, CHARGE association* and Goldenhar Syndrome i.e. Oculo-aurculo-vertebral (OAV) Syndrome. Vascular disruption caused by uterine constriction in the early embryonic period has been suggested as the mechanism for both the Mőbius sequence and Goldenhar Syndrome. This vascular disruption or 'subclavian disruption syndrome' causes a disturbance in the blood supply to the foetus, and as well as causing hypoxia and ischemia, could also cause secondary events which can affect other organs although evidence is only available from individual case reports. The medical features associated with CHARGE suggest deficits in crest cell development/migration. These theories provide us with some possibilities as to the aetiology of autism. However, it is

* CHARGE association describes a varied group of who exhibit at least four of the features prefixed by the letters of the acronym and including one or other of choanal atresia and/or coloboma. This is coloboma, heart defects, choanal atresia (which is a blockage of the passages at the back of the nose) retarded growth and development, genitalia anomalies, ear anomalies

difficult to know whether the deficits seen are related primarily to autism or if they are the result of the other conditions involved (Miller et al., 2005).

1.4.7. The MMR vaccine

Probably the most well known and recently suggested cause of autism is the MMR vaccination. A possible link was identified in a study carried out in February 1998, by Dr Andrew Wakefield and his team working at the Royal Free Hospital (Wakefield, 1999). This study put forward the theory that there was a link between: MMR, inflammatory bowel disease and autism, i.e. that the MMR caused pathological changes in the bowel/digestive system this leads to excess opioid peptides gaining access into the blood/brain system. This resulted in damage occurring to the (rapidly developing) brain and, ultimately, the symptoms we see as autism. Several studies have taken place since this time and a report by the Sunday Times newspaper has alleged that Wakefield manipulated the results of this study in order to link the vaccination to autism (Deer, 2009). Some studies have suggested that if there was a causal link then there would be a rising incidence in countries after MMR was introduced compared to other countries where MMR is not given. This is not borne out by research (Chen et al., 2004; DeStefano, 2007; Fombonne et al., 2006; Honda et al., 2005). Honda's study, in particular, is interesting since this looks at the increase in the incidence of ASD in the Japanese population after 1991 following the withdrawal of MMR from use. This showed that cessation of the use of the MMR vaccination does not lead to a decrease in the prevalence of ASDs. An epidemiological study in the UK also found no evidence of a causal link between the MMR vaccination and autism (Taylor et al., 1999). Taylor and colleagues identified 498 cases of autism, 293 cases confirmed by ICD10: 214 [82%] core autism, 52 [31%] atypical autism and 27 [38%] Asperger's syndrome. They found a steady increase in cases by year of birth but no sudden "step-up" or change in the trend line after the introduction of MMR vaccination. There was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated. There was no temporal association between onset of autism within 1 or 2 years after vaccination with the MMR and developmental regression was not clustered in the months after vaccination (Taylor et al., 1999).

The most recent study into the possible link between MMR and autism studied almost 250 children aged between 10 and 12, all of whom had been given at least one MMR vaccination. Researchers investigated through blood samples whether children with autism spectrum disorder (ASD) showed raised concentrations of measles antibodies or an abnormal immune response. They concluded that there was no difference in virus or antibody levels between children with ASD and the comparison groups. This was unaffected by whether or not the child had received both MMR doses and whether or not they had regressed (where children appear to develop communication skills, but then regress). The study also found no evidence of bowel symptoms (enterocolitis) among the autistic children, irrespective of whether or not they had regression (Baird et al., 2008).

The Medical Research Council of Great Britain reported that although there was not sufficient evidence to support a causal link between MMR and autism, greater research needed to be carried out in this area (MRC, 2001).

1.5. Physiology

1.5.1. Brain structure

Brain growth/development

Figure 1.4 MRI of a human Brain, Thanks to Miss Hesmita Patel of Aston University.

Several studies have indicated brain abnormalities in autism. These are summarised below figure 1.5.

At birth a person with ASD is likely to have a normal or slightly smaller brain (Courchesne et al., 2003; Courchesne et al., 2001; Dementieva et al., 2005; Gillberg and de Souza, 2002) which then undergoes a period of rapid and abnormal growth in the 1st year of life (Dementieva et al., 2005; Mann and Walker, 2003). At the end of the critical period, at 2-3 years old, MRI studies show the autistic brain to be 2-10% larger than normal (Courchesne et al., 2001; Piven et al., 1995; Sparks et al., 2002b). By adulthood the brain is within the normal size range (Aylward et al., 2002; Redcay and Courchesne, 2005). This abnormal growth has been shown using both MRI studies and post-mortem investigations.

Cerebellum	Cerebellar hyperplasia has been reported (Sparks et al., 2002a). Reduced Purkinje cell counts in the posterolateral cerebellar hemispheres (Bailey et al., 1998a; Kern, 2003) Abnormalities in the cerebellar vermis associated with decreased saccade accuracy (Allen and Courchesne, 2003; Catani et al., 2008; Quaia et al., 1999).
Brain Stem	Associated with cranial nerve dysfunction and deficits in Smooth Pursuit movements, Saccades and Optokinetic Nystagmus in autism (Miller et al., 2005) (Duckman, 2006b; Takarae et al., 2004a)
Amygdala	Bilateral hyperplasia of amygdala has been reported by (Sparks et al., 2002a) This may affect the sub cortical visual system, causing diminished attention to faces (Shultz, 2005)
Corpus Callosum	Significantly smaller size has been reported (Egaas et al., 1995; Stanfield et al., 2008; Vidal et al., 2006) Abnormalities in this area are consistent with deficits in neural connectivity in autism (Alexander et al., 2007).
Hippocampus	Bilateral hippocampi hyperplasia has also been reported (Sparks et al., 2002a) Studies have not made any connections involving this anomaly and visual function in autism.

Figure 1.5 Table of brain areas found to have abnormalities in ASD.

It has been postulated that this abnormal growth may be due to a failure of the "pruning process" which occurs several times during development after an initial wave of proliferation of synapses (Frith and Hill, 2004; Hazlett et al., 2006) This 'Pruning' gets rid of faulty connections and optimises co-ordinated neural functioning.

Feed-forward systems are laid down at an early stage of brain maturation but feedback connections take much longer to develop and undergo a proliferation and pruning cycle. Therefore, if these top-down systems fail to be pruned while the bottom up systems are normal, top-down control may be harder for basic perceptual processes. The consequences of this may be the cause of a lack of coordination between global and local level processing and reports of abnormal cortical organisation and connectivity in autism. Failure of pruning might also occur in different regions of the brain at different times during development and could explain the diverse mental functions across individuals with autism (McCaffery and Deutsch, 2005). Another possible consequence of accelerated early brain growth could be the abnormal sensorimotor and cognitive function seen in ASD (Takarae et al., 2004a). They suggest that there is a disruption of organisation in the terminal fields of developing

long nerve fibre tracks which are needed to connect areas of the brain which are far from each other. This disruption in neural development could compromise functional connectivity, i.e. the capacity to coordinate activity across many brain regions to produce complex behaviour.

This abnormal growth pattern alters the critical period for development of neural systems. Corchesne suggests that this "over-growth" leads to discord in connectivity between different brain areas possibly causing some of the characteristics found in autism (Courchesne et al., 2005).

"*cellular and growth abnormalities are most pronounced in frontal, cerebellar, and temporal structures that normally mediate the development of those same higher order social, emotional, speech, language, speech, attention, and cognitive functions that characterise autism"- (Courchesne et al., 2005)*

An abnormality of mini-columnar brain cells has been suggested as a cause of Autism (Casanova, 2006; Casanova et al., 2003; Casanova et al., 2002b). The mini column is the fundamental unit of information processing. Abnormal mini-columns and mini-column numbers may play a part both in an imbalance of excitation/inhibition and over or under connectivity of brain areas (Casanova, 2004; Casanova et al., 2002a). The areas affected by regional differences in mini-column size in autism are the dorsal and orbital frontal cortex and the temporal cortex. However, there has been no abnormality found in the primary visual cortex (Casanova, 2004; Casanova et al., 2002b). It is hypothesized by these researchers that micro structural maldevelopment results in over connectivity in the frontal cortex that is largely ineffective and in a failure of long-distance cortical–cortical coupling which leads to a reduction in frontal–posterior reciprocal connectivity. This altered circuitry impairs the essential role of frontal cortex in integrating information from diverse functional systems (emotional, sensory, autonomic, memory, etc.) and providing feedback to lower level systems (Courchesne et al., 2005)

It appears that ASD is associated with abnormal cortical organisation (Just et al., 2004; Minshew and Williams, 2007) and connectivity (Geschwind and Levitt, 2007; Hughes, 2007; Kleinhans et al., 2008; Villalobos et al., 2005). Reduced dendritic

arborisation has been found in areas of the brain associated with the limbic system (amygdala, septum, hippocampus and anterior cingulated) (Kemper and Bauman, 1998). It has been observed that lesions in these brain areas will also lead to social problems and autism like behaviours in animal studies (Machado and Bachevalier, 2003). It seems also that some tasks may be processed by the opposite hemisphere to that used by neurotypical individuals (Koshino, 2005)

Brain blood flow abnormalities

Blood perfusion impairments have been demonstrated involving the insula, temporal cortex, medial prefrontal cortex, anterior cingulate gyrus and hippocampus in patients having infantile autism (Burroni et al., 2008; Coleman, 2005; Ohnishi et al., 2000). These abnormalities could be related to cognitive dysfunction observed in autism, such as deficits in the theory of mind, abnormal responses to sensory stimuli, and obsessive desire for sameness.

Neurochemical Correlates

Studies into neurochemical correlates of autism have been complicated by the many co-morbid conditions which can occur with the disorder. Approximately one third of individuals with autism have been found to have high blood platelet concentrations of serotonin (Anderson and Hoshiono, 1997; Lam et al., 2006; Ritvo et al., 1970). Dopamine blockers have been shown to decrease stereotyped movements but, as yet, studies into dopamine metabolites in autism have found no consistent results to explain this (Minderaa et al., 1989). Significantly lower levels of overall plasma oxytocin have also been linked to the impaired sociability of autism, but this effect has only been investigated using small rodents (Muhle et al., 2004). New areas of study include possible dysfunction of the cholinergic system and amino acid neurotransmitters (Lam et al., 2006).

A full review of neurochemical correlates of autism can be found in "Neurochemical correlates of autistic disorder: A review of the literature" (Lam et al., 2006). This review discusses evidence for abnormalities of serotonin, dopamine, norepinephrine, acetylcholine, oxytocin, opioids, cortisol and GABA (amino acid neurotransmitter). The findings are summarised below.

- Overall, serotonin appears to have most evidence for a role in autism.
- There is little support for the notion that a dysfunction of norepinephrine or the endogenous opioids are related to autism.
- Findings concerning dopaminergic functioning have been conflicting so far.
- Existing studies main flaws are in subject variables such as race, sex, pubertal status and distress associated with blood draws which can affect measures of neurochemical function

1.5.2. Imbalance of global/local processing.

Uta Frith was the first person to suggest a theory of weak central coherence in autism (Frith and Happe, 1994). This refers to the idea that an autistic individual will typically think about things in the smallest possible parts. Frith's hypothesis is that children with autism actually perceive details better than normal people but that "they cannot see the wood for the trees." In the last 10 years there have been many studies carried out and evidence can be found on both sides. Below are some of the studies carried out figure 1.6.

For local bias	Against
Global-local visual processing in high functioning children with autism; structural vs. implicit task biases. (Iarocci et al., 2006)	Spatial cognition in ASD: superior, impaired or just intact? (Edgin and Pennington, 2005)
Processing of compound visual stimuli by children with autism and Asperger's syndrome.(Deruelle et al., 2006)	Executive Function Abilities in Autism and Tourettes Syndrome: An Information Processing Approach.(Ozonoff et al., 1994)
Gestalt perception and global processing high functioning autism. (Bolte et al., 2007)	Locally oriented perception with intact global processing among adolescents with high-functioning autism: evidence from multiple paradigms. (Mottron et al., 2003)

Figure 1.6 Studies for and against local bias in Autism.

The papers summarised in the table above suggest that individuals with an ASD process information as its constituent parts rather than seeing "the bigger picture" (Happe and Frith, 1996; Happe, 1996). This is demonstrated in that individuals with autism succumb less frequently to visual illusions, where the visual context induces illusory percerpts. It has been suggested that this may be due to an imbalance between the visual channels responsible for high and low spatial frequency information

processing (Plaisted et al., 1999). In a normal population the global advantage is modulated by low spatial frequency information and the local aspects by high spatial frequency channels (Sergent, 1982). These low spatial frequency signals which convey information about the global properties of a stimulus arrive at the cortex more rapidly than the high spatial frequency signals which convey information about the smaller detail aspects of a scene.

Impairment in the magnocellular pathway might underlie a bias for local processing in people with autism, which may also underlie the preference for local aspects of a stimulus to the overall global view (weak central coherence). This is discussed further in Chapter 4.

1.6. Associated conditions

1.6.1. Epilepsy

Children with autism have increased risk of epilepsy (Olsson et al., 1988; Tuchman and Rapin, 2002). In classic autism, the rate of epilepsy is 40% in those over 30yrs (Tuchman and Rapin, 2002). In Asperger's syndrome the rate is lower 3-10% (Cederlund and Gillberg, 2004). Overall the rate amongst ASD is around one third which is significantly higher than the 5-10 per 1000 reported for the general population (Sander, 2005). A significant portion of the mortality rate in ASD is due to epileptic seizures (Jordan, 1999). Between 15 and 36% of children who have an ASD but no epilepsy show abnormal activity on electroencephalogram (EEG) testing, which some have suggested may indicate sub-clinical seizures (Oslejskova et al., 2008; Tuchman and Rapin, 1997). The onset and distribution of epilepsy in the general population also differs in people with autism. Autism is associated with late onset epilepsy which first presents in late teens or early adulthood creating a bimodal distribution for onset (Volkmar and Nelson, 1990) with a peak in childhood followed by a second peak of late onset. In the general population epilepsy most commonly presents in the first year of life, with new onset numbers dropping rapidly after this until much later in life.

It is not certain at present what causes the link between autism and epilepsy although a genetic component has been suggested which with abnormal brain development in

autistic individuals acts to cause abnormal EEG activity and seizures (Gabis et al., 2005).

1.6.2. Attention deficit hyperactive disorder (ADHD)

The core concern regarding ADHD is that over-activity, impulse control problems and inattentiveness have negative effects on learning and functioning. This includes learning and tuning into social skills and communication skills which are at the crux of the problems for the child with PDD including ASD. Therefore, many children with an ASD are also found to suffer from ADHD (Jordan, 1999).

1.6.3. Mental Health problems and ASD

The strong association between autism and learning difficulties also leads to an increased risk of mental health problems (Morgan et al., 2003).

1.6.4. Obsessive compulsive disorder (OCD)

There is disagreement about whether some of the cases of OCD are truly separate mental health problems or simply misdiagnosed aspects of the person's autism (Caron and Rutter, 1991), OCD has been said to be more common in those with an ASD, but it has also been agued that because people with autism may exhibit ritualistic and obsessive behaviours, this is misdiagnosed as OCD, when it is, in fact simply part of the behavioural aspect of autism (Fischer and Probst, 2006; Jordan, 1999).

1.6.5. Anxiety

The most common mental health issues concerning ASD are anxiety related problems. Gillott suggests that individuals with autism are almost three-times more anxious than their non autistic peers (Gillott et al., 2001; Gillott and Standen, 2004). They are often described as highly anxious (Waller & Furniss, 2004). Anxiety is experienced by all children to some extent but it becomes a disorder when the physical and emotional response is so intense and unpleasant that it impairs the person's functioning. The apprehension the individual feels is disproportionate to the stimulus of the fear. The person may even have anxiety in circumstances that have no precipitant. They may experience severe internal stress for unknown reasons (Quinn, 2000).

1.6.6. Sleep disorder

Sleep disorder is another secondary manifestation of PDD/ASD. Lacking the internal mechanism to calm and comfort themselves, many individuals (particularly children) with ASD have difficulty falling asleep, and/or staying asleep through the night (Godbout et al., 2000; Johnson and Malow, 2008). Sleep problems in the autism spectrum may also be linked with the high prevalence of epilepsy since seizures and abnormal brain activity found in epilepsy can affect sleep patterns (Devinsky et al., 1994; Malow, 2004; Rajna and Veres, 1993).

1.6.7. Depression

There is emerging evidence that depression is probably the most common psychiatric disorder that occurs in autistic people (Ghaziuddin et al., 2002), occurring in around 39% of individuals, particularly those with Asperger's syndrome (Deudney, 2004; Ghaziuddin et al., 2002; Wing, 2001).

Bipolar disorder is less common, this may be found in around 10% of individuals (Wing, 2001).

1.6.8. Schizophrenia

Schizophrenia again has had some debate around its diagnosis with ASDs. Schizophrenia is a commonly stated differential diagnosis for ASD and Asperger's syndrome (Sasson et al., 2007; Stahlberg et al., 2004). Literature shows variation in the figure for frequency of schizophrenia in ASD as between 0.6% which is similar to the general population (Volkmar, 1991), and 7% (Wing, 2001). There is currently no evidence that people with autism spectrum conditions are any more likely than anyone else to develop schizophrenia (Deudney, 2004).

1.6.9. Other associated conditions

Tourette syndrome

Tourette syndrome (TS) is characterized by multiple motor and one or more vocal tics; the number, frequency and complexity of which change over time (Eapen et al., 2001). The prevalence, in the normal population, is between 2% and 3% (Mason et al., 1998). The prevalence of Tourette among patients with autism is estimated at 6.5% (Baron-Cohen et al., 1999).

Fragile X syndrome

Fragile X syndrome (Frax) is the most common inherited form of human mental retardation (Zafeiriou et al., 2007). The prevalence of Frax is between 1/3500 and 1/9000 in males (Crawford et al., 2001). The prevalence of autism among individuals with Frax is estimated at 25–33% (Bailey et al., 1998b; Rogers et al., 2001).

Tuberous sclerosis

Tuberous sclerosis (TS) is a neurocutaneous, autosomal dominant disorder that presents with a prevalence of 1–1.7/10,000 (Franz, 1998; Osborne et al., 1991). It leads to formation of growths in one or more body systems (skin, central nervous system, kidneys, heart, lungs, and retina)(Lewis et al., 2004). The occurrence of autism in individuals with tuberous sclerosis (TBS) is between 25 and 50% (Ahlsen et al., 1994; Hunt and Dennis, 1987). Conversley 5% people with classic autism have TBS.

Neurofibromatosis

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition caused by decreased production of the protein neurofibromin, which is a tumor suppressor, associated with the *NF1* gene in the long arm of chromosome 17 at 17q11.2 (Zafeiriou et al., 2007). It is mainly characterized by café-au-lait macules, neurofibromas, axillary or groin frecklings, optic pathway tumors, Lisch nodules and dyplastic skeletal findings (long bone bowing/pseudoarthrosis and/or sphenoid wing dysplasia). The prevalence of NF1 is estimated between 1/3000 and 1/4000 (Huson and Hughes, 1994) and its prevalence among individuals with autism varies from 0% to 0.14 in 1000 (Volkmar et al., 2005).

Sensory impairments

Impairments of hearing and vision (1.3% of people with ASD have a visual impairment (Gillberg and Billstedt, 2000) vs. 0.08% in the general population (RNIB website 2006).

Down syndrome

This is the most common chromosomal cause of learning disability with a prevalence of 1/1000 births (Olsen et al., 2003). The prevalence of Down syndrome (DS) in autism ranges from 0 to 16.7% and the rates of autism among DS individuals between

1% and 10%. It has been suggested that the co morbidity of DS and autism is not higher than expected by chance, once the affects of mental retardation, which is a risk factor for autism, are taken out (Volkmar et al., 2005). Research is focusing on the possible factors related to DS itself that may predispose to autism (Zafeiriou et al., 2007). One suggestion is that the association is mediated by infantile spasms, which are more common among babies with Down syndrome and, also, a risk factor for autism (Gillberg C and M, 2000; Gillberg and Coleman, 2000). A long duration of infantile spasms (because of late response to treatment) has been reported to be associated with more autistic features and poorer mental development (Eisermann et al., 2003).

1.7. Ocular Complications and Associations in ASD

Visual perception is fine tuned during development and as a part of learning in response to changing environmental conditions. Abnormalities of sensory perception have been implicated as possible primary or at least contributory causes of some of the characteristic features of ASD (Dakin and Frith, 2005). There are many different theories as to why these abnormalities may occur. As discussed in section 1.4, brain physiology in autism is different to that of typically developing individuals, with cerebellar and brain stem anomalies as well as macrocephally (increased head diameter) reported in several studies (Courchesne et al., 2003; Frith and Hill, 2004; Hazlett et al., 2006; Nowinski et al., 2005; Takarae et al., 2004b). MRI studies have also demonstrated abnormal activity in certain regions of the autistic brain when viewing certain types of stimuli (Courchesne et al., 2001; Critchley et al., 2000; Koshino, 2005; Pierce et al., 2004). One of the recurring explanations for deficits in perception is a general lack of 'neural connectivity' in autism and further evidence for this can be found in the genetics of autism. Most explanations must take into account both psychological and physiological aspects of autism. It is important to note that there is no clear consensus about the causes of any of these deficits and new research continues to take place all the time.

There are several anomalous ocular and visual findings which have been associated with ASD.

1. Significant refraction
2. Increased rate of Strabismus (squint or eye turns)
3. Visual dyslexia
4. Over response to lights and/or patterns
5. Oculomotor dysfunctions
6. Deficit in motion perception
7. Abnormal looking patterns
8. Abnormal face perception
9. Abnormal electroretinogram (ERG) findings

These abnormalities are discussed and referenced in more depth in the following sections.

1.7.1. Ocular refraction

Ocular refraction may seem to be of little relevance to a condition like ASD but refractive abnormalities are found in many different neurological developmental abnormalities and are also more prevalent in those with learning disabilities (Aitchison et al., 1990; Maino et al., 1990; Scheimann, 1984; Woodhouse, 1998). Visual function is important to these individuals who have problems with communication and many of the communication systems designed to help the individual with an ASD in everyday life rely on a good level of visual acuity. For example, the use of pictures to illustrate things which are going to or are likely to happen during the course of the day or week.

There have been few investigations dedicated to investigating basic visual data in autism. All of these studies suffer from small sample sizes which makes it difficult to draw conclusions from the general population. A comprehensive investigation of visual function was carried out by Sharre and Creedon in 1992 (Scharre and Creedon, 1992). They found a high prevalence, 41%, of significant refractive error (defined as myopia, hyperopia or astigmatism greater than 1 dioptre) although no trend was found for any particular type of error. They did not gather monocular visual acuities. Denis *et al.* (Denis et al., 1997) reported hyperopia in seven cases in a sample of ten, and

astigmatism over 1 dioptre in 6 cases. A more recent study, of fifty five subjects with an ASD, at the University of Sheffield in 2007, found a significantly lower visual acuity than a typically developing control group. However, they found that the mean spherical equivalent refraction (as measured by auto refraction) was not different between the 2 groups (Scope et al., 2007). Ashwin et al. recently measured visual acuity in 15 individuals, with either high functioning Autism or Asperger's syndrome, and found that they showed greater levels of visual acuity in comparison to a control group (Ashwin et al., 2009). However their results have been queried by Crewther and Sutherland, who suggested that the visual acuity measures produced for both the control and ASD group in Ashwin's study are unrealistically high (Crewther and Sutherland).

1.7.2. Strabismus

A number of studies have found a higher rate of strabismus in individuals with ASD compared to the general population. Creedon and Sharre found that 21% of the thirty four children in their study had strabismus compared to around 3% in the general population (Scharre and Creedon, 1992). This 31 percent was made up of one individual with an esotropia and 6 with exotropia. Denis *et al* found that 6 of their 10 subjects with an ASD had strabismus; with 4 cases of exotropia. (Denis et al., 1997). In the same study 14 children out of 17 children that were tested for stereopsis exhibited only 550 seconds of arc (which is indicative of poor binocular vision). Schulman (1994) reported that 84% (27 out of 32) of individuals with ASD exhibited strabismus. However, nine of these 27 showed paradoxical strabismus with both exo and esotropia found in the same individual at the same distance (Shulman, 1994). This finding is much higher than reported by Scharre, Creendon and Denis et al. and, considering the high level of paradoxical strabismus may not be reliable. It appears from the current research that strabismus is more common in ASD than in the general population, although sample sizes have been small.

1.7.3. Specific reading disorder/coloured lens use

Dyslexia is often considered as being co-morbid with ASD and ADHD (Terrell and Passenger, 2006). The literature in this area is sparse and according to the National Autistic Society of the UK there are no official figures for the percentage of people with ASD who also are diagnosed with dyslexia.

Meares Irlen syndrome was first described in 1980 (Meares, 1980). Symptoms of this condition include eyestrain, spatial distortions and headache. These are experienced while reading and can be alleviated by using coloured overlays or coloured filters. Educational psychologist Helen Irlen later described similar symptoms while she was working with adult learners in the early 1980s. These symptoms were also found to be more prevalent in people with dyslexia (Irlen, 1991; Kriss and Evans, 2005; Nandakumar and Leat, 2008). The premise of Irlen's theory was that this condition causes perceptual distortion and could be an obstacle to reading and learning. Coloured overlays and lenses could be a remedial intervention in such cases. According to Irlen, 12 to 14 per cent of the population suffers from Irlen syndrome and this figure rises to 46 per cent of those diagnosed with dyslexia, attention deficit disorders and learning difficulties (Irlen, 1997). Individuals with Meares Irlen syndrome are described as seeing letters moving on the page, blurring or forming strange patterns. These symptoms generally get worse the longer a person tries to read or do other visually intensive activities and bright lights, fluorescent lights or glossy paper are described as often making the symptoms worse (Irlen, 1997; Nandakumar and Leat, 2008). The syndrome is thought to manifest itself most strongly when reading words or music because of the repetitive patterns on the page. When the eyes scan across the page, the patterns of words on the page and persistent images will jumble in a manner that is difficult for the brain to interpret properly. Two methods of intervention have been developed:

1. The use of coloured transparencies or overlays (to improve reading).

2. The use of tinted lenses (to improve visual perception of the environment, including reading).

Irlen syndrome is discussed further in chapter 5 coloured filters and autism.

Many features of the autistic spectrum are also characteristic of dyslexia and visual stress. These features include:

- pregnancy and birth complications;
- mini-columnar abnormalities;
- developmental delay in reaching milestones for motor, visuomotor and /or language development;
- a possible magnocellular defect has been found by researchers in both ASD and dyslexia, although this has been disputed;
- there is an increased frequency of allergic or auto immune disorders in the individual and their relatives, there also seem to be familial associations between these conditions;
- large male bias in numbers affected;
- difficulties in tracking words and lines when reading;
- Poor concentration

References: (Casanova et al., 2002a; Casanova et al., 2002b; Ludlow et al., 2006; Ludlow et al., 2008; Pellicano and Gibson, 2008; Richardson, 2000b; Richardson and Ross, 2000; Rumsey and Hamburger, 1990; Terrell and Passenger, 2006):

It has been suggested that the use of coloured lenses can improve symptoms in both dyslexia and autism (Bulmer, 1994; Ludlow et al., 2006; Williams, 1999). Donna Williams a well known autistic author and artist, was one of the first people to report a benefit from using coloured lenses (Williams, 1999). In autism, the claims are for improvements in many areas of behaviour from motor control to eye contact. The anecdotal accounts of improvements range form mild to dramatic but there are currently no placebo controlled trials available to confirm the benefits. Benefits may be due to placebo effects and many claims come without studies to back them up (Evans and Drasdo, 1991). According to the Irlen website (www.irlen.com accessed Nov 2008), up to 50% of people with autism may have perceptual processing problem which could be improved with coloured filters. They report that they have found improvements in all the following areas when using coloured filters:

- gross and small motor coordination
- communication skills
- body awareness
- behaviour control
- listening skills
- eye contact
- self-control
- social skills
- attention

In 2006 a study was carried out to look at the Effect of coloured overlays on reading ability in children with autism (Ludlow et al., 2006). This study found some dramatic results. Fifteen out of 19 (79%) children with autism showed an improvement of at least 5% in reading speed when using a coloured overlay, whereas only 3 of the 19 (16%) in the control group children showed such an improvement. Ludlow repeated her study in 2008 and findings from the original experiment were confirmed. These studies support the theory that coloured tints may be beneficial to the reading skills of individuals with an ASD; however no controlled trials have been carried out to look at possible behavioural benefits which may be produced, only case report evidence is available (Jackson, 2002; Ludlow and Wilkins, 2009; Williams, 1999).

A more detailed examination of the use of coloured filters in autism and dyslexia can be found in chapter five.

1.7.4. Oculomotor dysfunction

There have been significant differences reported in the eye movements of those with autism (Itoh, 1987; Kemner et al., 1998; Manoach et al., 2004; Minshew et al., 1999; Nowinski et al., 2005; Rosenhall et al., 1988; Takarae et al., 2004a). These differences are discussed below.

Autism and pursuit eye movements

Takarae et al. found that individuals with autism showed differences to a control group in pursuit movements. The study included 60 individuals with an ASD and 90 controls (Takarae et al., 2004a). Individuals with ASD showed deficits in open loop pursuit when tracking targets in to the right visual field, bilateral deficits in closed loop pursuit unrelated to target direction and an association of pursuit deficits with poor manual praxis (the ability to carry out movements with the hands. The closed loop pursuit [†] deficits were more pronounced in the older participants (over 16) which was thought to be due to a possible delay in maturation in autism for this system. In a foveofugal ramp test the target is presented first centrally for 2-4s then stepped away from the centre by 3 degrees where it continues moving in the same direction from the centre at a constant speed. Here the saccade typically occurs at 200ms after the onset of target motion followed by an initial stage of the pursuit response first 100ms after the saccade (the open loop stage) then the rest of the pursuit is defined as the closed loop stage. Pursuit gain is defined as the ratio of the average velocity of pursuit movement to the target velocity (Takarae et al., 2004a).

Autism and Saccades

Abnormal saccades are commonly found in autism (Kemner et al., 1998; Manoach et al., 2004; Mercadante et al., 2006; Nowinski et al., 2005; Rosenhall et al., 1988). During infant saccadic responses to a single peripheral target, saccadic latency is often long and in the wrong direction, with a succession of corrective saccades needed in order to turn the eyes in the correct direction (Duckman, 2006a; Johnston and Pirozzolo, 1988). Duckman (2006) suggests that because the processes underlying attention and perception of the location of objects and decision making are located in cortical areas of the brain, the characteristics of saccades in infants may be the result of immature cortical mechanisms (Duckman, 2006a). This could implicate developmental delay in abnormal saccades which may be associated with autism.

Nowinski et al. (2005) reported increased amplitude of intrusive saccades (or square wave jerks) and a reduced latency of target fixation after these intrusive saccades were

[†] Closed loop pursuit stage is the movement which occurs after the first 100ms of tracking and relies on memory of target velocity, predictions about target motion and feedback about performance to control the tracking.

observed. This was most pronounced when the subject fixated on a remembered target location without sensory guidance (Nowinski et al., 2005). Intrusive saccades (square wave jerks) are those which interrupt a smooth pursuit by taking the eye away from the target. They can occur during pursuit and fixation when a small pair of saccades move the eye in opposite directions. One saccade takes the eye away from fixation on a stationary or moving target and, after 200ms, another saccade moves the eyes towards the target again. Square wave jerks occur with a variety of cerebellar diseases but can also be caused by cerebral lesions (Elidan et al., 1984; Nowinski et al., 2005). They are also called 'saccadic nystagmus'. Nowinski also reported that the size of the first intrusive saccade was increased and the time interval between the first and second 'corrective' saccade was reduced. This may mean that there is a subtle imbalance between the excitatory and inhibitory modulation of eye movement control systems within the brainstem (Nowinski et al., 2005). This could be caused by reduced inhibition of saccade generators. Their study concluded that although neural pathways associated with cerebellar-brainstem inhibition of intrusive saccades are not compromised in autism, there may be a subtle abnormality of cerebellar function, causing reduced inhibitory input from the cerebellum to the brainstem.

Takarae et al. (2004) measured visually guided saccades in autistic individuals in order to investigate cerebellar function in autism (Takarae et al., 2004a). Individuals with autism who did not have language delay demonstrated mildly hypometric (i.e. undershooting) saccades and reduced consistency of saccade accuracy over trials. Individuals with autism who did have an early language delay displayed a mixture of both hypometric and hypermetric saccades. The observation of reduced saccade accuracy suggested a deficit in motor function rather than in visual attention in autism, implicating the cerebellum as the cause of the increased variability because it is responsible for determining the accuracy of saccades. The finding is consistent with histopathological and neuro-imaging evidence of abnormalities in the cerebellum. For example, increased cerebellar volume and reduced Purkinje cell counts in the posterolateral cerebellar hemispheres and the archicerebellar cortex (Johnston and Pirozzolo, 1988; Takarae et al., 2004b). There is also evidence of markedly hypometric and hypermetric saccades seen immediately after cerebellar lesions. Takarae et al. concluded that because cerebellar pathology in autism has neuro-

developmental causes rather than being the result of an acute event, the expected pattern of oculomotor deficits is more similar to chronic effects of cerebellar lesions.

Kemner et al (1998) found children with an ASD made more saccades during presentation of stimuli and between stimuli then those without the condition (Kemner et al., 1998). They suggested that subcortical brain systems may be to blame for this abnormality.

In a memory guided anti-saccade test, a subject first fixates a central stimulus; a stimulus is then presented in the peripheral field which the subject is instructed not to look at but to remember its location. The stimulus is then extinguished and the subject asked to fixate where they think the target was. In a predictive saccade test, the subject looks back and forth between two alternately illuminated targets. During the anti-saccade test, the subject fixates centrally then random peripheral targets are presented. The subject is instructed not to look at the peripheral target but to look in the exact opposite direct where a new target appears where the subject is expected to be looking. Goldberg et al (2002) found (1) a higher percentage of directional errors on an anti-saccade test, (2) higher percentage response suppression errors on a memory guided saccade task and (3) lower predictive eye movements on a predictive saccade task. (Goldberg et al., 2002).

Overall, evidence suggests that saccadic eye movements are abnormal in people with ASDs, probably due to abnormalities of brain development discussed in previous sections.

1.7.5. Abnormal looking patterns

Abnormal looking behaviour is characteristic in autism and manifests as a lack of gaze following which is apparent at around eighteen months. It is one of the earliest detectable symptoms of an ASD (Baird et al., 2000; Baron-Cohen et al., 1996) Gaze following can be found in children with high functioning autism and Asperger's syndrome but it is delayed (Leekam et al., 2000).

Joint attention is the ability to coordinate attention between people and objects in the environment. It has been found to be impaired in ASD (Bruinsma et al., 2004; Leekam et al., 2000; Naber et al., 2008). It has been suggested that a low level attentional or perceptual impairment may affect the ability of an autistic individual to make a response to another person's eye movements and gaze (Clifford and Dissanayake, 2008; Osterling and Dawson, 1994). However, Swettenham et al (2003) reported that people with autism were as likely as others to follow the direction of eye gaze in a picture (Swettenham et al., 2003). The difference in findings from other studies may be because the stimulus used was not in a social context. Instead, it was a picture of a face only on a blank ground with no distractions in the view. Klin et al (2003) used eye tracking technology to monitor gaze when viewing a social scene. They found discrepancies between both viewing patterns and gaze direction when viewing a scene with social context by an individual with ASD and a normal individual (Klin et al., 2003; Klin et al., 2002).

In short, the ability to coordinate attention between people and objects in the environment appears to be impaired in ASD, leading to abnormal use of gaze by people with an ASD.

1.7.6. Viewing social scenes

Eye-tracking studies about the patterns of gaze when individuals with autism look at the faces of others have yielded inconsistent findings. People with autism spend more time making saccadic movements than controls when freely observing social pictures. In Autism, subjects do not show any difference in the amount of time spent in saccadic movements when they observe social pictures or non social pictures. This is in contrast to the control group who spent more time making saccadic movements to the non-social pictures than they did when they observed social pictures (sample: 10 autistic subjects and 10 controls) (Mercadante et al., 2006).

Pelphrey *et al.* (Pelphrey et al., 2002) reported that, compared to controls, high functioning adults with autism view 'non-feature' areas of faces significantly more often than controls and 'feature' areas of the face (i.e. the eyes, nose and mouth). Klin *et al.* (Klin et al., 2002) used infrared eye-tracking technology to measure visual scan

paths and percentage viewing time on predefined regions of interest while watching films of naturalistic social situations. Typically developing controls visually fixated on actors' eyes for twice as much time as the participants with autism and that the individuals with autism looked significantly longer at the mouth region. These findings are supported by Dalton et al. 2005 who reported that high functioning males with autism spent significantly less time fixating on the eyes than typically developing adolescents. The autistic individuals and controls did not differ in the amount of time spent fixating on the mouth region or face in general (Dalton et al., 2005). It is interesting to note that Dalton also found that the variation in eye-gaze fixation among autistic individuals was strongly and positively associated with amygdala activation, which suggests that gaze fixation is associated with a heightened emotional response in autism. Klin *et al.* (2002) concluded that face processing deficits in autism are caused by hyperactivation in the central circuitry of emotion that produces an increased sensitivity to social stimuli, leading to diminished gaze fixation and, therefore, to atypical activation of the fusiform gyrus.

In contrast Van Der Geest *et al.* (2002) found no difference in gaze behaviour between high-functioning children with autism and typically developing children when viewing upright faces with and without emotional expression (Van der Geest et al., 2002). They also found that children from both groups made most of their first fixations on the eyes region making significantly fewer on the mouth region. This difference in results may have been because the experimental tasks were not embedded within a natural, social context or because static faces were used, so this was not the same as the fast processing of dynamic faces which is required to process natural environments. Bar-Haim (Bar-Haim et al., 2006) also found that autism and typical control groups displayed a similar pattern of attention allocation to the eyes and mouth region of faces. Individuals with autism, as well as typically developing individuals, made an initial attentional shift to the eyes and did not show a tendency to disengage quickly from this region (within 400ms from stimulus presentation). They suggested that the abnormal viewing behaviour of faces found by other studies might be due to avoidance or to lack of interest in the eyes region at later, more controlled stages of processing. This may indicate hyperactivation of the amygdala associated with an emotional response, as mentioned by Dalton *et al.* (2004). However, the task presented by Bar-Haim *et al.* (2006) also featured static stimuli and faces with neutral

expressions, even though it has been suggested that abnormal processing in autism is linked to social and emotional threat cues which might be especially apparent when viewing faces with emotional expressions. Therefore, it might be more appropriate to use faces engaged in social context of showing emotional expression to represent real life situations.

In summary, research suggests that there are significant differences in the eye movements used by those with an ASD when compared with the normal population, using more differing saccadic movements and concentrating on different areas when viewing faces, this is further discussed in chapter 7.

Abnormal gaze strategy and hypersensitivity

Hypersensitivity has been considered by some studies as a possible cause of some of the characteristics of autism (Asai and Sugiyam, 2007; Dalton et al., 2005; Davis et al., 2006; Frith and Hill, 2004; Klin et al., 2002). In studies relating to face processing deficits in autism, Klin *et al.* (2002) and Dalton *et al.* (2006) have suggested that it is the hyperactivation in parts of the brain associated with emotion (i.e. amygdala) that produces an increased sensitivity to social stimuli, leading to diminished gaze fixation. Therefore, as opposed to there being a lack of interest in the face and eyes, perhaps there is so much emotional interest in the eyes (almost too much), that individuals with autism avoid them. Autistic individuals may have a heightened sensitivity to minute differences in stimuli, be they in sound, sight, taste or touch (Frith and Hill, 2004). Iarroci *et al.* (Iarocci et al., 2006) suggest that there is an overabundance of information embedded in objects observed by autistic individuals and this may be due to enhanced attention to local information. It is commonly observed that individuals with autism have a tendency to be overly attentive to, and distressed by small changes to minor features of their environment (including the visual environment) and this could be a result of this heightened sensitivity. Enhanced perceptual function and the ability of autistic individuals to avoid context may also be associated with this hypersensitivity (Dakin and Frith, 2005). The stereotypical behaviours reported by Scharre and Creedon (1992) such as eye pressing, light gazing and repeated blinking during motion processing may also be coping strategies to deal with this sensory overload.

Another frequently observed coping strategy in individuals with autism may be lateral glance (Filipek et al., 1999; Ritvo et al., 1986). Mottron et al. (2003) found that autistic children more commonly exhibited lateral glances towards moving stimuli (Mottron et al., 2003; Mottron et al., 2007). Eccentric viewing by lateral glance produces a low-pass filtering of information, which removes details, leaving only the low spatial frequency information. Regarding movement perception, which produces a temporal flickering, it is notable that the capacity to see temporal frequency information also changes with eccentricity (Faubert, 1991). In terms of frequency preference, temporal processing has a reverse trend from spatial information. Moving from central viewing decreases the capacity to see low temporal frequency information, while the capacity to see middle to high temporal frequency information remains more constant. Increasing eccentricity selectively filters temporal frequency information and, therefore, simplifies the cortical interpretation of the image. For this reason, peripheral vision is often considered as being specialized for motion or flickering information. Lateral glancing may be compensatory behaviour aiming to make use of excessive amounts of local information and a deficit in motion perception (Mottron et al., 2007).

1.7.7. Face perception in autism

Individuals with ASD have marked deficits in face perception (Bar-Haim et al., 2006; Behrmann et al., 2006; Goldstein, 1975; Joseph and Tanaka, 2003; Klin et al., 2002; Trepagnier et al., 2002; Van der Geest et al., 2002; Volkmar et al., 1989). Using home movies from children later diagnosed with an ASD, those with autism showed significantly less interest in the faces of others and were less likely to (1) show objects to other people, (2) to point to objects or to (3) orient to persons calling their name (Schultz, 2005). The lack of interest in the faces of others is evident in the first 6 months of life is one of the best predictors of later ASD diagnosis.

While typical viewers converge on the eye region of an image of faces some individuals with autism converge on the mouth regions, while others focus peripheral to the face. Relative to controls, individuals with autism, (sample: 15 ASD subjects, 15 controls), focus twice as much time on the mouth region of faces and 2.5 times less on the eye region of faces when viewing social scenes (Klin et al., 2002). There were no group differences on two visual perceptual control tasks. Therefore, Klin et al

(2002) proposed that the perceptual deficit was specific to faces and did not suggest a more pervasive deficit in object perception. Other studies (Behrmann et al., 2006; Dalton et al., 2005) have also found this selective impairment to be true. Individuals with autism are slower and less accurate at experimental tasks on face perception; they appear to rely too heavily on 'feature level' (i.e. local) analysis and do not adequately make use of configural strategies (Schultz, 2005). Autistic participants viewed non-feature areas of the faces significantly more often and core feature areas of the faces (i.e., eyes, nose, and mouth) significantly less often than did control participants (sample: 5 ASD, 5 control subjects) (Pelphrey et al., 2002). Autistic participants also display less fixation on the central face than do control-group participants (sample: 5 ASD, 6 control subjects) (Trepagnier et al., 2002).

This over reliance on "feature level" local analysis could also be linked to impaired global perception in ASD. The weak central coherence (WCC) hypothesis has been implicated in deficits involving face processing because of the bias towards local information. It has been suggested that because faces are perceptually similar, face processing relies on configural processing (Behrmann et al., 2006). Since individuals with ASD tend to place undue focus on local stimuli, rather than seeing the bigger picture, this may be a significant disadvantage for face processing.

Some studies have found little or no difference between autistic and control group patterns of looking. In a study of face scanning in autism participants showed normative visual fixation patterns when viewing photographs of human faces relative to controls (17 ASD and 17 control participants) (Van der Geest et al., 2002). There are a number of possible reasons for these differences between results. Firstly, they could be due to differences in the participant groups – the studies that found no difference involved children, whereas the majority of studies (with the exception of Dalton et al. 2006) that have found a difference in gaze behaviour have involved adult participants. Second, specialist training on emotion recognition, as occurs in some educational units for individuals with autism, could have an impact on how an individual performs in testing (Boraston and Blakemore, 2007). Alternatively, the critical difference could be in the nature of the stimuli used. It has been suggested (Kemner and van Engeland, 2003) that gaze differences in autism only exist in response to dynamic stimuli (Klin et al., 2002) and are due to impaired dorsal stream

function. Studies that failed to find a difference have used static stimuli (Van der Geest et al., 2002). However, other studies using static stimuli have found gaze abnormalities in autism (Dalton et al., 2005; Pelphrey et al., 2002; Spezio et al., 2007). Finally, the specific instructions given to the participant could be a crucial factor as they impact on what precisely is being measured – differences in the gaze strategies used when a subject is completing a specific task versus differences in spontaneous behaviour. Individuals with autism might conceivably look at the face in a normal way when required to do so by a task, yet fail to explore a face visually without specific reason to do so. On the other hand, they might show normal spontaneous gaze behaviour, but an inability to examine the appropriate parts of a face, when performing the task. It should be noted that one study included both a free-viewing and a task-directed condition in their study, and found the same pattern of results in both (Pelphrey et al., 2002).

Another interesting feature of abnormal face processing in autism is the decreased 'inversion effect'. For typical individuals, faces which are inverted by 180 degrees are much more difficult to accurately recognise that upright faces (Goldstein, 1975; Valentine, 1988), as we can see from looking at these two pictures below, of myself (figure 1.7).

Figure 1.7 Inverted and upright image.

Performance of individuals with Autism is not much degraded for the recognition of upside down faces versus upright faces (Langdell, 1978; Swettenham et al., 2003; Van

der Geest et al., 2002; Volkmar et al., 1989). This supports the hypothesis that individuals with autism may rely less on 'holistic' processing when viewing faces. Behavioural studies (Morrison and Schyns, 2001) cited by (Schultz, 2005) have shown that face recognition among typically developing controls is facilitated more by low spatial frequencies than high spatial frequencies, and during infancy, the preference for faces appears to be mediated by low spatial frequency components of the face. They found that among typically developing young adults, the optimal spatial frequency range for face perception ranges from 8-32 cycles per face. In contrast, young adult males with Asperger's Syndrome rely on much higher spatial frequencies, i.e. they needed over 45 cycles per face to make identity judgments. This provides further evidence for a bias towards high spatial frequency information in autism.

1.7.8. Abnormal gaze strategy and the brain

Abnormal activation and physiology of the Fusiform Face Area (FFA) and the Amygdala have been implicated as a cause of face processing deficits in autism (Critchley et al., 2000; Dalton et al., 2005; Howard et al., 2000; Kleinhans et al., 2008; Pierce et al., 2004; Schultz, 2005; Shultz, 2005). The FFA is a patch of cortex, within the lateral aspect of the middle part of the fusiform gyrus, that is more strongly activated during face perception than any other class of stimulus (Schultz, 2005).

Fusiform Face Area (FFA)

Lesion studies have confirmed the importance of this tissue for face recognition, showing that damage to this tissue results in Prosopagnosia –an inability to recognise faces. Schultz *et al.* (2004) have found a significant enlargement of the right fusiform gyrus in the older group of their subjects with ASD in comparison with controls. This may be associated with abnormal brain hyper-perfusion (which is a feature of autism) and also suggests that developmental maturity may play a role in face processing deficits within autism.

Figure 1.8 Fusiform face area, shown here in green. Image with thanks to Miss H Patel Aston University.

A number of investigations have reported that individuals with ASD have shown significantly less activation in the FFA (figure 1.8) compared to controls (Schultz *et al.*, 2004, Behrmann *et al.*, 2006). Joseph *et al.* (Joseph and Tanaka, 2003) suggest that individuals with ASD might be performing a more object-related, feature-based search of faces instead of the expected configural processing. However the results of the neuro-imaging studies are inconsistent, with some reporting normal fusiform activation in ASD (Hadjikhani et al., 2004; Pierce et al., 2004) with a greater signal for familiar than unfamiliar faces. Functional magnetic resonance imaging (fMRI) has been used to map out FFA responses to high and low spatial frequency filtered faces in autistic individuals (Gauthier et al., 2003). Hypo activation of the Fusiform Face Area to broad (i.e. low) spatial frequency faces was demonstrated but also showed a greater than normal FFA activation to high spatial frequency face (Gauthier et al., 2003). These findings provide further evidence for the proposed enhancement of high spatial frequency information in autism. Individuals in the subject group with classic autism had significantly less FFA activation than the combined Asperger's and PDD NOS group which, in turn, had significantly less activation than normal controls. These findings provide evidence of a possible correlation between the severity of the ASD and activation of the FFA.

Amygdala

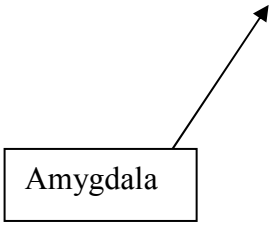


Figure 1.9 The brain and Amygdala.

The Amygdala plays a critical role in the early stages of processing facial expressions (Haxby et al., 1994; Kanwisher et al., 1997; Vuilleumier et al., 2003). It has dense reciprocal connections with the ventral visual processing stream and therefore would be able to influence and amplify processing of complex object perception areas, including the FFA. Schultz (2005) suggests that a congenital abnormality, possibly at first only involving the Amygdala, is responsible for the diminished attention to faces in autism by affecting the sub cortical visual system (i.e. the ventral pathway) (Schultz, 2005).

The preference for faces shown by typical newborns and young infants is also believed to be mediated by the sub-cortical visual system, which passes information from the retina to (1) the superior colliculus, then (2) the pulvinar nucleus of the thalamus, and (3) the Amygdala.

At birth, the visual cortex is functionally immature and, therefore, probably incapable of supporting a preference for face-like patterns. This abnormality of the amygdala, which may be present in ASD (Howard et al., 2000; Schumann and Amaral, 2006), could be responsible for abnormal face perception. The sub-cortical visual pathway is biased towards low spatial frequency information rather than high spatial frequency

information (Vuilleumier et al., 2003). This evidence further supports the theory that people with ASD have a high spatial frequency bias and also implicates the Amygdala further in the pathogenesis of autism

1.7.9. Abnormal Electroretinogram (ERG)

The electroretinogram (ERG) is used to investigate the integrity of retinal function by measuring the electrical responses of various cell types in the retina, including photoreceptors and the ganglion cells. Electrodes are placed on the cornea and the skin near the eye. The patient watches a standardized stimulus and the resulting signal is interpreted in terms of its amplitude (voltage) and time course. Approximately 48% of autistic individuals in a sample of 22, had abnormal ERG responses (Ritvo et al., 1989a). Full details concerning electro-retinography are found in Chapter 9.

1.7.10. Motion perception

Perception of moving stimuli is impaired in ASD (Bertone et al., 2003; Dakin and Frith, 2005; Spencer et al., 2000b). Individuals with ASD show raised thresholds for perceiving coherent motion (Milne et al., 2002; Spencer et al., 2000a) and also postural hyporeactivity to visual motion (Gepner et al., 1995a; Gepner and Mestre, 2002). Thus there is a lack of physical response to an illusion which induces a sense of self motion.

Motion perception deficit

The apparent deficit in motion perception could support the theories of a magnocellular deficit and global and local processing imbalances in autism (Dakin and Frith, 2005; Gepner et al., 1995a; Spencer et al., 2000a). Because of the functional properties of the magnocellular pathway, a high motion coherence threshold indicates a possible impairment in this pathway. Milne et al, (Milne et al., 2002) found that the majority of children with an ASD showed an abnormally high motion coherence threshold (autistic children required about 10% more coherent motion to reliably report direction) using a random dot kinetogram (the ability to detect coherent motion from an array of randomly moving dots where a certain proportion of the dots move with a motion vector which is coherent and the others move randomly in Brownian motion). The random dot kinetogram has been shown to provide a sensitive measure of magnocellular processing (Talcott et al., 2000). However, recent investigations have suggested that this may also be caused by weak

central coherence or an impairment of global processing rather than a physiological problem, to support this, Pellicano (Pellicano et al., 2005) reported that an autistic group required the same amount of contrast as a control group to identify modulation in a Gaussian patch.

In chapter 4, the clinical examination of the magnocellular visual pathway using specific techniques of visual fields testing is discussed.

Visual motion and postural responses

Postural reactivity is the physical response (change in posture) by an individual to an illusion which induces a sense of self motion. Gepner et al (Gepner et al., 1995b) demonstrated that children with autism showed less postural change in response to movement in the visual environment compared to children without (although they found that children with Asperger's syndrome showed a similar response to the control group) (Gepner and Mestre, 2002).

2. Rationale

2.1. Rationale

There is relatively little research into the visual function and characteristics of individuals with Asperger's syndrome. Previous research has shown differences in brain development and function in these groups in areas which may suggest that there could be differences in the visual performance of these individuals compared to the normal population. In chapter one, the current research concerning vision and visual performance has been reviewed. The remaining parts of the thesis concern studies designed to find supporting evidence for findings in the literature and to explore the possibility of developing a battery of tests applicable to evaluation of these patients in optometric practice.

2.2. Aims

In order to translate the findings of the studies reviewed in chapter one into clinical practice, a specific protocol for the eye examination of an individual with an autism spectrum disorder was developed. To accomplish this, a number of basic optometric measurements were taken in order to compare (1) a group with Asperger's syndrome against (2) a neurotypical control group and (3) a group with autism and learning disability.

A study was also carried out to determine whether those with Asperger's syndrome are more likely to suffer from Meares-Irlen syndrome and whether their educational development be augmented by using coloured overlays. Testing visual fields using methods which are designed to be selective for the M-cell pathway in optometric practice were employed in order to investigate this theory and also to describe the nature of any defects found.

The second part of this study involved evaluation of eye movement strategy in Asperger's syndrome as part of the autistic spectrum. Eye movement differences have been noted by several previous studies (Boraston and Blakemore, 2007; Kemner et al., 1998; Pelphrey et al., 2002; Takarae et al., 2004a; Van der Geest et al., 2002). In the current study a series of investigations were carried out to look at differences in eye movements and eye movement strategies to both text and images in a group with

Asperger's syndrome and a neurotypical control group. These investigations were also designed to evaluate the most appropriate methodology for investigating eye movements; namely optical digital eye tracking and electrophysiology methodologies.

2.3. Location and participants

All of the research was conducted in the Vision Sciences department and Aston University Day Hospital with approval from the Aston University Human Science Ethical Committee (Project 06/6 and Project 07/O: Visual function in autistic spectrum disorders).

The neurotypical controls were recruited from University staff, students and the general public. Controls were matched for educational level with the Asperger's group. No control group was gathered for the intellectual disabilities group from Gheel, Dublin, Eire due to the limited time window available to examine this group. The Gheel group were not originally part of the experimental design but was added after the Aston was contected by Gheel Autism Service about the possibility of vision testing their clients.

In previous research into Asperger's syndrome and Autism, both IQ (intelligence quotient) and educational matching have been used. Some researchers have used educational matching in studies of Asperger's syndrome, rather than intelligence quotient scores owing to the difficulties of performing accurate IQ scores on this group (Dawson et al., 2007; Fletcher-Watson et al., 2009; Scheuffgen et al., 2000). In the present study educational matching was used. This was partly due to issues of funding; as these tests would need to be administered by a psychologist for which no funds were available. In addition to this there was a precedent for use of educational matching as a suitable alternative.

Any volunteer for the normal group was excluded if they had any first degree relatives with an Autism spectrum disorder or Asperger's syndrome. Subjects with Asperger's were sourced via adverts placed in local and national publications for those with Autism spectrum disorders. The Autism with learning disability group was sourced

from a visit to the Gheel Autism Service in Dublin. Service users from two of their day support services attended for visual screening.

All diagnostic details were supplied by either the volunteer or his/her carer as appropriate and were used to group the patients, see Table 2.1.

Total number (n)	Control group	Asperger's syndrome (no ID)	ASD mild intellectual disability	ASD moderate intellectual disability
Volunteers	19	26	19	16
Average age	23	20	29	30
SD age	8	10	7	6
Range	10 to 48	10 to 45	18 to 40	20 to 40
Ratio M:F	13:6	14:5	18:1	12:4

Table 2.1 Total numbers and details of recruited volunteers.

The non-intellectual disability (Asperger's syndrome) group was comprised of volunteers who provided a clinical diagnosis of Asperger's syndrome with no learning disability. This group had attended or was attending mainstream education. The other groups were formulated by the two clinical psychologists at the Gheel Autism Service in Dublin who carried out cognitive assessments on all of the volunteers, using a combination of the Autism Diagnostic Interview (ADI) and pre-existing IQ scores. The ADI is a structured interview rather than a simple check list. This means that it builds a picture of how the individual functions in areas of language, communication, social development and play. A trained individual, who then evaluates the responses, administers the test (Le Couteur et al., 1989; Rutter and Schopler, 1987).

Each participant was given a detailed verbal and written explanation of the study which they were taking part in before they were formally enrolled. Written informed consent was obtained and they were given the opportunity to ask any questions.

Recruitment of volunteers with an ASD was more difficult than anticipated. This limited the numbers of volunteers and led to the inclusion of the children in the total group rather than making a separate group (in both control and Asperger's group 3 individuals were age 10 to 13 all others were over 16). Adverts for the research studies were placed on the National Autistic Society web pages, in local publications and

newsletters for people with ASD's. Visits were made to support groups in the West Midlands area in the hope that potential volunteers would become familiar with the author of this thesis and would then be more likely to volunteer. A high rate of non-attendance and cancellation of appointments hindered the progress of this study. For individuals with an ASD, a visit to an unfamiliar location to take part in unusual activities can be unsettling and disturbing to their daily routines. This may cause them anxiety, stress and other difficulties. Sixty nine individuals with an ASD expressed an initial interest in taking part in these studies. Approximately 87% of these subsequently took part in one or more of the studies. One major limiting factor in this study was a lack of funding to pay travel expenses. This put off some of the people who enquired about volunteering. Many individuals with an ASD experience difficulties using public transport, so had to come by private methods, incurring time off work for themselves, and possibly a supporting individual, as well as travel costs.

3. The Eye examination

Abstract

Purpose: To evaluate standard optometric measurements to examine for any correlates in individuals with an autism spectrum disorder (ASD), without severe learning disability, and to develop a protocol for optometrists examining people with this type of disorder. **Methods:** Subjects were divided into three groups; Asperger's syndrome including high functioning autism (n=19, mean age 21.3 +/- 10.7 years, range: 10-46 years), Autism with mild learning disability (n=18, mean age 30.4 +/- 6.4 years, range: 20-45 years), and Autism with moderate learning disability (n=16, mean age 29.9 +/- 6.1 years, range 19-40 years). For each patient the following parameters were assessed in comparison with normal controls (n=19, mean age 23.1 +/- 8.2, range 10-48 years); previous ocular and family history, visual acuity, oculomotor muscle balance (using cover test), stereopsis (using TNO test) , colour vision (using D-15 test) and auto-refraction. **Results:** Lower binocular visual acuity was found in individuals with autism and learning disability compared to the control group (p=0.02). There was no difference in the distribution of refractive error or oculomotor balance between the groups or in the extraocular muscle balance (p = 0.91 and p = 0.48 respectively). Individuals with Asperger's syndrome higher stereopsis compared to individuals with a learning disability; mean value 57 and 179 minutes of arc were recorded for both groups respectively (p = 0.03). The prevalence of colour vision deficits did not exceed that expected in the general population. A higher than expected percentage of the individuals tested stated they had previously been diagnosed with dyslexia (22.6%). **Conclusions:** Existing recommendations for the optometric assessment of patients with autism are sufficient but could benefit from additional recommendations relating to communication with such patients. As the needs of the individual vary according to age and ability, special attention needs to be given to tailor communication aspects to each individual. Optometrists should be aware of the greater likelihood of dyslexia in this patient group.

3.1. Introduction

3.1.1. ASD and the eye examination

There is little published research on the visual function and visual characteristics of people with autism. To date, very few studies of refractive and binocular status have been documented (Denis et al., 1997; Kaplan et al., 1999; Scharre and Creedon, 1992) and these have examined autism as an entire spectrum in children ranging from 2 to 19 years of age. Individuals with Asperger's syndrome are, diagnostically, part of the autism spectrum, although it has been argued whether there is a need to create a specific diagnostic sub-section of the spectrum or whether these individuals should be, in fact, diagnosed as having a mild form of autism (Gillberg, 1992; Jordan, 1999; Kugler, 1998; Trevarthen, 1996; Wing, 1996b). Investigating the refractive and binocular status of individuals with Asperger's syndrome could show whether they suffer from similar visual problems compared to others from the general autism spectrum. Any differences revealed between this group and those with classic autism may prove to be useful diagnostic tools that differentiate this group. Further, studying people with Asperger's and ASD's may lead to recommendations or specific tests which should be carried out on one or both of these groups.

Autistic children have unequal developmental profiles in all of their sensory areas (Bernabel et al., 2003; Burack et al., 2001; Burack and Volkmar, 1992; Dunn et al., 2002; Iarocci and McDonald, 2006; Leekam et al., 2007). Leekam et al (2007) found that over 90% of individuals tested showed a sensory abnormality in smell, taste or vision. This finding is similar in the Asperger's syndrome section of the autism spectrum; Dunn et al (2002) found a difference in sensory profile, from typically developing children, in 96% of individuals. As a consequence they may show hypo- or hyper-sensitivities to different sensory stimuli. It may be these atypical responses to sensory stimuli which first lead to suspicions of a problem in young children or babies. Individuals with Asperger's syndrome have also been shown to have sensory abnormalities

Individuals with an ASD may be difficult to examine due to their limited communication skills and sometimes unpredictable behaviour. Individuals with autism often exhibit "atypical gaze or gaze avoidance" and manifest stereotyped behaviours

such as eye pressing, hand flicking and light gazing (Scharre and Creedon, 1992; Wong, 1993).

Visual symptoms associated with Autism

The following is a list of visual problems that have been reported to be associated with autism.

Over response to lights and/or patterns Atypical gaze or gaze avoidance Hyperlexia (advanced decoding skills) Self-stimulating behaviours- hand flicking, eye crossing, eye pressing, light gazing, and holding objects very closely. Abnormal ERG findings Refractive error Strabismus Oculomotor dysfunction	Scharre and Creedon (Scharre and Creedon, 1992)
Poor depth and motion perception. Imbalance between peripheral and central vision Distorted/ jumping around vision Visual dyslexia	National autistic society information (NAS, 2005)
Side looking Visual inattention Poor visual awareness of surroundings Fascination with spinning objects, lights and shadows, and bright metallic objects	Creedon and Scharre (Creedon and Scharre, 1991)

Figure 3.0 Visual symptoms found in autism disorders

Visual research in autism

Scharre and Creedon (1992) examined 34 children, (32 male and 2 female, age range 2-11 years). Binocular visual acuity, stereopsis, ocular alignment (presence of latent or manifest strabismus) and refraction using non-cylcoplegic near retinoscopy were measured. The authors stated that the children had been previously diagnosed as autistic based on the criteria of DSM –III and had developmental levels from average intelligence to severe learning disability; the method of establishing the developmental level or learning disability was not stated.

Visual acuity ranged from 6/4.5 to 6/480 using teller acuity cards as the testing method. Teller acuity cards are a forced choice preferential looking technique of visual acuity measurement. A card is presented to the child. On the right or left side of

this card is a grating pattern, the spatial frequency of which varies by card (figure 3.1). The examiner views the subject's reaction to the card from a small peephole in the centre; the child should look at or indicate in some way the location of the stripes as an object of interest in preference to the blank side of the card if the grating is visible.

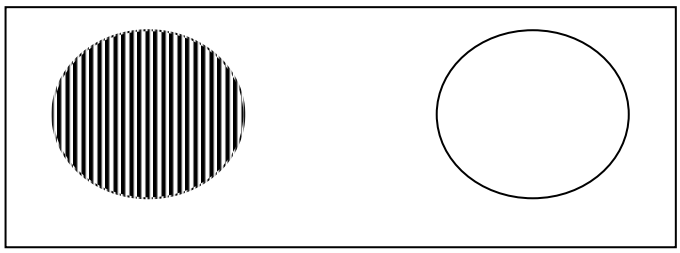


Figure 3.1 Teller acuity card.

There was a high prevalence (41%) of significant refractive error, defined as greater than 1D spherical or astigmatic error, although no trend was found for any particular classification of refractive error. The children were averse to occlusion and so no test for amblyopia was possible. Strabismus was found in 21% of the children, of which most were exotropes and nearly all intermittent. These values were much higher than the 3% prevalence in the general population (Kvarnstrom et al., 2001).

Scharre and Creedon's study did not gather any control data with which to compare their results. Also the 34 children who participated were of varying developmental levels, ranging from normal intelligence to severe intellectual disability. Furthermore, there was no segregation into sub-groups which could have caused variability in their findings since children who have an intellectual disability are more likely to suffer from ocular and refractive deficits than typically developing children. Thus they may also be more likely to suffer from these problems than the normal intelligence autistic group (see section 3.1.2). The age range examined (2-11 years) could also have been a limiting factor as it spanned the normal critical period for ocular development leading to an expectation of differences in results between the older and younger children in the group. Additionally, compliance and ability in the testing procedure would have been expected to be lower in the younger ages examined. Denis *et al.* (Denis, Burillon et al. 1997) used an even smaller sample size of 10 autistic children (6 male) aged between 1 and 14 years (mean = 8.5 +/- 3.8). The children were also diagnosed with autism based on the DSM-III criteria and were of varied developmental levels as the

Scharre and Creedon study. Refraction using non-cylcoplegic near retinoscopy showed hypermetropia in (>1D) 7 cases, more than 1 D of astigmatism in 6 cases (bilateral in 4 cases). The axis of astigmatism was oblique in 8 eyes; with the rule in 6 eyes and against the rule in 2. Strabismus was present in 6 cases, including 4 cases of exotropia.

Kaplan et al (1999) (Kaplan et al., 1999) examined strabismus in autism spectrum disorders. Thirty-seven children and teenagers with a diagnosis of autism ranging between 7 and 19 years of age (median 14) received an independent diagnosis of autism from a physician or psychologist, using an unstated methodology. Their autism functional level ranged from low to high, with the majority functioning at a moderate level. The presence of strabismus was determined using the cover test and the Hirschberg corneal reflex test. Of the 34 participants, 17 (50%) had strabismus, 11 had exotropia and 6 had esotropia. Above the median age of 14 years, 13 (68%) exhibited strabismus, whereas only 4 of the 15 individuals (27%) below the median age exhibited strabismus.

The investigation by Kaplan et al could also be considered to be flawed in that the participants were all children from a heterogeneous sample of autism. The possibility for large variations in the level of development and potential learning disabilities could have skewed their results significantly. It is known, for instance that the prevalence of refractive error and strabismus are different in the learning disabled population (Courtney, 1977; Green and Courtney, 1977; Karadag et al., 2007; Kwok and Cheung, 2007; Woodhouse et al., 2003). It is also difficult to separate findings which are specific to autism from those found in the general population of individuals with learning problems. Also, when describing the techniques used, they state that the alternate cover test was used and that when using this test the eye which is covered is observed for movement. This would, in fact, be testing for a heterophoria (or latent strabismus) rather than a manifest strabismus (or heterotropia). If this is the way in which strabismus was detected then it would create a falsely high prevalence since the prevalence a latent strabismus (heterophoria) will be much less than a manifest (heterotropia). However the researchers did state that they were looking for “crossed eyes” which would normally be assumed to refer to manifest convergent strabismus or an esotropia.

Most recently Ashwin et al. (2009) investigated visual acuity in individuals with Asperger's syndrome and high functioning autism. They found a striking difference between the visual acuity scores of the autism spectrum conditions (ASC) group and controls, ASC group having VA 2.8 times greater than the controls. They stated that the ASC group had a mean VA which was in the range of a bird of prey (Ashwin et al., 2009). They also found that there was no difference in the VA of the Asperger's group and the HFA group. Methodology was not standard optometric testing for visual acuity in this study. The testing was carried out at a near distance (60cm) and then corrected to give a distance VA score, also single Landholt C targets were used rather than a line of letters, so crowding effects were not the same as in a Snellen or Bailey Lovie test chart (section 3.1.4).

3.1.2. Refraction and ocular defects in people with intellectual or learning disabilities

Definition of Learning Disability

Many people who are diagnosed with autism also have some kind of learning or intellectual disability (Coleman, 2005; Jordan, 1999). So it is important to consider these individuals as well as those who do not have this disability.

A learning disability (LD) is defined as "*a cognitive impairment which makes it harder for children and adults to make sense of information to a significant degree*." (College-of-Optometrists, 2008). This term is not a precise definition and does not describe a specific condition or group of conditions. Rather it describes the outcome of one or more conditions (a developmental disorder for example). Prevalence rates vary depending on the study design and the population studied but according to the World Health Organization the prevalence of intellectual disability is close to 3% (WHO, 1994). Roeleveld et al. (1997) undertook a review of prevalence studies and reported that many studies were hampered by imperfections in study design which influenced their estimates of prevalence rates. Individuals with mild disability represent the largest proportion (approximately 2.5% of the intellectually disabled population); moderate intellectual disability involves approximately 0.4% of the

population; severe and profound levels combined account for approximately 0.1% (Roeleveld et al., 1997).

Health and Vision Problems in Learning Difficulties

Individuals with a learning disability can have the same health problems as the general population. They are, however, likely to suffer from a wider range of health problems and of greater severity. This includes visual problems and ocular defects such as, strabismus, eyelid abnormalities or cataract (Aitchison et al., 1990; Balogh et al., 2008; Kwok and Cheung, 2007; Maino et al., 1990). It is not uncommon for individuals with learning difficulties to suffer from multiple disabilities, both sensory and physical. A lack of understanding by carers and educators of a visual impairment could influence the understanding and ability of these individuals to learn the essential skills that might lead to a better quality of life and a more independent lifestyle (Band, 1998; Levy, 1996; Woodhouse et al., 2003).

The RNIB (2003) investigated the sight problems of 60 learning disabled community service users known to social workers. 52 had undetected sight difficulties (RNIB, 2003); although what constituted a sight difficulty was not specified. Developmentally delayed and neurologically impaired people have a significantly higher rate of strabismus and refractive error (Karadag et al., 2007; Orel-Bixler et al., 1989; Warburg, 2001; Woodhouse et al., 2003). Vision in this population shows a wide range of visual acuity (mostly recorded using preferential looking or matching techniques) but it seems that visual acuity (VA) is lower in those more severely disabled. Woodhouse et al (2000) found a median VA of 6/11.5 in mildly intellectually disabled (ID) people and 6/19 in moderate to severe ID of a sample of 154 adults aged between 20-74 (mean 37 years) (Woodhouse et al., 2000). In a later study, the same author reported that median VA in an ID group of 518 individuals to be 6/14 in the right eye and 6/16 in the left but there was no sub-classification of acuities by intellectual disabilities (Woodhouse et al., 2003). Strabismus prevalence rates show a large variation ranging from 22%, (34% esotropia, 57% exotropia, 9% vertical) (Orel-Bixler et al., 1989) to 71% (Woodhouse et al., 2003). Orel-Bixler's figure of 71% seems very high compared to the general population but, again, their findings suggest that the prevalence of strabismus increases with severity of intellectual disability. McCulloch (1996) reported strabismus rates of 25% in mild ID compared to 60% in more severely disabled individuals (McCulloch et al., 1996).

Woodhouse et al. (2000) found a difference in strabismus rates with varying intellectual disability levels, though much smaller, 22.6% and 28.2% for lower and higher levels respectively (Woodhouse et al., 2000). All of these investigations report that strabismus prevalence is significantly higher than the general population prevalence of between 2 and 4% (Adler, 2001).

Prevalence of significant (>1D ametropia) refractive error in individuals with ID has been reported as between, 73% (Orel-Bixler et al., 1989) and 56.1% (Woodhouse et al., 2003), The findings of other studies fall between these two values (Haugen et al., 1995; Warburg, 2001; Woodhouse et al., 2000). In the general population, the prevalence of significant refractive error is approximately 15% (Sorsby et al., 1960). All used non-cycloplegic methods of refraction; using retinoscopy techniques (Woodhouse also used an autorefractor in her 2003 study).

3.1.3. Eye examination in patients with learning disabilities

Examination of a person with a disability relies somewhat upon an understanding of the patient's condition. If possible, it is useful of know in advance what the individuals needs may be. This may range from something simple like being able to accommodate a wheelchair in the test room or perhaps the need to alter testing distance, to a little prior research on some syndromes so as to be aware of any possible complications.

People with learning disabilities are at much higher risk than members of the general population of ocular and refractive defects, including refractive errors (Aitchison et al., 1990; Amos, 1977; Courtney, 1977; Maino et al., 1990; McCulloch et al., 1996). This population is, however much less likely to receive eye care (Levy 1996) due to lack of awareness of the importance of eye examinations, or lack of opportunity due to being in residential care. A study by McCulloch et al in 1996, found that 89% of adults in institutional care had no record of any eye examinations. In England, around 33,300 of the 115,000 (29%) people with learning disabilities live in residential care (Warner, 2003). In a study looking at athletes competing in the special Olympics in 2003 it was found that the number of athletes who had never had an eye examination was 15% but could have been as high as 25% given that some participants could not recall whether they had one previously or not (Woodhouse et al., 2003). This group

consisted of 505 participants, 191 females and 313 males (range 9-69, mean = 27.3 years, SD 11.2). No data were presented stating whether the participants had any co-existing physical disabilities as well as intellectual ones. An earlier study by Woodhouse et al found that 41% of 154 subjects (mean age 37.5; SD 11) with an intellectual disability (ID) who were not currently wearing spectacles had a significant refractive error defined as an error greater than 1D myopia, 2D hyperopia or astigmatism greater than 1D. They also found that 26% of the group had a non-defined strabismus. Dividing the sample into less and more severe ID groups showed no significant difference between the groups. In the mild/moderate ID group, 28.2% had a strabismus compared to 22.6% in the severe group. Other investigations have reported the percentage of strabismus in individuals with an ID to range from 19% (16 cases of Esotropia, 14 of Exotropia and 1 of hypotropia in a population of 166) to 31% (Aitchison et al., 1990) and 41.3% (McCulloch et al., 1996). Overall 60% of the group with intellectual disability had below normal VA (<6/9, varying from 6/3 to 6/420). The more severe the ID the more likely the person is to have lower VA (Woodhouse, Griffiths et al. 2000).

Guidelines for eye examinations

In 2008, the College of Optometrists published guidelines for optometrists examining a patient with a learning difficulty (College-of-Optometrists, 2008).

a) Whenever appropriate or possible, encourage the patient to visit the premises prior to the appointment so that they are more familiar, comfortable and confident in the practice environment;

b) Whenever possible, attempt to determine the patient's method of communication and any "special needs" i.e. does the patient communicate by speech, sign language or other methods.

c) Communicate clearly and effectively with the patient and their carer at all times;

d) Whenever appropriate, seek a briefing from family members, carers and key workers, provided explicit consent has been obtained from the patient, as many patients may not be able to provide a reliable history. In addition any recent signs, symptoms and/or behavioural changes might be relevant. Some patients may have a personal care plan that would assist in this aspect of the examination;

e) When necessary, adapt techniques and use alternative methods for assessing the patient;

f) Be prepared to take longer to complete the examination and consider repeat visits to obtain full and valid results;

g) Visual field assessment should be attempted, even if this can only be done using confrontation techniques;

h) Cycloplegic examination may be necessary in some cases to determine the full refractive error. Clear unambiguous information about the effects of the eye drops need to be given to the patient and the carer;

i) The use of mydriasis may be necessary for internal examination of the eye;

j) The extent of the examination possible and results obtained may be more limited than in patients who do not have learning disabilities. If this is so, the reasons for these limited results should be recorded;

k) Consideration should be given as to whether referral for further investigation (e.g. examination under anaesthetic, or electrophysiological tests) is in the patient's best interest or would be of purely academic interest.

Woodhouse (1998) also suggested advice for examining children with a learning difficulty (Woodhouse, 1998).

a) Be aware of correct terminology. Today we refer to `children with disabilities', and not to `disabled children'. The emphasis is always to consider the child first, and not the disability. Political correctness can seem clumsy, but is essential in demonstrating a professional approach and in establishing good rapport with parents and carers.

b) Practitioners should avoid the use of the word `normal' when making comparisons of a child's performance. A child with the most profound disabilities will be `normal' in some respects and none of us are perfect. It is fairer and certainly kinder to say to a parent `a child with good sight would be reaching this level, whereas your child is achieving this' than `a normal child would be reaching this level, whereas your child can only get to this level'.

c) During the examination, emphasise the positive. This is important with ordinary children but even more so with children with special needs who will be so aware of failure in almost every aspect of life. When assessing visual acuity, for example, we have to reach a point beyond the child's ability in order to establish the limit the child has to fail. At this point always return quickly to a level at which the child can easily succeed. Let the last thing the child does for you be successful.

d) Be prepared to be flexible in your approach. Indeed, this aspect is what makes working with patients with special needs so interesting since every patient presents entirely different challenges. Be prepared to take considerably more time than usual to put the child and parent at their ease, to carry out the investigations and to explain your findings at the end.

3.1.4. The routine eye examination

Many techniques are utilised in the eye examination to gain important information about the ocular health and refractive status of a patient. Most eye examinations performed by an optometrist will contain a sub-set of tests selected according to the patient's needs. Guidelines on what tests should be carried out in a standard eye examination are published by the College of Optometrists (College-of-optometrists, 2007).

History and Symptoms

Taking a patient's history and symptoms would typically include the patient's reason for visit, detailing any symptoms or signs of ocular and/or visual problems which they might be experiencing. Any symptoms would be accompanied by details such as the onset and duration of those symptoms. Information is gathered about the patient's general health to determine whether any conditions are present which could cause ocular complications or refractive changes (e.g. diabetes) as well as information on their previous ocular health and any treatments which they may have undergone in the past (e.g. cataract surgery or strabismus treatments). Any medications which the patient is using should also be recorded in case of any ocular reactions or side effects. Family history of ocular and systemic conditions is recorded so that any genetic predisposition to certain conditions can be accounted for and additional testing carried out. Finally, an assessment of ocular demands should be made to help determine how best to test and advise the patient. It should be determined if the patient has any specific occupational or leisure need with respect to vision and optometric devices (e.g. does the patient drive or play sports which might require eye protection).

Vision and visual acuity

Vision in this instance is taken to mean the unaided acuity of the eye. Visual acuity refers to that aided by refractive device, if one is needed. Visual acuity is defined as the ability to see distinctly the details of an object (Millodot 1997). This can be quantified in different ways:

a) The reciprocal of the minimum angle of resolution (taken in minutes of arc); the resolution visual acuity.
b) The Snellen fraction, usually measured using letters or equivalent targets. The numerator is the test distance in metres and the denominator the distance at which the smallest Snellen letter read by the eye has an angular size of 5

minutes arc. For example, a measure of 6/9 means the subject can see a letter at 6m which would measure 5 minutes arc at 9 metres.

c) The level of vision can also be recorded using "logMAR" notation. This is the logarithmic value of the minimum angle resolution (MAR), using log base 10.

A VA in the range of 6/6 or better is generally considered to be in the normal range, although many patients might be expected to achieve better measurements than this.

Visual acuity can be measured using a variety of different methods; most have benefits and draw backs to their use. The chart used in this project was the Bailey-Lovie chart.

The Bailey-Lovie log MAR chart.

Bailey and Lovie advocated that the test task should be essentially the same at each size level on the chart (Bailey and Lovie, 1976). Such standardisation of the test task requires the use of letters of equal legibility, the same number of letters on each row and uniform between-letter and between-row spacing. They also advocated that, combined with the test task standardization, there should be a logarithmic progression of letter size. For example, at a distance of 4 m, the top lines will give a score of 1.0. Each line below will give a score 0.1 less than the line above. Owing to the design of the chart, using a balanced distribution of Snellen letters that are graded in difficulty, each of the five letters, in each line, count for a score of 0.1/5 = 0.02. Therefore, if a patient reads the 0.4 line in its entirety they will have a score of 0.4. If they read the 0.4 line plus three letters of the 0.3 line, they will have a score of 0.34, which results from the five letters of line 0.4 minus the score for each letter read from the 0.3 line (Bailey and Lovie, 1976; Hussain et al., 2006). Using an equal number of letters per line also negate the problems of crowding which may be present with the Snellen chart. Figure 3.2 shows the LogMAR chart side by side with the Snellen chart.

Figure 3.2 The Bailey-Lovie Log MAR chart.

3.1.5. Measurement of oculomotor balance

Examination of the oculomotor balance is mainly used to quantify the ocular alignment under binocular viewing conditions and to classify and quantify any deviation, primarily as a heterophoria or heterotropia. Ocular deviations are usually measured using the cover test. Here, the subject is asked to fixate an object. The practitioner covers one eye in order to observe how either the covered (test for heterophoria) or uncovered eye (for heterotropia) moves.

Heterophoria- a latent deviation of the eyes

This is the tendency of the two visual axes not to be directed towards the point of fixation in the absence of adequate stimulus to fusion (e.g. when one eye is occluded). This means that active and passive positions don't coincide for the fixation distance in question (Millodot 1997). This deviation is classified as:

a) Esophoria- the covered eye turns in when fusion is disrupted.
b) Exophoria- the covered eye turns out when fusion is disrupted.
c) Vertical heterophoria- the covered eye moves up or down relative to the other eye when fusion disrupted.

Heterotropia- a manifest deviation of the eyes

Also known as strabismus, heterotropia is the condition where the lines of sight of the two eyes are not directed at the same fixation point when the subject is actively fixating on the object. So the image of the object is not projected onto the fovea of the deviated eye. Heterotropias are classified in much the same way as heterotropia,

a) Esotropia/ convergent strabismus- the deviating eye turns inwards.
b) Exotropia/divergent strabismus- the deviating eye turns outwards.
c) Vertical heterotropia- the deviating eye is higher or lower relative to the normally fixating eye.

3.1.6. Ocular motility assessment

This is used to evaluate any deviations of the eyes in various positions of gaze and the integrity of the extra-ocular muscles. It involves direct observation of the patient's eyes as they fixate a moving torch light.

3.1.7. Objective refractive findings

This may, in some cases be the only possible method of measuring refractive error. For example, when patients are unwilling or unable to comply with refractive methods that require a verbal response. In the routine eye examination, it provides the first indication of the level of refractive error present in a patient. The two main methods of objective refraction are Retinoscopy and auto-refraction.

Retinoscopy

In retinoscopy, a light source is projected into the eye via a condensing lens and mirror, enabling the practitioner to view the patient's eye along the length of the light beam. The light forms a path onto the patient's retina and by moving the path in a given direction and then observing the direction in which the reflected light appears to move, the observer can determine whether the patient's retina is focused in front of, on, or behind the retinoscope's sight hole. By this method it is possible to determine the refractive error of the patient.

Auto-refraction

Auto-refraction is a useful alternative to retinoscopy in some patients. Results may however be inaccurate in those with high refractive errors, small pupils or media opacities. Media opacities interfere with the internal calculations of the machine. Aberrations found in high refractive errors also effect results. Some studies have found that auto refractors may give more negative refractive errors compared to subjective refraction, due to proximal accommodation caused by the instrument itself. The results tend to be more myopic for myopes and less hyperopic in hyperopic individuals (Chat and Edwards, 2001; Harvey et al., 1997; Mallen et al., 2001; McCaghrey and Matthews, 1993). Manufacturers of auto-refractors have tried to counter this by utilising internal targets which are projected to infinity or by using an open field for the patient to look through at a distant object within the room. The advantage of auto-refraction is that results are gained quickly and are accurate in a large percentage of patients.

3.1.8. Ancillary test procedures

Stereopsis

Stereoscopic visual acuity is the ability to detect the smallest difference in depth between two objects. Stereoscopic vision will be absent in any patient with strabismus and may be absent or reduced in an amblyopic patient. There are two basic types of stereo test, those which use goggles/glasses to create the difference between the two eyes when viewing the test and those which use characteristics of the test material, for example the thickness of a Perspex plate in the Frisby test, to create the difference in depth.

One of the most commonly used tests is the TNO stereo test (Walraven and Janzen, 1993). For this test the patient wears a set of red and green goggle or spectacles, over their normal correction if necessary. Each plate in the TNO test consists of a stereogram in which the images presented to each eye have been superimposed and printed in complementary colours. When viewed with each eye separately the images have no apparent depth, so there are no monocular clues as to depth of image. The patient is the asked questions about what they see on the page in each stereogram. Plates I-IV have large disparity and can be used to check for suppression and presence

of gross stereopsis. Plates V-VII have graded stereo acuities from 15 to 480 seconds of arc. It is considered that a stereo acuity of 60 seconds of arc or less is clinically normal (Elliot, 1997; Kulp and Mitchell, 2005). A number of investigations have reported that all stereo-tests have variable sensitivity for detecting strabismus and/or amblyopia (Farvardin and Afarid, 2007; Ohlsson et al., 2001). Research has shown that all amblyopes should be detected by the TNO test's recommended referral criterion of 240 sec arc (binocular threshold parallax in sec arc) and a stereo acuity of less than or equal to 120 sec arc is a good predictor of normal or correctable normal vision (Walraven and Janzen 1993). The red and green colours used in the test do not pose problems for individuals with a colour vision deficiency.

Colour vision testing

It is important to test colour vision, especially in first time patients, for educational and occupational reasons.

A congenital colour vision deficiency is found in both eyes and will not vary over time. These are almost entirely of the red-green type and are far more common in males than females being X-linked. Eight percent of the male population and 0.5% of the female have a red-green type deficiency (Birch, 1998; Cole, 2007a).

The The Farnsworth D-15 (figure 3.3) test was chosen for this study, as discussed in section 3.3. This test can grade the severity and classify the nature of the deficiency. The test has good test-retest reliability for pass/fail outcomes (Cole, 2007b). The patient arranges 15 loose colour caps in order of colour starting from the fixed colour cap. After they have reviewed the arrangement and are satisfied with it, the order of the colours as arranged by the patient is recorded. Patients with normal colour vision usually make no error but may make one or two minor transpositional errors, as do those with mild colour vision defects (CVD). Those with a moderate to severe CVD make more dramatic errors. They place colours that lie on the opposite side of the colour circle, those that lie on their confusion locus, next to each other. These are diametrical errors and two or more diametrical errors are a ‘fail’. If diametrical crossing errors are made, the orientation of the crossing enables a diagnosis of protan, deutan or tritan to be made (Cole, 2007b; Committee_On_Vision, 1981).

Figure 3.3 D15 test courtesy of Dr R. Cubbidge, Aston University.

Acquired colour vision defects tend to be monocular, or unequal between eyes. They are more often characterised by a loss of blue sensitivity (blue-green or yellow-violet defects). They often arise due to side-effects of medication and in some eye diseases. Acquired colour vision defects can sometimes be ignored due to attention being paid to the more obvious complaints from the primary cause, such as visual field defects or vision loss. However, the acquired colour vision defect is still important.

3.2. Aims

The primary aim of this study was to develop a specific protocol for the eye examination of an individual with an autism spectrum disorder. This population may be potentially difficult to examine depending on the severity of their condition and recommendations on a protocol for examination would be helpful to optometrists to get the most useful results from an eye examination.

The secondary aim was to establish whether there were any optometric correlates of autism spectrum disorders, such as refractive error or strabismus, so that screening methodologies could be adapted further to the learning disabled population.

3.3. Methods

3.3.1. Inclusion criteria

Subjects were recruited (see section 2.3) via advertising in local and national publications for those with Autism and from the Gheel autism service in Dublin, Ireland (Table 3.1). All subjects had a diagnosis from a clinical psychologist detailed in chapter 2. A non-intellectual disability group was made up of the high functioning volunteers who provided a clinical diagnosis of Autism disorder without learning disability, or Asperger's syndrome. Two other groups were formed by clinical psychologists at the Gheel Autism Service who performed cognitive assessments, using a combination of Autism Diagnostic Interview (ADI) and pre-existing IQ scores (Bailey et al., 1995; Rutter and Schopler, 1987). The ADI is a structured interview rather than a simple check list. This means that it builds a picture of how the individual functions in areas of language, communication, social development and play. A trained individual, who then evaluates the responses, administers the test.

Group	**Non intellectual disability (ID)**	**Mild ID**	**Mod ID**
Total number of volunteers	19	18	16
Number of eyes	38	36	32
Mean age (years)	21.3	30.4	29.9
SD	10.74	6.43	6.14
Age range	10-46	20-45	19-40

Table 3.1 Volunteer details

3.3.2. Ethical approval and informed consent

The Aston University Ethics Committee approved the project and all patients were asked for their written informed consent prior to taking part.

3.3.3. Eye examination procedures

History

A detailed personal and family ocular and general medical history was taken from the Asperger's group to discover any pre-existing known ocular or general health issues such as Diabetes or glaucoma. This was similar to the history and symptoms taken during a standard eye examination but with questions targeted to the patient group. All adults gave their own histories. Histories for those under 16 years were given by their parent or guardian. Some individuals completed histories but did not go on to attend for further visits meaning participant numbers varies from Table 3.1 (Table 3.2).

Total	Male	Female	Age (years)	Age standard deviation	Age range
31	23	8	20.23	9.43	10 to 45

Table 3.2 Participants giving histories.

Questions asked were those asked during a standard eye examination with the addition of some targeted questions related to factors which have previously been noted to be abnormal or of raised frequency in Asperger's syndrome or autism (table 3.3).

Questions	**Reason for asking**
Age	For comparison to typical population
Sex	For correlation with other variables
Handedness	Left handedness is reported to be more frequent in autism, does this correlate with other features? (see discussion)
Dyslexia	For comparison with binocular vision abnormalities and with relevance to later chapters (colour and reading)
Epilepsy	It is important to be aware of any light sensitive epilepsy before performing an eye examination due to risk of triggering a seizure, also with respect to medication see below.
Attention deficit disorder	Testing may be more challenging in subjects lacking in the ability to attend to the test. May also be more likely to be taking medications see below.

Anxiety or depression	Do these commonly found conditions affect the individual's ability to complete visual testing; also again medication may be taken which could affect visual function.
Medications taken	Some medications are known to affect visual function, for example visual fields and colour vision. For a review see Santella and Fraunfelder (Santaella and Fraunfelder, 2007)
Family history of any eye condition	As in a normal eye examination, to establish if the individual is at an increased risk of any eye conditions. This affects eye testing interval recommendations.
When was the last eye examination?	Are people with Asperger's syndrome having regular eye examinations, as recommended to the general population?
Do they currently wear spectacles?	Could be used in advice as to whether the subject should seek further testing after the study. Also is the individual wearing their spectacles appropriately?

Table 3.3 Questions asked in history taking.

Visual Acuity/Vision

In each subject, vision (V) and visual acuity (VA) were measured if the subject habitually wore spectacles. Both measures were taken using a computerised Bailey-Lovie Log MAR chart (City university Test chart 2000, David Thompson software). The selection of acuity targets was based upon the subject's ability. Letter reading was used wherever possible. For individuals unable to verbalise the chart signing of letters or a matching card was used. The computer test chart does have the facility for using picture testing but this was not necessary in this patient group.

Test	Number individuals
Letters spoken or signed response	35
Matching	13
Monocular VA	45
Binocular VA	48

Table 3.4 Methods of VA measurement used.

The examination was carried out at 4m, due to space constrictions of the testing areas. With the chart calibrated to this testing distance the letters are scaled down in size so that results can be read as the standard 6 metre version. Monocular VA was measured

where possible, see above table. Few (3) of the moderate LD group would not tolerate the occluder used during the measurement of monocular VA. In these cases the subject or carer's palm was used to occlude the non-tested eye.

Oculomotor balance

Oculo-motor balance was tested using a standard cover, uncover test as used in a routine eye examination at distance and near. This was followed by the alternating cover test in order to estimate the size and quality of recovery of any deviation and whether or not it was latent or manifest. The cover test was chosen as the only test for this study due to constraints of time with each individual and the portability and ease of use of the test. Additional tests would have run the risk of not being tolerated by the more sensitive subjects.

Refraction

Refraction (Rx) was performed using autorefraction. The Shin Nippon open field auto refractor (figure 3.4) was used to minimise the proximal accommodative response and was less aversive for some of the subjects to use as they were not fully enclosed within the machine. This autorefractor allows a binocular field of view through a large beam splitter and so permits fixation of a target external to the instrument. This autorefractor calculates refractive error in two stages. First a ring target of infra-red light is imaged after reflection off the retina (figure 3.5). On the initial measurement, a lens is rapidly moved on a motorised track to place the ring approximately in focus. The image of the ring target is then analysed digitally, in multiple meridians to calculate the refractive error (Mallen et al., 2001).

Figure 3.4. Shin Nippon operator's view.

Figure 3.5 Shin Nippon subjects view; red spots visible are the infrared ring target used.

The autorefractor can take static measurements of refractive error in the range of 22D sphere and 10 D cylinders in steps of 0.125 D for power. Cylinder axis is measured in 1degree steps. Vertex distance can also be altered (to 0, 10, 12, 13.5, 15 or 16.5 mm) and the instrument can take up to 45 static prescription readings in 1 minute. The mean spherical equivalent accuracy can be improved to within 0.25 D in 55% of eyes by using the `shift sph data' option in the instrument's control menu to decrease the reading by -0.25 D. The spherical bias of the instrument is then reduced to -0.09D, but the cylindrical component is unaffected by this change. (Mallen, Wolffsohn et al.

2001). Clinical evaluation of the Shin Nippon SRW-5000 autorefractor (Mallen et al., 2001) found that although the SRW-5000 read slightly more plus than subjective refraction (mean spherical equivalent +0.16 +/- 0.44 D), it was found to be highly valid (accurate) compared to subjective refraction and repeatable over the prescription range of +6.50 to -15.00 D which was examined. Also it was found to be repeatable by the same study, with second visit findings being within +/-0.50D of the first visit. In children, non-cycloplegic auto refraction with the Shin-Nippon autorefractor yields a less hyperopic result than cycloplegic subjective refraction with 95% of spheres being within 1.34 D of each other (Chat and Edwards, 2001). Thus, control of accommodation with the autorefractor in young children is not ideal, despite its open-field design, but there may be scope to improve control of accommodation via a more interesting fixation target, such as a favourite toy or picture (Chat and Edwards 2001). In order to better control accommodation, a target of personal interest to each participant was held at a distance of 4m by a carer during the examination.

Stereopsis

The TNO test was used to measure stereopsis and results recorded in seconds of arc.

Colour vision

The D-15 arrangement test was selected for colour vision testing as it is independent of numeracy skills. Timing could be considered to be an issue due to the presence, in some individuals of attentional problems. Two or more diametrical crossings of the results diagram were selected as the criterion for a fail (National research council 1981).

3.4. Results

Histories were obtained from 31 of the total sample (19 Asperger's syndrome group, 12 autism with mild learning disability). Histories were not available for the moderate learning disability group as they were seen in residential care and the information was not accessible. A frequency distribution of history data is presented in Figure 3.6. Most of the sample were not taking any medications which might affect vision, did not have an attention deficit diagnosis, depression or epilepsy. Most had not previously been diagnosed with dyslexia or a strabismus.

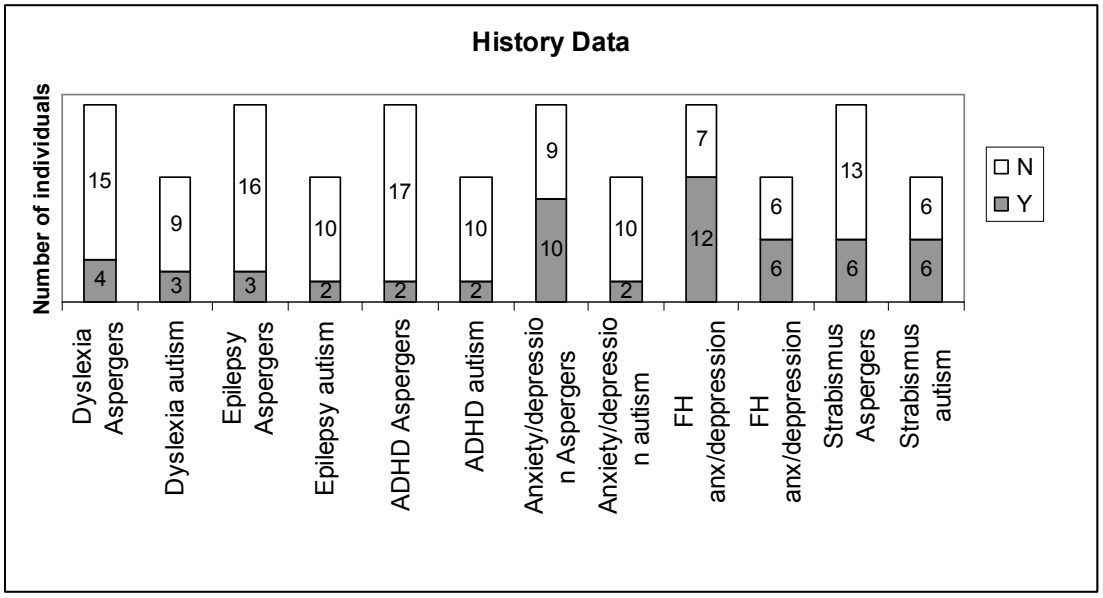


Figure 3.6 Information from subject histories.

Chi test for frequencies, on the data shown in figure 3.6, showed no statistically significant differences in the responses by the Asperger's and autism group.

This study did not find a statistically significant difference in left-handedness in the autism and Asperger's syndrome group compared to the controls (p=0.35). Eighty four percent of the control group stated they were right handed and 16 % left handed. In comparison 74% of the autism and Asperger's syndrome group were right handed and 26% left handed. None of either group was ambidextrous.

Three of the 31 individuals in the Asperger's group were taking Melatonin to relieve short-term insomnia. This compound is known to produce visual disturbances in some individuals (British National Formulary 2008). None of these subjects reported any such disturbances.

Twenty six (26%) had not had an eye examination for over 2 years, thus 61% of the sample had received an eye examination from an optometrist within the recommended interval for the general population (Figure 3.7). Of the 26% who had not had a test for over two years, 75% had not had any form of eye check for over 5 years.

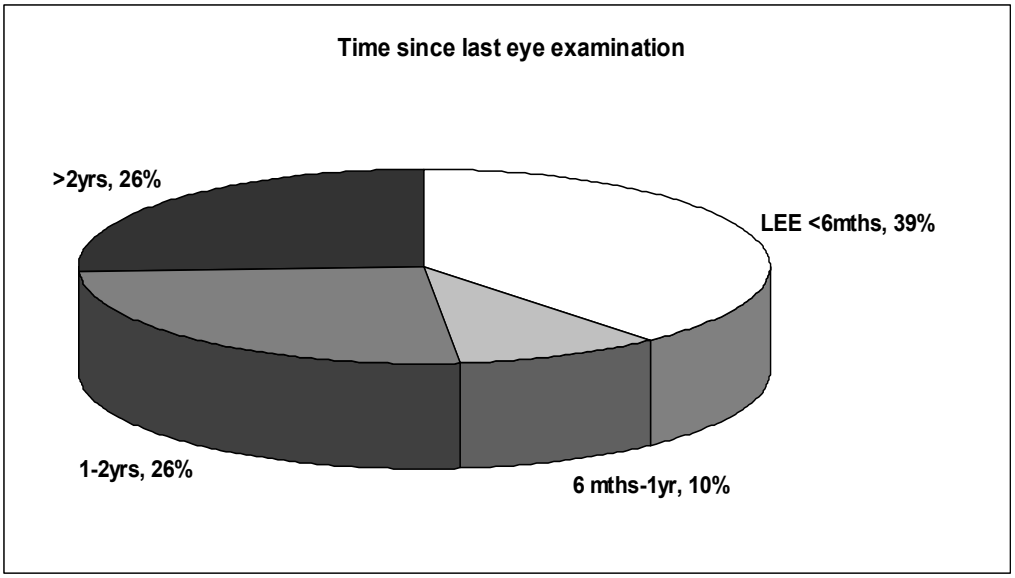


Figure 3.7 Time since last eye examination in individuals with Asperger's syndrome

Most of the subjects were able to complete all of the optometric tests measured, some however were not able to complete one or more of these tests. It was mostly the moderate learning disability group who were unable to complete certain tests. This was mainly due to problems with lack of comprehension of the test requirements or lack of co operation caused by anxiety about test equipment. Details of participation are shown in table 3.5.

	Asperger's	Autism mild ID	Autism Moderate ID	learning disability total
VA monocular	19 (100%)	18 (100%)	10 (63%)	28 (82%)
VA (binocular)	19 (100%)	18 (100%)	15 (94%)	33 (97%)
Refraction	19 (100%)	18 (100%)	16 (100%)	34 (100%)
Stereopsis	19 (100%)	17 (94%)	4 (25%)	21 (62%)
Muscle balance	19 (100%)	18 (100%)	16 (100%)	34 (100%)
Colour vision	19 (100%)	10 (56%)	8 (50%)	18 (53%)

Table 3.5 Subject numbers participating in each test.

Visual acuity testing was carried out using the Log MAR chart as described in the method. Analysis of variance (ANOVA) was performed first. Then, in order to investigate whether learning disability, irrespective of degree, affects the visual acuity the control, Asperger's and autism with learning disability were analysed separately. Again ANOVA was used for investigation. There was no significant difference in VA

of either eye between the groups (ANOVA) (right eye p=0.3, left eye p=0.4). There was no statistically significant difference in the visual acuity of the right and the left eyes in any of the four groups using t-tests (control p=0.4, Asperger's p=0.9, mild LD p=0.3, moderate LD p=0.7).

A statistically significant difference in binocular VA was found between the groups (ANOVA p=0.001). Post hoc (Bonferroni test was chosen because of the conservativeness of its results and the lower likelihood of a type 1 error) revealed that statistically significant differences occurred between the control and moderate learning disability group (p=0.01) Figure 3.8.

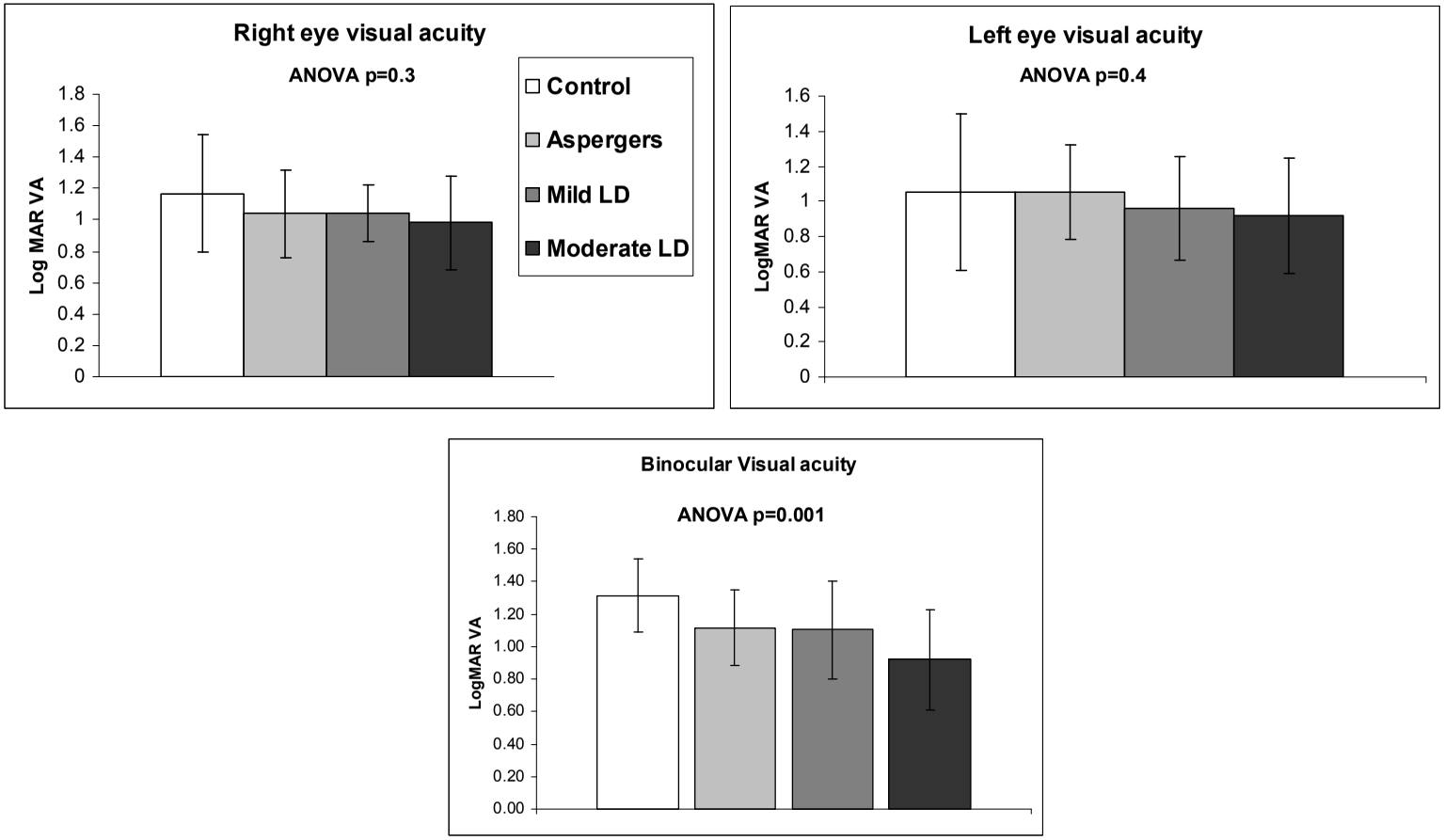


Figure 3.8 Visual acuity in four groups (error bars indicate ±1 SD of the group mean).

In order to investigate the distribution of oculomotor muscle balance in the different groups a Chi squared testing of distribution frequencies was performed. This showed no significant difference (P=0.5) in distribution between the four groups at either distance or near fixation distance. Figure 3.9 and 3.10 show the distributions.

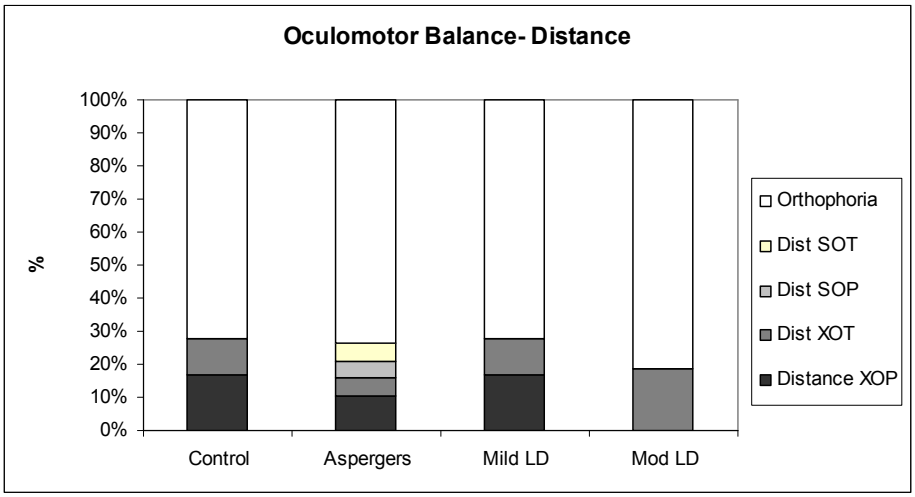


Figure 3.9 Percentage of the participants found to have different types of oculomotor balance at distance viewing.

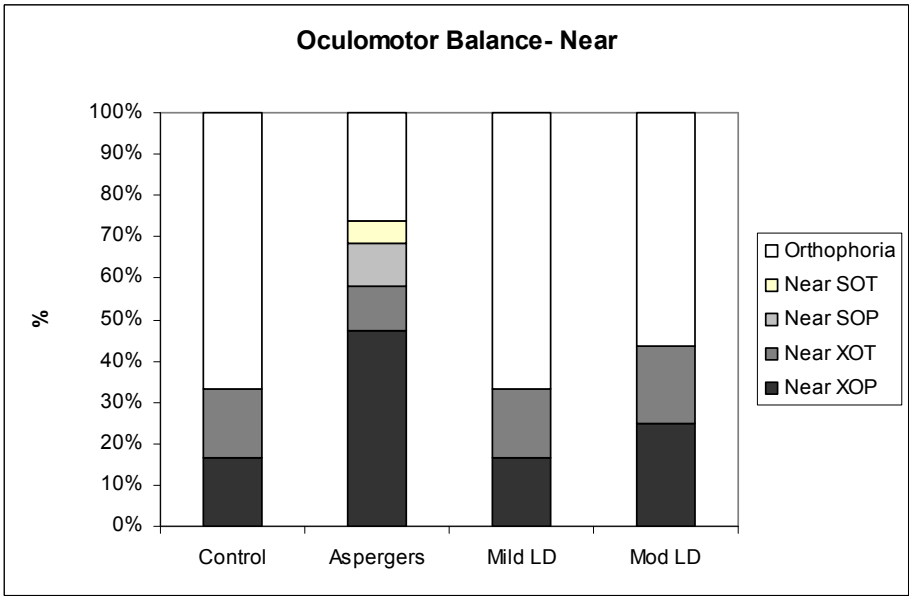


Figure 3.10 Percentage of the participants found to have different types of oculomotor muscle balance at near viewing.

Further classification of oculomotor balance was carried out. This was based on the OMB at distance and near (figure 3.11). It was observed that the most common condition is orthophoria at distance and near. Convergence Weakness was the most frequently occurring abnormal classification. A chi squared distribution test was performed on the frequency of the classifications occurring, this showed the difference in distribution was not significant p=0.15.

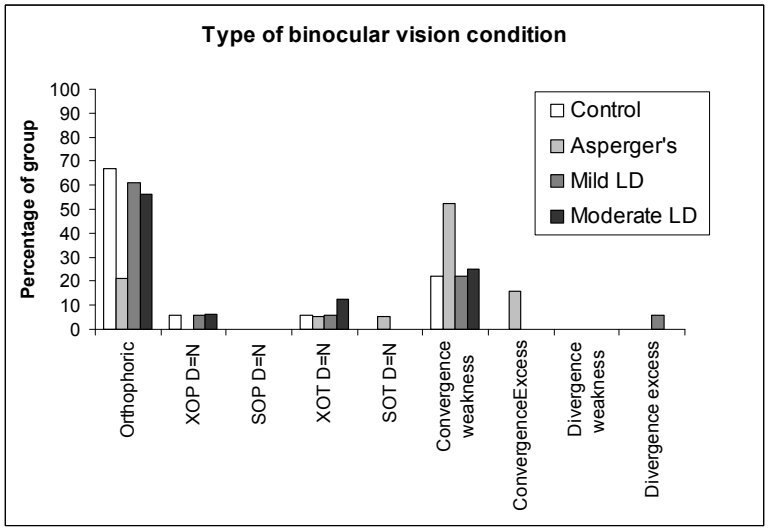


Figure 3.11 Types of binocular vision condition comparison between groups.

Refractive errors were grouped into seven categories (Table 3.6), after Woodhouse et al. (Woodhouse, Griffiths et al. 2000; Woodhouse, Adler et al. 2003).

High hyperope	Moderate hyperope	Low hyperope	Emmetrope	Low myope	Moderate myope	High myope
+6.00 or more	+3.00 to +5.75	+1.00 to +2.75	+0.75 to -1.00	-1.25 to -3.00	-3.25 to -6.00	Over -6.00

Table 3.6 Refractive error groupings

The distribution of refractive error (figure 3.12) was tested for difference between the four groups using Chi squared testing for a 4x7 table. This showed that there was no significant difference in distribution of refractive errors between the three groups (P= 0.9).

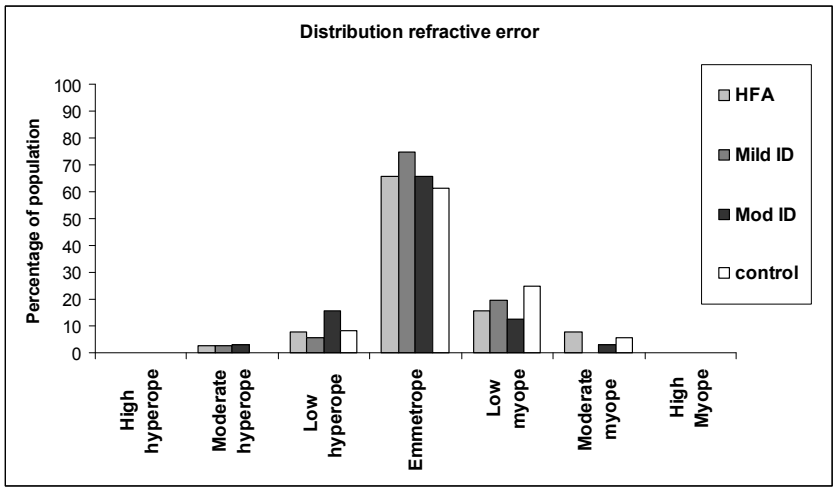


Figure 3.12 Refractive errors found within the three groups.

Astigmatic refractive errors were classed as low (1DC or less), medium (1.25 to 3DC) and high (>3DC) and the results plotted in figure 3.13. The percentage of individuals with moderate to high astigmatic errors appeared to be greater in the autism and Asperger's syndrome groups but this was not statistically significant (chi squared test for 4x3 frequency table, p=0.3). Looking solely at the autism group there is also no difference in distribution of refractive error between the mild and moderate intellectual disability sub groups (chi square test for a 3x3 frequency table, p=0.9).

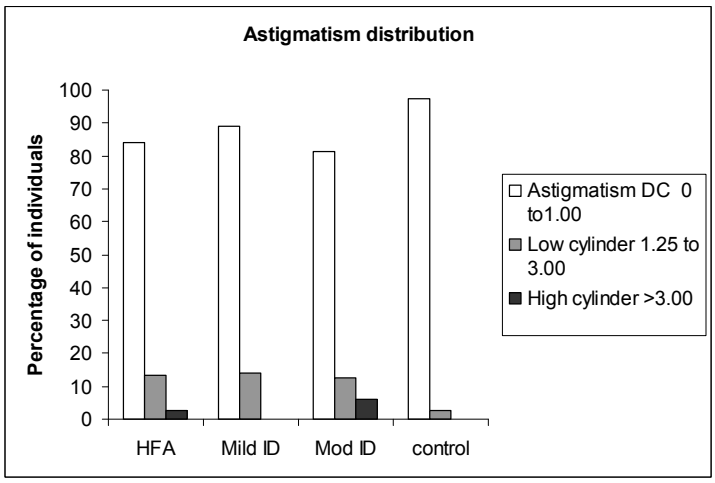


Figure 3.13 The distribution of astigmatic error.

The number of each group who wore a refractive correction was noted. Of those who were not currently wearing a correction, the number whose visual acuity could potentially be improved by the use of a refractive correction was recorded. The findings are shown in figure 3.14. Both the mild and moderate learning disabled group appeared to have a higher rate of uncorrected refractive errors than the non learning disabled Asperger's syndrome group. However the Chi squared test for 3x3 distribution tables revealed that this was not statistically significant (p=0.7). This lack of statistical significance may be due to the small numbers tested.

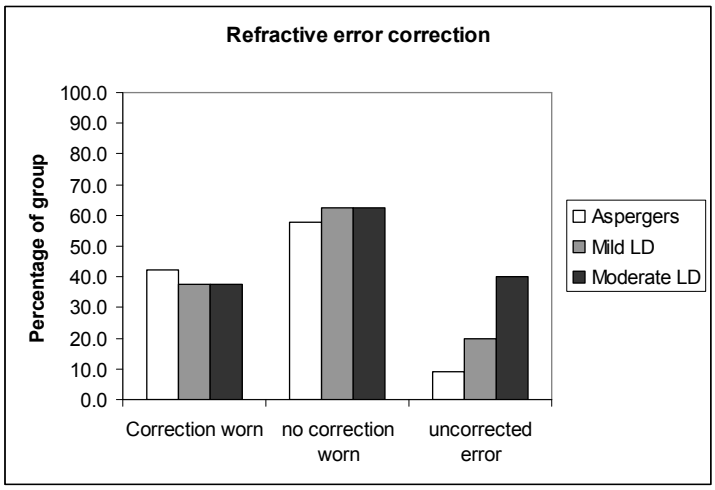


Figure 3.14 Numbers of corrected and uncorrected refractive errors.

Stereopsis was measured using the TNO stereo test. The results (figure 3.15) were analysed using a one way ANOVA. This showed no difference between the three autism groups (p=0.1). When groups are split solely into two Asperger's and intellectual disability groups then the Asperger's syndrome group had better stereopsis and this was statistically significant (P=0.03). Only six individuals were able to complete the test from the moderate intellectual disability group, so this may have had an effect on the statistical power.

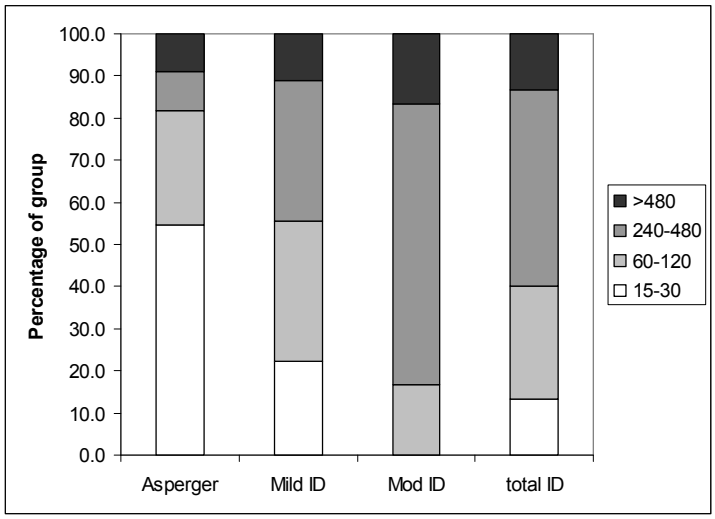


Figure 3.15 Stereopsis (seconds of arc) in Asperger's syndrome vs. Autism groups.

There was no statistically significant difference in the rate of colour vision deficiencies between the groups (figure 3.7), and all are similar to the typical population, where the rate of red green deficiency is around 8% (the individuals found to have a colour vision deficiency were male in both cases). Rate of colour vision defects was not increased in ASD.

Group	Number of participants	Number with colour deficiency.
Asperger's	19	1
Mild learning disability	10	1
Moderate learning disability	8	0

Table 3.7 Colour vision testing results

3.5. Discussion

This study did not find a statistically significant difference in left-handedness in the autism and Asperger's syndrome group compared to the controls. This does not support previous research studies which have reported an increased rate of left-handedness in those with Autism. (Dane and Balci, 2007; Fein et al., 1984; Gillberg, 1983; McManus et al., 1992). People with autism have been found to display increased levels of inconsistent handedness, similar in levels to the non autistic developmentally delayed population (Satz et al., 1988). Previous studies have found the rate of left handedness to be around 10-25% in the typically developing population (Dane and Balci, 2007). Some researchers have linked the increased amount of left

handedness to an abnormal lateralization in autism (Dane and Balci, 2007; Escalante-Mead et al., 2003). In typical brain lateralization, the right hemisphere has dominance for language and motor skills, the left hemisphere for spatial processing. A review of lateralization and autism can be found (Dane and Balci, 2007).

Nearly 23% of the ASD group had previously been diagnosed with dyslexia. This is high in comparison with the prevalence in the general population of 2-10% (Blomert and De Vries, 2008; Parliament, 2004; Rutter, 1978; Yule, 1988). There are no current official figures as to the prevalence of dyslexia in the autistic population (NAS, 2006b). Dyslexia and ASD share many characteristics and it might be the case that some of the causes of the two conditions are also shared. These are discussed in chapter 1. The key points, are poor concentration is common in both conditions, history of pregnancy or birth complications, delay in reaching developmental milestones for motor skills or language. Most interestingly is the proposed magnocellular deficit for each condition. This is a highly debated point and is discussed further in chapter 4. This raised prevalence of dyslexia in the autistic population indicates that individuals might benefit from screening for dyslexia as part of their educational and developmental profile so that potential interventions to improve learning and educational performance could be used.

Just over 61% of the individuals who gave a full history had received an examination within the recommended interval for the average person (2 years). Further, 75% of the individuals who had not had a test for over two years (6/8 people) had not had any form of eye check for over 5 years. As previously mentioned, a study looking at athletes competing in the Special Olympics in 2003 found that the number of athletes who had never had an eye examination was 15% (Woodhouse et al., 2003). Factors which may explain the lack of frequency of eye examinations at the optometrist may be a lack of awareness of the necessity or importance of eye care or the perception that the optometrist may not understand or be able to examine someone with their condition (in the case of more severely affected individuals).

Monocular VA findings were unremarkable, there being no statistically significant difference between any of the groups in mean VA scores. Binocular VA was greatest in the control group. This contrasts with Ashwin's paper (2009) which found VA was

greater in individuals with an ASD, although methodology could be partly the cause of this difference in findings. There was a statistically significant difference (of $P<0.05$) between the control and autism group but the difference between the Asperger's group and the control group failed to achieve statistical significance ($P<0.1$) this is supported by the finding of Ashwin (2009). There was also no statistically significant difference between the mean binocular VA of the mild and moderate intellectual disability groups ($p=0.12$). More subjects with an intellectual disability were able to have binocular vision measured than monocular so the difference in the numbers may have affected the results, perhaps if a greater number of learning disabled individuals had taken part in the monocular VA measures then the results may have been significant. Theses results do not support previous research (Woodhouse et al., 2003; Woodhouse et al., 2000), but a study with increased group numbers would be useful. Power analysis of the current study found that, given a moderate effect size, the statistical power of the analysis performed was 0.7, which is less than optimal power ($p=0.8$), therefore a larger population study would be desirable to confirm the studies findings.

In this study, there was no difference between the frequencies of strabismus or different types of strabismus between the groups. Larger studies on learning disabled populations have found an increased rate of strabismus in this group (Woodhouse et al., 2003; Woodhouse et al., 2000). Scharre and Creedon's study found Strabismus in 21% of the children, mostly exotropes. Schulman found 84% (27 out of 32) of the patients studied exhibited strabismus. These groups were made of individuals of mixed development rather. This could lead to falsely high prevalence's of strabismus due to a mixing of groups with differing rates, however again the number of individuals investigated in the current study not enough to give optimal power to the statistical analysis (power=0.3).

Distribution of refractive error did not appear to be significantly different between any of the groups tested for this study. Previous research has found a difference in the refractive error distribution in those with learning difficulties compared to the typically developing population. Woodhouse et al. examined 500 participants in the Special Olympics in 2203 and found that there were fewer emmetropic individuals and more low myopes in this population compared to a typically developing

population.(Woodhouse et al., 2003). Other studies have found more general conclusions that there is an increased rate of significant refractive errors in the learning disabled population (Aitchison et al., 1990; Amos, 1977; Maino et al., 1990). Autorefraction only provides an estimate of refraction and so may not be a completely accurate expression of the refraction of an individual, tending to underestimate hyperopia due to proximal accommodation and overestimate astigmatism (Woodhouse et al., 2003). Errors in over or underestimation will occur in all the groups as all were tested using the same method. Objective refraction via Mohindra technique which has previously been used for screening (Woodhouse et al., 2000), would be difficult to perform in these groups due the necessity for total darkness. Being immersed in complete darkness could be stressful for individuals with autism and lead to further problems with co-operation, so autorefraction is a more useful method in this situation requiring only momentary fixation to get an estimate of refraction. No statistically significant difference was found in the number of uncorrected refractive errors between the groups tested. The lack of significance of this result may have been due to the small numbers tested and a larger extended study would be useful to further investigate this trend, given a moderate effect size for the chi square analysis power for this group size was 0.7 which is less than the ideal 0.8. It might be that individuals with no learning disability are more likely to be able to complain of problems with their visual acuity or would go themselves for an eye examination if they have problems. Individuals with learning disability are perhaps more likely to be in the care of others who might not recognise that the person is having visual difficulties or might perceive that the individual would not tolerate a correction being worn, further investigation in this area, again would prove useful.

There was no significant difference in the levels of stereopsis between the non learning disability and mild learning disability group ($p=0.5$ t-test). This is consistent with the findings relating to strabismus since an increased rate of strabismus is likely to be linked to an increased rate of poor or absent stereopsis. The moderate learning disability group was not included in the analysis, as only four individuals were able to perform the test. The TNO test could not be used on the moderate intellectual disability group. TNO required the use of special red green glasses and some participants found the instructions difficult to follow. It is suggested that a Frisby or

Lang stereo-test would be better as both can be carried out without any type of filters and need only very simple patient instruction.

Colour perception has previously been shown to be abnormal in autism (Franklin et al., 2008). This was with regard to colour memory and detection of coloured targets on a coloured ground, not specifically colour discrimination testing. The rate of colour vision defects was not found to be increased in ASD in the present study so a colour vision deficit may not be the cause of aversion or particular affinities to specific colours found in many people with autism.

3.6. Conclusions

This study has found that many aspects of vision are the same in the autistic population and the general neurotypical populations, whether in Asperger's syndrome or autism with learning disabilities. This applied to refractive error, monocular visual acuity, strabismus and colour vision.

Those with an ASD and normal intelligence are at no increased risk of strabismus but previous research indicates that individuals with learning problems are more likely to show eye turns. Therefore, once again regular eye examinations, at the age appropriate current recommended recalls, and EOM balance testing is of extreme importance in this group especially in young children who may be at risk of developing amblyopia.

Some people with ASDs are not having frequent enough eye examinations; they should be encouraged to attend for sight tests more frequently. This is a problem common to many sections of the population, particularly people with learning disabilities (Woodhouse et al., 2003; Woodhouse et al., 2000). Any individual with a learning disability is at increased risk of visual problems through refractive errors or ocular abnormalities; this includes individuals with autism and a learning disability which accounts for around 75% of the autistic population. Therefore, it is of special importance that these individuals should have regular eye examinations.

This study found a higher incidence of dyslexia in high functioning ASD than the general population. With this finding in mind, it may be suggested that persons with an ASD presenting for eye examination should be questioned concerning any

symptoms that might indicate they should be tested for dyslexia and/or visual stress, particularly if they complain of reading problems or visual discomfort. Further research in this area would be useful with a larger population size to establish whether rate of dyslexia is raised in the autistic or Asperger's populations. If so perhaps screening for this should be a part of the diagnostic test battery in this condition to add to the individual's statement of needs.

Considering the findings of this study and the previous recommendations for eye examinations in people with learning disabilities, the following suggestions are put forward. A person with Asperger's syndrome or autism, without any learning disability, should be tested using the same methods as a member of the general population. Instructions should be given carefully and unambiguously to avoid any problems of communication. The examiner should take extra care to provide the patient with information about what is about to happen during the test. Take time to explain that, during ophthalmoscope examination of the eye, for example, the optometrist will get very close and will be shining a bright light into the eyes, rather than simply instructing that they are about to look at the patient's eyes.

People who are on the autistic spectrum have a wide range of abilities and may exhibit different behaviours, for those who have a learning disability the guidelines from the college of optometrists, given earlier in this chapter, are a good starting point for the test. The earlier advice, which was given by the paper by Woodhouse, is particularly useful in this group, which is that the optometrist must be flexible in their approach and testing methods. Someone who has autism may have difficulty in communication while being highly intelligent. So, although at initial observation they may appear to be difficult to examine, in fact most normal testing methods could be achieved with a little extra time.

4. Using Perimetric methods to investigate magnocellular function in Autism

Aims: To investigate whether a deficit in magnocellular pathway function can be detected in individuals with high functioning autism and Asperger's syndrome using perimetric methods tuned to this pathway. If a deficit is discovered it could be used as part of the diagnostic test battery or may be used to identify a sub classification of ASD's. **Methods:** A group of 14 volunteers with Asperger's syndrome, including high functioning autism (mean age 24.8 +/- 9.9 years, range 13-43 years) and a control group of 11 individuals (mean age 27.6 +/- 4.4 years, range 19-34 years) performed three different visual fields tests with stimuli designed to selectively test the magnocellular pathway. Two tests used the frequency doubling illusion technique (FDT) and the third used critical flicker frequency. All volunteers were tested on two separate occasions and tests were carried out in random order to minimise the effects of learning and fatigue. **Results:** Mean deviation was greater in the Asperger's group ($p<0.01$). 57% of the Asperger's group yielded a defect with all three types of perimetry and one patient yielded a significant defect with FDT alone. Pointwise analysis revealed a generalised reduction in sensitivity for all techniques in the Asperger's group which was slightly greater in the inferior hemifield for FDT using small stimuli and in flicker perimetry ($p<0.05$). The FDT large stimulus test exhibited the lowest between-subject variability. **Conclusions:** These findings support the theory of an M-cell pathway deficit in Asperger's syndrome and might help to explain some sensory issues suffered by the individual being tested, such as hyposensitivity to some stimuli or some mobility issues. The FDT large stimulus is a suitable test to use in examination of individuals with Asperger's syndrome owing to its short duration compared to other techniques and low levels of testing errors.

4.1. Introduction

4.1.1. The magnocellular pathway

From the retina to the visual cortex and posterior parietal lobe, the visual system consists of two distinct subdivisions: the magnocellular and the parvocellular pathways (figure 4.1).

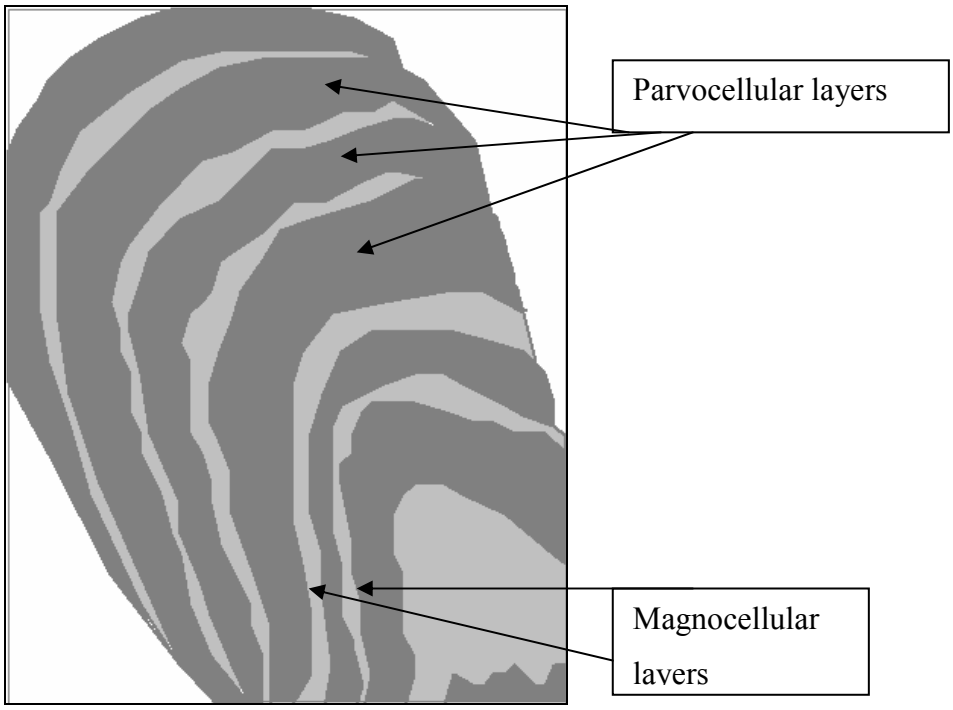


Figure 4.1Magnocellular layers shown in a cross section of the lateral geniculate nucleus (LGN).

In the retina, the magnocellular (M) pathway receives information from larger Type A ganglion cells. Smaller type B-ganglion cells project to the parvocellular (P) pathway (Adler and Farber, 1986; Hendry and Calkins, 1998; Leventhal et al., 1981; Weber et al., 1998).

Magnocellular neurons (M-cells) project preferentially to the dorsal or "where" system; such as middle temporal area MT/V5 which processes motion and location information.

Parvocellular neurons are more sensitive to fine detail, higher spatial frequency and low temporal frequency information. Parvocellular neurons project preferentially to

ventral or "what" system, visual stream structures which process form and identity (Livingstone and Hubel, 1987; Schechter et al., 2003).

Magnocellular neurons have faster temporal resolution, higher contrast sensitivity and lower spatial resolution than parvocellular neurons, and are unable to detect colour (Livingstone and Hubel, 1988b; Merigan and Maunsell, 1993).

The M-cell pathway is considered to be deficient in several different conditions. Abnormalities in this pathway maybe present in dyslexia (specific reading difficulties) (Livingstone et al., 1991; Pellicano and Gibson, 2008; Stein, 2001; Stein and Walsh, 1997), schizophrenia (Kim et al., 2006; Laycock et al., 2007; Schechter et al., 2003) and possibly autism (Laycock et al., 2007; McCleery et al., 2007; Pellicano and Gibson, 2008).

4.1.2. Magnocellular deficit in Autism spectrum disorders

A magnocellular deficit or imbalance in function has been suggested by several authors as a cause for some of the characteristics of autism (Laycock et al., 2007; McCleery et al., 2007; Milne et al., 2002; Spencer et al., 2000a). A recent study suggested that a measure of the functioning of the M-cell pathway could be of use as an early detection tool for diagnosis of autism spectrum disorders (ASDs) (McCleery et al., 2007). These researchers discussed the relevance of the M-cell pathway to other abnormalities which have been recorded in ASD; face perception and movement detection abnormalities. Anatomical studies in primates have shown that the M pathway (far more so than the P pathway) provides input to the superior colliculus (Perry and Cowey, 1984; Schiller et al., 1979), which, in turn, projects to the amygdala (Jones and Burton, 1976; Linke et al., 1999; Romanski et al., 1997). Abnormalities of the amygdala and sub-cortical face processing pathways have both been linked to an imbalance in the M cell pathway (Howard et al., 2000; Mills and Amaral, 2006; Shultz, 2005). McCleery concluded that abnormal M-pathway processing early in development could disrupt the normal development of the sub cortical face-processing system, leading to the face gaze strategy abnormalities seen in autism (Chapter 8).

Although some researchers have suggested that a magnocellular deficit is present in autism (Milne et al., 2002; Spencer et al., 2000a), another suggestion is that there is an imbalance between the magno and parvo cellular pathways rather than a deficit (Laycock et al., 2007; McCleery et al., 2007). Pellicano et al (Pellicano et al., 2005; Pellicano and Gibson, 2008) suggested that there is a deficit in the dorsal pathway but at a higher perceptual level than that of the magnocellular pathway.

Local advantage

As discussed in chapter 1, it has been suggested that there may be weak central coherence in autism (Frith and Happe, 1994; Happe and Booth, 2008; Happe, 1996; Pellicano et al., 2005). This refers to the idea that an autistic individual will typically think about things in the smallest possible parts. This theory is supported by many studies looking at global Gestalt versus local information processing (Bolte et al., 2007; Brosnan et al., 2004; Happe and Booth, 2008; Iarocci et al., 2006; Laycock et al., 2007; Wang et al., 2007). One of the most repeatable findings in this field of research is better performance by individuals with autism compared with typically developing individuals on the Embedded Figures Test (Bolte et al., 2007; Jolliffe and Baron-Cohen, 1997; Mottron et al., 2003; Pellicano et al., 2005; Shah and Frith, 1983; Witkin et al., 1971). This test requires the participant to locate a shape hidden within a larger meaningful figure (figure 4.2).

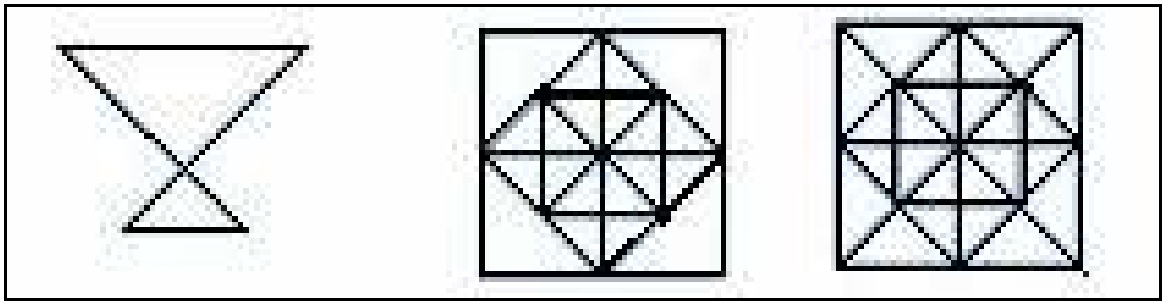


Figure 4.2 Embedded Figure Test example: which of the second two figures contains the first?

Answer: the second figure.

Weak central coherence in autism has also been suggested by heightened performance on the Block Design task, attributed to a superior facility for segmentation of the design (Bolte et al., 2007; Shah and Frith, 1993), and a local advantage on the Navon

task (Plaisted et al., 1999; Wang et al., 2007). Stimuli for the Navon task are large letters made up of smaller letters of the same or different kinds. The task is to respond to the target letter which can appear at either the global or local level. Plaisted et al (1999) found that the global form took precedence in processing over the local elements for typically developing children. Children with autism on the other hand showed a local advantage. It has been shown that the global advantage seen in typically developing individuals on the Navon task is due to the faster availability of signals carried by channels sensitive to low spatial frequencies (Badcock et al., 1990). Therefore, it has been speculated (Mottron et al., 1999; Plaisted et al., 1999) that the underlying mechanism for the local processing bias in autism might be an abnormality at a perceptual level. Specifically, the bias might be due to increased sensitivity of those channels responsible for processing high spatial frequency information. Impairment in the magnocellular pathway might underlie a bias for local processing in people with autism, which may also underlie the preference for local aspects of a stimulus to the overall global view or weak central coherence (Pellicano et al., 2005).

Motion coherence

Because of the functional properties of the magnocellular pathway, a high motion coherence threshold indicates a possible impairment in this pathway (Skottun and Skoyles, 2006). Studies have found that individuals with an ASD show an abnormally high motion coherence threshold using random dot kinetograms (Milne et al., 2002; Spencer et al., 2000b; Talcott et al., 2000; Tsermentseli et al., 2008). However, some researchers have disputed the conclusions of these studies suggest (Smith et al., 1994). When low spatial frequencies were removed from global motion displays, it has been found that the perception of global motion remained intact, thus demonstrating that global motion perception is not reliant on low spatial frequency information (Dakin and Frith, 2005). Further research based on this finding has been carried out considering that a deficit occurring on different levels of processing could affect the individual in different ways. At the earliest levels, M cells in the LGN and in area V1 are sensitive to flickering stimuli (Merigan et al., 1991; Schiller et al., 1990). At higher levels of the dorsal cortical pathway, single-cell recording studies have shown that area MT/V5 is crucial for motion processing (Newsome et al., 1989; Pellicano et al., 2005). The neuronal firing rates in this region correlate strongly with perception of global motion (Britten et al., 1992; Newsome et al., 1989). It is at this stage that local directional signals are combined to form a global percept. A few studies (Bertone et

al., 2003; Pellicano and Gibson, 2008) have been carried out to investigate different level processing along the dorsal visual pathway in children with and without autism. These examined sensitivity to first-order (luminance-defined) and second-order (texture-defined) motion stimuli, the latter of which requires more 'complex' perceptual processing (Bertone et al., 2003). Children with autism performed more poorly than typically developing children on the second-order motion task, suggesting a specific deficit in the integration of 'complex' information at the global level. They further proposed that this deficit might not be restricted to the processing of dynamic stimuli, but might also include the processing of static stimuli. However, other researchers have suggested that apparent deficits may be caused by attentional problems experienced by the autism groups while testing (Pellicano et al., 2005). This field of research is complex and many studies are contradictory. A full review is provided elsewhere (Pellicano et al., 2005).

4.1.3. Measurement of the visual field.

Everywhere in the visual field has its own level of threshold sensitivity. Sensitivity is established by finding the level of illumination needed for detection at a specific retinal point i.e. the minimum brightness of stimulus for the subject to detect the stimulus. The sensitivity is then the reciprocal of the differential light threshold. The visual field is usually measured using perimetry, a non-invasive method of measuring the differential light threshold sensitivity across the retina.

A defect in the field is any departure from the normal pattern of sensitivity across the field. An area of reduced sensitivity is called a relative scotoma, while one with no light perception is called an absolute scotoma. An overall loss of threshold sensitivity across the retina is termed diffuse loss and loss in the peripheral retina (greater than 30 degrees) is called contraction.

4.1.4. Factors that affect the visual field

Excluding anatomical features, a number of factors can influence the visual field. Changes in pupil size may affect the intensity of both the stimulus and the background, by altering the amount of light entering the eye. The effect of both pupil miosis and pupil mydriasis was investigated by Wood *et al.*, 1988 and sensitivity was

reported to improve with increased pupil size (Wood et al., 1988). Spherical defocus results in a reduction of sensitivity that is greater in the periphery (Atchison, 1987). Examples of non-physiological factors which may influence test results are testing times and repetition. Long examination times may induce fatigue effects even in a clinically normal population, causing a reduction of threshold sensitivity (Hudson et al., 1994b). The effects are greater in an elderly population (Gonzalez de la Rosa and Pareja, 1997), with increasing eccentricity (Hudson et al., 1994a) or locations adjacent to visual field defects (Holmin and Krakau, 1979). Several methods are available for overcoming the effects of tiredness: patients may pause the test when they feel tired, regular breaks may be taken or a shorter algorithm chosen. A learning effect may also occur whereby the threshold sensitivity is reported to increase either between or during perimetric examinations. The effect is, however reported, to lessen with increasing number of visits Wood et. al, suggesting that it is advisable to exclude the first examination performed (Wood et al., 1987).

4.1.5. Techniques for measuring the visual field

The method of perimetry used for this study was static perimetry. In static perimetry the target is kept in the same location while the intensity of the stimulus varies. This technique not only measures the boundary of vision but also the threshold sensitivity at each location. Most static perimetry is now computerised, meaning the technique is more easily standardised than kinetic perimetry which must normally be performed manually. Studies have reported static perimetry to be superior to various methods of kinetic perimetry in detecting small isolated areas of focal loss in glaucomatous eye disease (Drance et al., 1967; Lynn, 1969). Agarwal *et al.* (Agarwal et al., 2000) documented that static perimetry using the Humphrey Field Analyser was superior to kinetic perimetry using the Goldmann perimeter when detecting progression of visual field loss in primary open angle glaucoma.

4.1.6. The Frequency doubling illusion

A subgroup of M cells known as M-y cells can be distinguished in both the retina (Benardete et al., 1992) and the LGN (Kaplan and Shapley, 1982). These M-y cells account for approximately 5–15% of all M-cells (Crook et al., 1988) and are characterised by larger cell diameters (Blakemore, 1981) as well as faster conduction rates (Kaplan and Shapley, 1982) and less retinal coverage than other M-cells (Crook et al., 1988) These M-y cells mediate the frequency doubling illusion. When a low spatial frequency (0.25 cpd) sinusoidal grating undergoes a rapid phase reversal, the grating appears to the viewer to have approximately twice as many light/dark bars, i.e., its spatial frequency appears doubled (figure 4.3). The frequency doubling illusion has been utilised in visual fields testing to isolate the M cell pathway. This is useful as this pathway is said to be sensitive to early deficits in glaucoma (Anderson and Johnson, 2003; Cello et al., 2000; Chaturvedi et al., 1993; Johnson and Samuels, 1997; Nomoto et al., 2009).

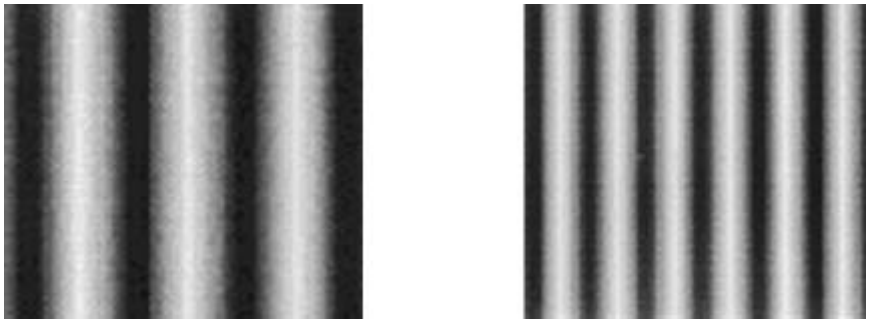


Figure 4.3 An example of the frequency doubling effect. If the grating on the left undergoes rapid phase reversal the viewer perceives the image on the right. So the grating on the right appears with twice the spatial frequency of the original grating on the left.

4.1.7. The FDT and Matrix visual field screeners

Figure 4.4 The Humphrey FDT perimeter

The Humphrey Frequency doubling technique (FDT) perimeter (fig.4.4)

Frequency doubling technology (FDT) is designed to selectively test the Magnocellular pathway. During a threshold program square stimuli are shown in 19 locations in the central 30°. The location of each stimulus is randomly selected. Stimulus size is approximately 10° × 10° peripherally and 5° × 5° centrally. Stimuli consist of a 0.25 cycle per degree sinusoidal grating undergoing 25-Hz counter phase flicker (contrast reversal of light and dark bars). Each stimulus is presented for a maximum of 720ms. In the first 160ms of this time, the contrast is increased gradually from 0 to the selected contrast for the trial. If it is not seen, the stimulus remains at this higher contrast for up to 400ms. It is then decreased in the last 160ms to avoid abrupt contrast changes. The time between the stimuli presentations is up to 500ms and the time given for the patient to respond is from 100ms to 1sec after initial presentation.

The time taken for a full-threshold test is around three minutes per eye. The thresholds (minimal contrast of the pattern that is perceived) are determined by a modified binary search strategy (MOBS), and can range between 0 dB (maximum contrast) and 56 dB (minimum contrast).

The FDT Matrix perimeter

Due to the large stimulus size, it was considered that the FDT screener's ability to spatially localise visual field defects was reduced. This might limit the feasibility of using FDT perimetry to grade and monitor progression of visual field damage (Anderson and Johnson, 2003) and classify neuro-ophthalmic disorders (Wall et al., 2002). This lead to the development of the *FDT matrix* perimeter, which uses a stimulus grid size of 5°, a spatial frequency of 0.5 cpd and contrast reversal of 18Hz. Due to the smaller stimulus size the programmes of the matrix perimeter test a higher number of locations within the field (the 24-2 programme of the matrix tests 55 locations) and can test out to peripheral points similar to the Humphrey 30-2 programme. The test time is slightly longer for the new machine, taking around 5 minutes to perform the 24-2 programme. Also the degree of ametropia that does not need correction is less in the matrix perimeter, stated as +/-3D by the manufacturers.

The staircase strategy used in the matrix perimeter is the Zippy Estimation by Sequential Testing method (ZEST). This makes use of the information gained from every response at a given location when determining the final estimate of sensitivity.

Comparison of qualities of the two types of FDT perimetry program are shown in table 4.1

	FDT	**FDT matrix**
Stimulus size (degrees)	10	5
Number of locations tested	19	55
Threshold procedure	MOBS	ZEST
Analysis	• Mean deviation	• Mean deviation • Total deviation plot
Average test duration (minutes) as stated by manufacturer.	4	5

Table 4.1 Comparison of the two FDT perimeters.

4.1.8. Flicker Perimetry

Flicker perimetry also targets the magnocellular pathway (Lennie, 1980; Livingstone and Hubel, 1988a; Sample, 2001) and is more robust to blur and media opacities than standard perimetry (Del Romo et al., 2005; Lachenmayr and Gleissner, 1992; Rota-Bartelink, 1999). The patient has one eye occluded and is asked to fixate on either a green central spot target or a cross hairs target. Around the periphery, stimuli are presented and the patient must decide if they are constant or flickering. A response button is pressed only if the stimuli are seen to flicker. Flicker perimeters may measure Critical Flicker Frequency (CFF) or Temporal Modulation Perimetry (TMP). Critical Flicker Frequency is the maximum flicker rate at which the subject still reports the perception of flicker. This technique is used in the Octopus 301 perimeter is of use in detecting glaucoma (Dudzinski et al., 2003; Lachenmayr et al., 1991; Yoshiyama and Johnson, 1997). Temporal Modulation Perimetry measures contrast thresholds for a given fixed temporal frequency. This is used by the Medmont perimeter. TMP has been found to be better at differentiating glaucoma patients from normals (Casson et al., 1993; Yoshiyama and Johnson, 1997) and reveals losses in glaucoma earlier than standard perimetry (Casson et al., 1993; Phipps et al., 2004).

The Octopus 301 perimeter

The Octopus 301 perimeter uses the CFF to determine threshold sensitivity values, where the flicker contrast remains constant and the frequency of flicker is varied. The threshold is measured as the highest frequency at which the flicker is detected. The user can set the variables of the test. Five sets of user-defined preferences can be saved as programmes C1-5 (table 4.2.) The staircase strategy used in the Octopus perimeter is dynamic strategy.

Variable factor	**Options**
Test area shape	Round/square
Number test locations	Round (16-100) Square (12-76)
Pattern of stimulus distribution and locations	
Fixation to be used	Central single or area
Strategy for examination	Dynamic or TOP
Stimulus size	Goldman III or V
Stimulus duration	100-500ms
Reports	Format of print out

Table 4.2 Options for user defined tests in the octopus flicker perimeter.

The Dynamic Strategy

Steps in the staircase strategy are adapted to the sensitivity of the tested points (wide steps in low sensitivity points) according to the physiological threshold width in low sensitivity areas. In contrast to the traditional 4-2 2-dB strategy, the step sizes are not constant but vary between 2 and 10 dB depending on the sensitivity. The dynamic strategy decreases the test time for patients. This may be around half the time of normal strategy programmes and mean sensitivity and loss variance (LV) values are comparable to those of normal strategy (Maeda et al., 2000).

4.2. Aims

Since certain modes of perimetry selectively sample the function of the magnocellular pathway, they could potentially be used to test the hypothesis of a magnocellular deficit in the autism spectrum. The primary aim of this study was to establish whether a defect in magnocellular function is a characteristic of the autism spectrum in Asperger's syndrome. If deficits in magnocellular function in Asperger's syndrome are established, instrumentation available in optometric practice could be used as part of the diagnostic test battery, or may be used to identify a sub-group of people with an autism spectrum disorder.

The secondary aim of this study was to compare and contrast three methods of magnocellular perimetry; large and small stimulus FDT and flicker perimetry in order to make a recommendation for an appropriate screening methodology which can be applied to Asperger's syndrome.

4.3. Methods

4.3.1. Sample

	Number	Mean age (years)	Age range (years)
Asperger's	14	25±10	13-43
Controls	11	27±4	19-34

Table 4.3 Summarises the sample tested in this study.

Exclusion criteria were: any personal or family history of conditions likely to affect the visual fields, medications known to affect the visual field, previous ocular surgery/trauma, ametropia >6DS or >2.50 DC or visual acuity <6/9.

4.3.2. Ethical approval and informed consent

This study was approved by Aston University's Ethical Committee. All volunteers were provided with information about the study in advance of taking part and were able to ask questions. Written consent was provided by all volunteers at the time of participation. In the case of volunteers under 16, parental consent as well, as the assent of the child, was given.

4.3.3. Procedures

Volunteers were examined over 2 visits. Each visit lasted up to 90 minutes (3 tests of around 10-15 minutes interspaced by a 10 minute breaks between tests). The same tests were used in both visits. Each visit was separated by a week in order to reduce the influence of the perimetric learning effect. The test and eye order were randomised across the group, but the protocol adopted for a given volunteer remained constant. For each test the volunteer had one eye occluded. They were instructed to concentrate on the central fixation target throughout the test and this instruction was repeated during the test.

The Humphrey Frequency doubling technique (FDT) perimeters

During the examination, each subject viewed the screen monocularly through an objective lens which projected the stimulus to optical infinity. The patient was instructed to look at the screen and fixate a central black target, then press the response button each time they saw the stimulus appear, trying not to look around the screen but keep constant fixation on the central target (figure 4.5). Volunteers were shown a demonstration of the stimuli before testing began, so they were aware of the nature of the stimulus.

The Program chosen was the N-30F threshold (figure 4.6). This was chosen because it was the most similar in terms of duration and area covered to the other field tests used. This program is equivalent to the threshold program of the original FDT perimeter.

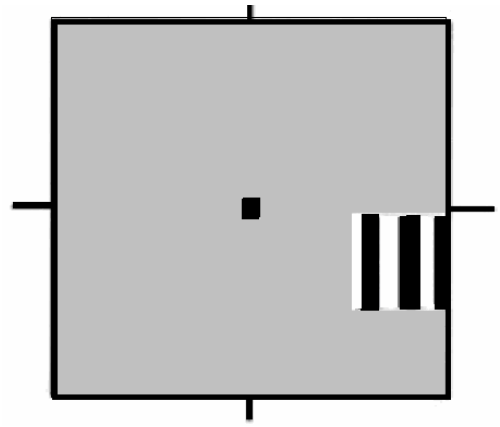


Figure 4.5 Example of the FDT stimulus as seen through the view port, black central square is the fixation target.

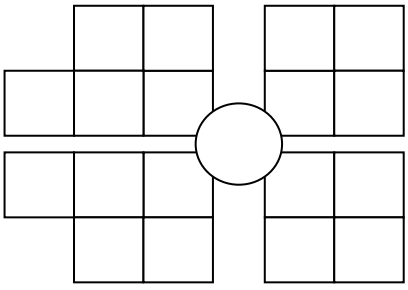


Figure 4.6 Test locations in the N-30f program (right eye shown, left is the same pattern reversed).

Humphrey Matrix perimeter small stimulus program

The program used to examine patients using the Matrix was the 24-2 threshold program which presents 55 stimuli in a regular grid pattern, each stimulus separated by six degrees (figure 4.7).

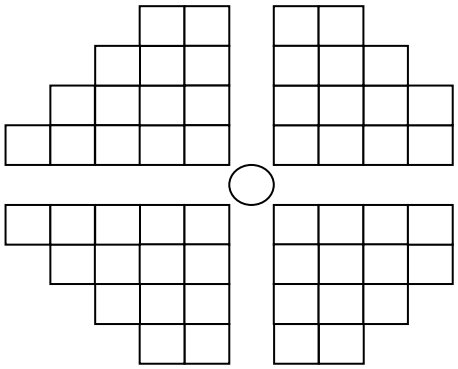


Figure 4.7 Test locations in the 24-2 program (Right eye shown, left is the same pattern reversed).

Octopus 301 flicker perimetry

The volunteers were again instructed to maintain fixation of the central target, which was a green spot. They were told that around the screen they would see orange/amber small lights which would appear for a short time then disappear, the volunteer should only press the response button if they felt the light appeared to be flickering. If the amber light appeared constant they should not respond.

A custom program was defined to replicate the stimulus pattern of the FDT matrix 24-2 threshold program to facilitate comparisons between the two techniques.
The program created uses;

- round test area
- 52 test locations
- Central spot fixation light
- Stimulus size Goldman III
- Dynamic threshold algorithm (a linear pattern of distribution of test locations)
- Stimulus duration 1000ms
- Spacing of the test grid locations 6° (figure 4.8)

This test was designed to yield a similar examination time compared to FDT in order to equalise any fatigue effects that may have been present.

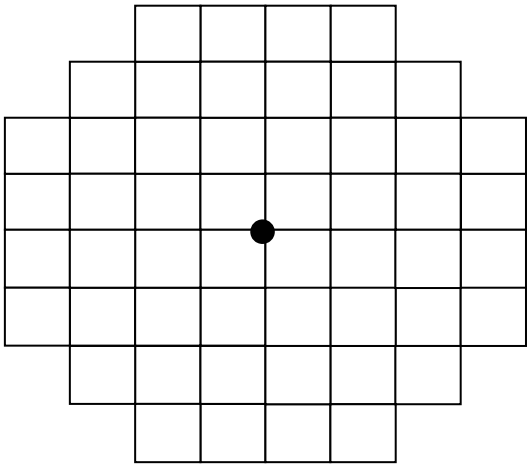


Figure 4.8 Stimulus locations of the flicker test program

4.3.4. Perimetry reliability criteria

Fixation losses

The FDT perimeters used Heijl-Krakau (blind spot) fixation monitoring (Heijl and Krakau, 1977). A smaller size (5 degree) stimulus was presented at approximately 15 degrees temporal to central fixation. Any patient response given at this location, which is over the blind spot, indicates poor fixation. Such methods sample the patient's fixation during the visual field examination and do not necessarily indicate whether the patient maintained good fixation throughout the examination. Often fixation is unstable only in the early stages of an examination and in tests where relatively few trials are carried out, the percentage of fixation losses may never reach the reliability criteria. Thus, although fixation losses are useful to establish visual field reliability, some clinical judgement by the perimetrist is also required. During the examination, fixation was checked 6 times in the FDT programs used in this study. A fixation loss rate of >20% originally indicated an unreliable outcome. It has been suggested that the acceptable fixation loss percentage be increased to 33% (Sanabria et al., 1991). In this study fixation losses >33% were considered when determining the reliability of the visual field.

False positive and negative catch trials

All stimuli in full threshold testing were presented at regular intervals. Periodically, a stimulus was not presented at the expected time. If a patient responded to this non-existent stimulus, a false positive was recorded. In a false negative catch trial, a stimulus is presented periodically where the threshold has already been determined at a brighter than the measured threshold level. If the patient failed to respond to this stimulus, a false negative was recorded. False positives and negatives were checked 3 times respectively during each program tested to give a measure of patient reliability. If false positive or negative rates were greater than 33% the results were considered unreliable (Anderson and Johnson, 2003; Katz and Sommer, 1988).

4.3.5. Statistical analysis of visual field sensitivity

The first visit was used to minimise the presence of a learning effect. The mean deviation was statistically greater in the first visit in both the FDT techniques (t-test $p<0.05$), the flicker results were not significantly different on the second visit. Thus only the results from the second examination were considered for analysis. Mean sensitivity was calculated for each field globally and by dividing the visual field into central and peripheral sectors; the central sector encompassed all stimulus locations within 10 degrees of fixation. The sensitivity at each location was also compared to age-matched normal values contained within the perimeter database. In the FDT, the deviation of the measured value and normal value at each stimulus location were averaged and expressed as the mean deviation. An increasingly negative value indicates abnormality which is indicative of diffuse visual field loss or a large area of focal visual field loss. In flicker perimetry the normal value is subtracted from the normal value at each stimulus location and the average yields the mean defect index. This index becomes increasingly positive in diffuse visual field loss. To enable comparison between techniques, the mean defect values of flicker perimetry were converted to mean deviation.

The sectoral analysis and mean deviation index gives an indication of visual field abnormality, but at the expense in a loss of spatial information. Pointwise analysis was carried out for each visual field by examination of the total deviation probability. The measured value is compared to the range of normal values at each location. Deviation

from these values outside a given confidence interval for normality is expressed as a probability symbol denoting the level of significance of abnormality. This analysis is known as total deviation probability.

4.4. Results

4.4.1. Reliability criteria

Fixation errors

In flicker perimetry with the Octopus perimeter, fixation was not monitored using the Heijl-Krakau method. Fixation was, instead, continuously monitored using optical methods and any break in fixation automatically paused the test until fixation was regained. The Asperger's syndrome group yielded more fixation losses than the control group in both the FDT large and small stimulus tests but this was only statistically significant for the small stimulus method p=0.007. The large stimulus test produced less fixation errors than the small stimulus in both groups, but again this was only statistically significant for the Asperger's group ($p<0.0001$) figure 4.9 (error bars are standard deviation).

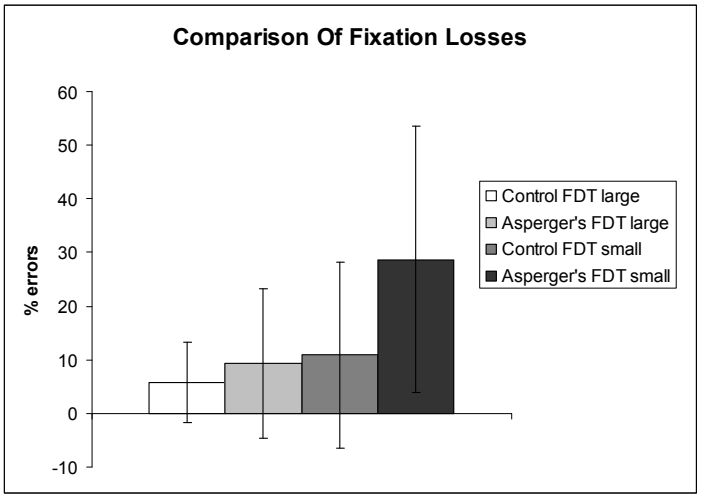


Figure 4.9 Fixation loss comparisons between the FDT small and large stimuli.

False positives and negatives

ANOVA testing was used for analysis with Bonferroni post hoc testing where needed. Flicker perimetry yielded the greatest percentage of false positive errors compared with both FDT tests in both the Asperger's and control group ($p<0.001$). The FDT large and small stimuli tests showed no significant difference in either the Asperger's group ($p=0.2$) or the control group ($p=1$). The Asperger's group did not produce more false positive errors than the control group for any test condition ($p=0.3$).

False negative error rates were low in all conditions, and rates were similar in all the tests ($p=0.4$) and groups ($p=0.7$) (table 4.4).

	FDT Large Stimulus Asperger's	FDT Large Stimulus Control	FDT Small Stimulus Asperger's	FDT Small Stimulus Control	Flicker Asperger's	Flicker Control
Mean % False Positive	3.0 (±4.6)	3.0 (±4.2)	9.1 (±11.0)	2.3 (±2.8)	15.8 (±18.0)	16.8 (±13.0)
Mean % False Negative	1.2 (±4.3)	0.0 (±0.0)	2.5 (±7.0)	0.8 (±2.5)	1.3 (±3.6)	0.8 (±2.1)

Table 4.4 Mean values for reliability measures.

4.4.2. Test duration

Flicker perimetry took significantly longer to complete than either of the FDT test in both ASD and control groups (single factor ANOVA: $p<0.01$). The control group completed their tests in a shorter time for all tests than the ASD group. However, differences in duration were only statistically significant in the FDT small stimulus test ($p<0.01$). There was greater variability within the test groups for completion of flicker perimetry, reflected in the greater standard deviations for this test figure 4.10.

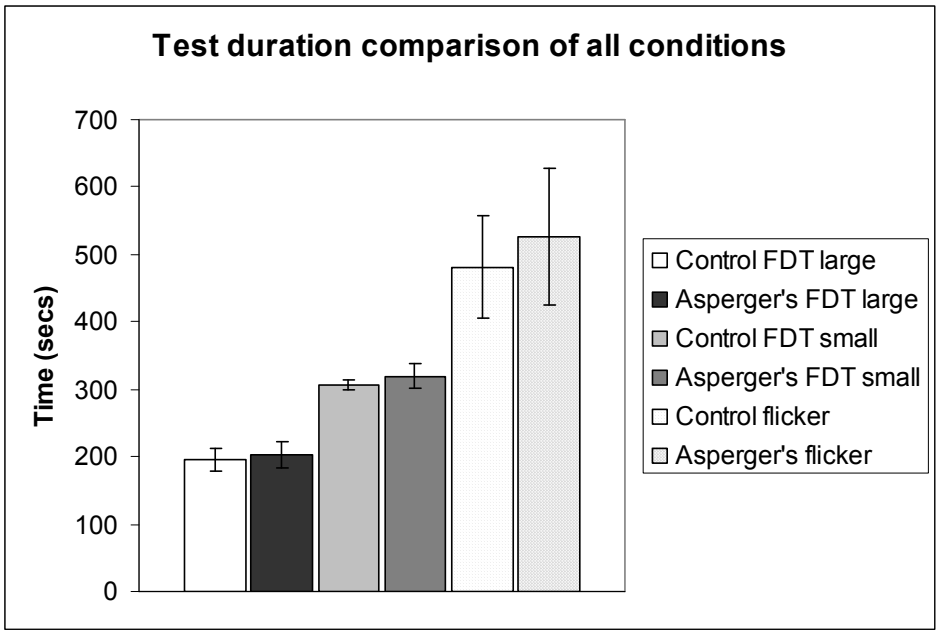


Figure 4.10 Test duration comparisons for FDT using large stimuli, FDT using small stimuli and Flicker perimetry. Error bars represent 1 standard deviation above and below the mean.

4.4.3. Mean sensitivity

Frequency doubling technique large stimulus

Mean sensitivity of the field was greater in the control group by 3.8dB (p=0.003, unpaired t-test) (figure 4.11).

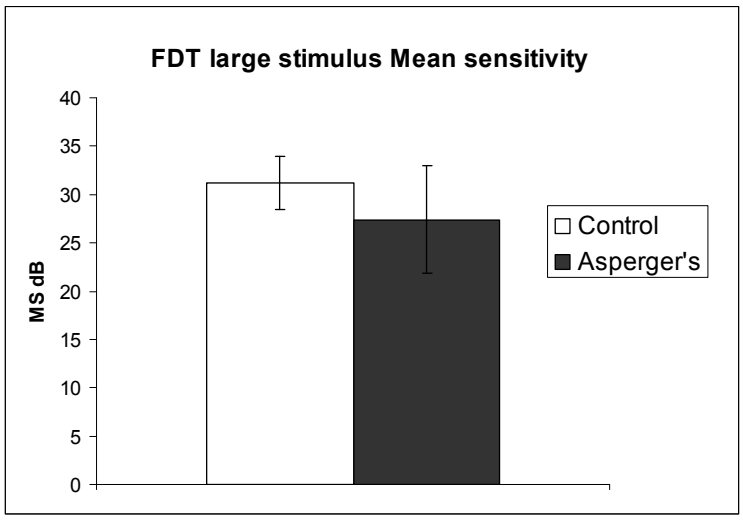


Figure 4.11 Mean sensitivity comparison of whole field FDT.

As expected, for the control group the central sensitivity was greater than peripheral sensitivity (p= 0.04 paired t-test). In the Asperger's group the difference between central and peripheral sensitivities did not prove to be statistically significant (p=0.2, paired t-test), (figure 4.12).

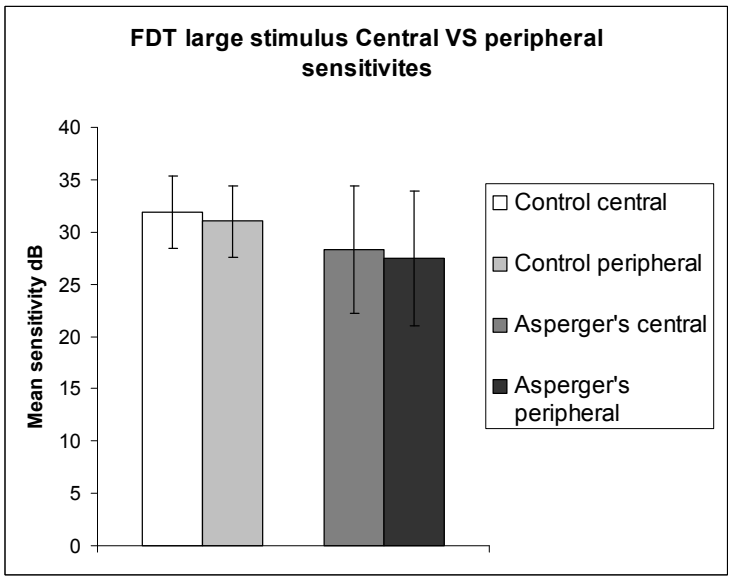


Figure 4.12 Central versus peripheral field in FDT large stimulus.

Frequency Doubling Technique (FDT) Small Stimulus

Globally, the control group yielded a greater mean sensitivity than the Asperger's group by 3.3dB (unpaired t-test, p=0.01) (figure 4.13).

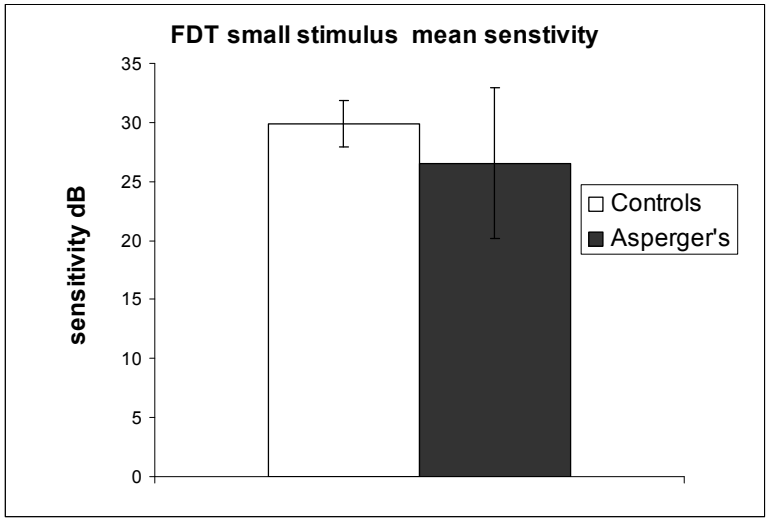


Figure 4.13 FDTm mean sensitivity whole field.

The central mean sensitivity was greater than the peripheral sensitivity for both control and Asperger's groups (paired t-tests, p<0.001), (figure 4.14).

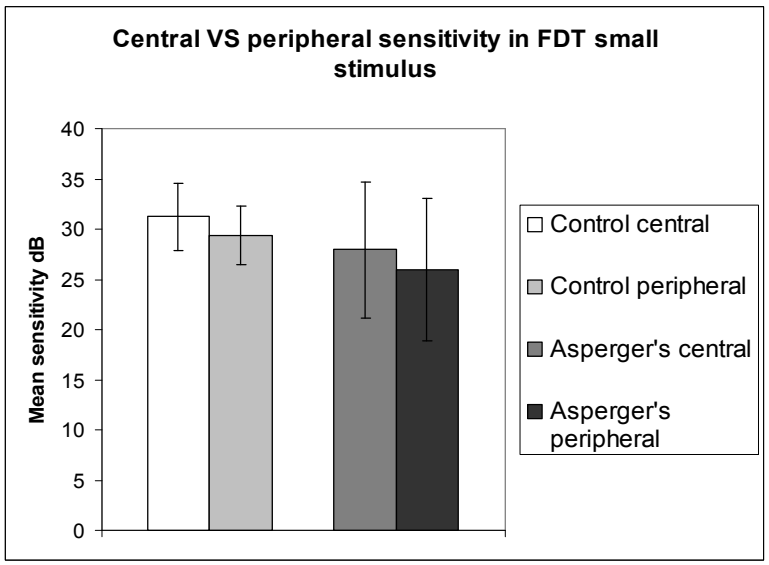


Figure 4.14 FDTm Central vs. peripheral fields.

Flicker Perimetry

Flicker mean sensitivity was greater for the control group than the Asperger's group by 7.4dB ($p<0.001$, unpaired t-test), (figure 4.15).

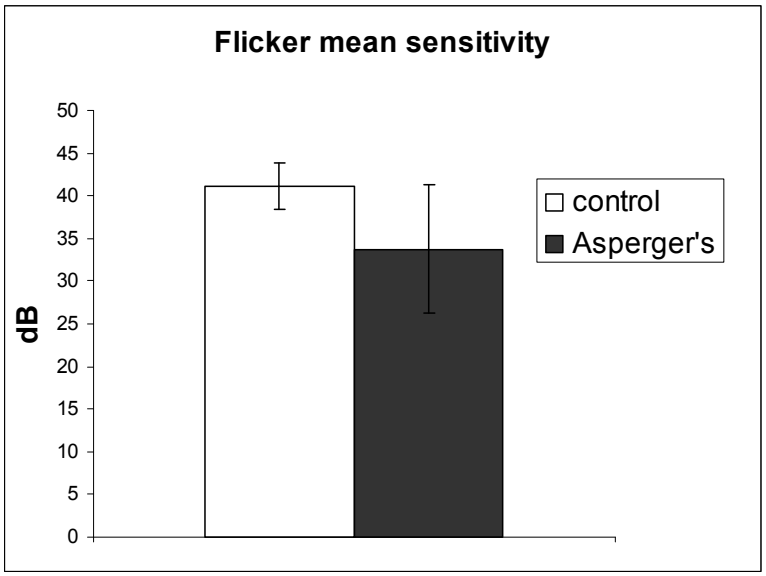


Figure 4.15 Mean sensitivity for Flicker perimetry.

Central flicker sensitivity was greater than the sensitivities in the peripheral sectors for both groups (paired t-test, $p<0.0001$), (figure 4.16).

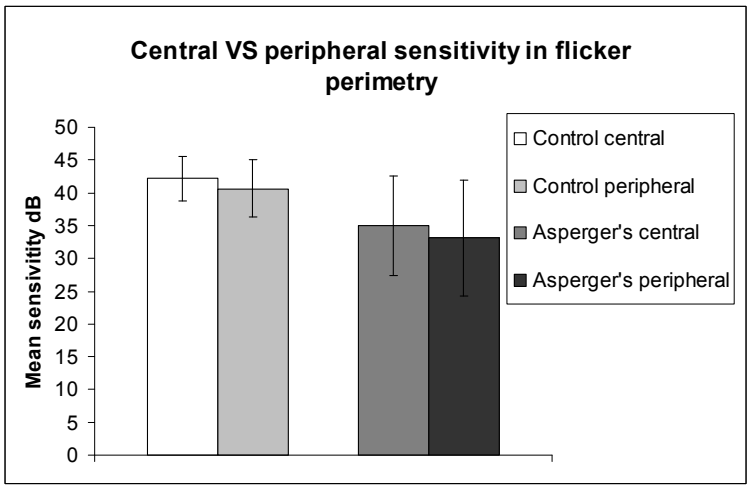


Figure 4.16 Flicker sensitivity for central versus peripheral field.

4.4.4. Mean deviation

The group mean deviation (MD) at the second examination was significantly more negative in the Asperger's group than the control group for all tests (P<0.01 for all techniques by ANOVA). This indicated that there may be a diffuse magnocellular pathway deficit present in this group (figure 4.17).

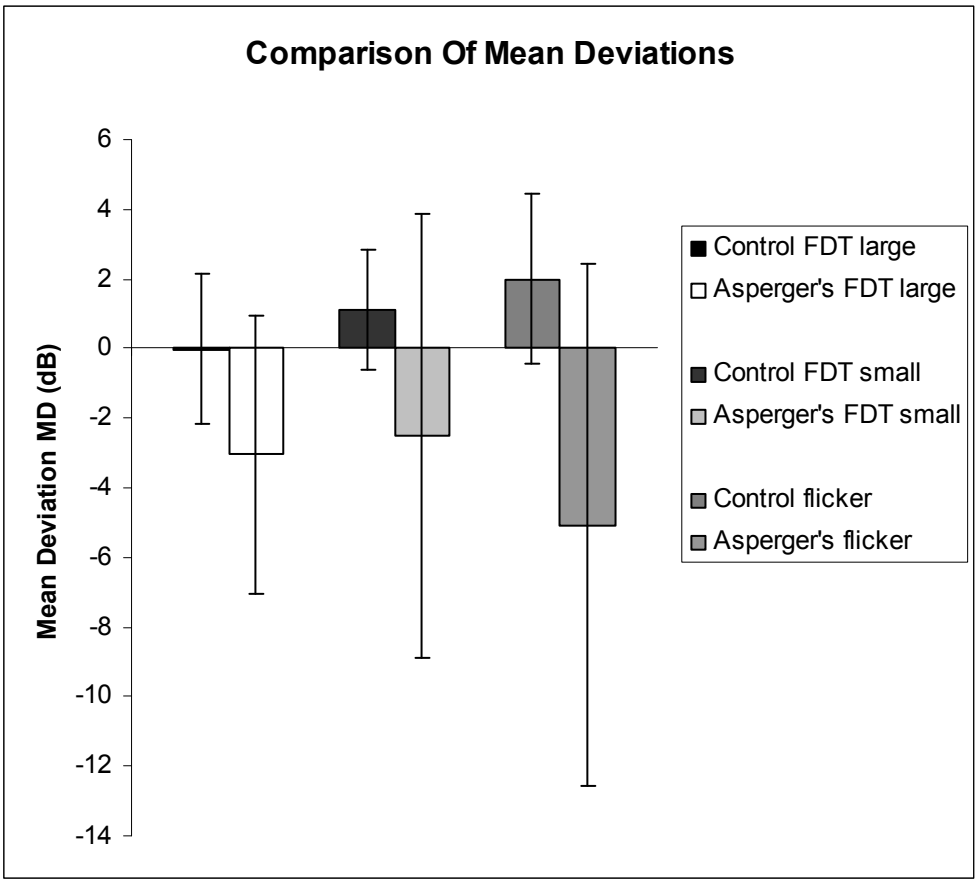


Figure 4.17 Mean deviation comparisons.

In the Asperger's group the MD was very similar for all the tests (p=0.2, Bonferroni post hoc testing). For the control group, however, there was a difference found between the tests (table 4.5). The mean deviation was smallest and therefore closest to expected normal values, in the FDT large stimulus test.

Test	Test	Mean Difference	Std. Error	P
FDT large	**FDT small**	**-2.01**	**0.66**	**0.01**
FDT large	flicker	-1.14	0.64	0.24
FDT small	flicker	0.88	0.66	0.57

Table 4.5 ANOVA, with post hoc Bonferroni analysis.

Threshold sensitivities were analysed on a pointwise basis by calculating the frequency at which each stimulus location was found to be depressed in those individuals in the Asperger's group with a field defect at the P<0.05% probability level or greater Figures 4.18, 4.19 and 4.20. The Chi test for frequencies was applied to the frequency of defects in each hemisphere, no statistically significant difference was found between the inferior and superior hemispheres, Chi values were 1.33 (P=0.95), 2.13(P=0.90) and 3.78(P=0.90) for the FDT large, FDT small and flicker tests respectively.

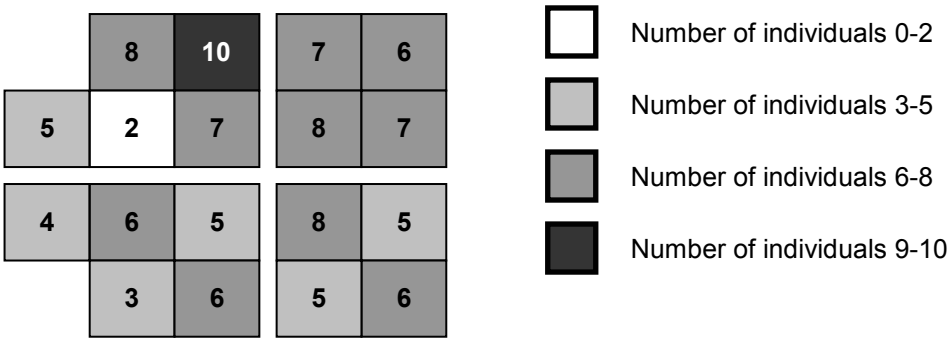


Figure 4.18 Frequencies of defects in the Asperger's group for large stimulus FDT.

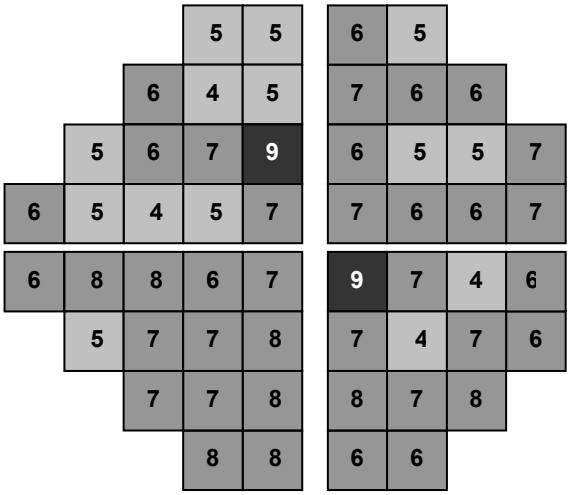


Figure 4.19 Frequencies of defects in the Asperger's group for small stimulus FDT.

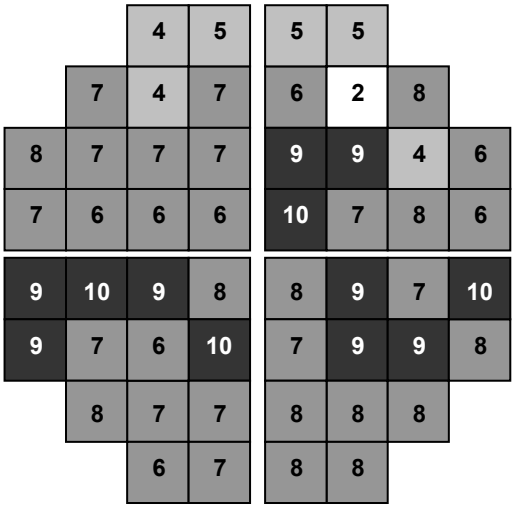


Figure 4.20 Frequencies of defects in the Asperger's group for flicker perimetry (right eye view).

For the large stimulus FDT, a visual field defect was defined as (1) a cluster of two or more adjacent locations of depressed sensitivity at the P<0.05% level or greater on total deviation probability analysis and/or (2) a significant mean deviation value. In the Asperger's group, 8 of the 14 (57%) volunteers yielded such a defect with large stimulus FDT.

For the FDT small stimulus, a defect was defined as (1) a cluster of three or more adjacent locations (more than the large stimulus owing to the smaller area covered by each location) at the P<0.05% level or greater or (2) a significant mean deviation. Again 8 of 14 people from the Asperger's group yielded a defect. The same criteria were used for flicker perimetry as for the small stimulus FDT; 7 of 13 individuals (54%) yielded defects, figure 4.20. These results are summarised in a Venn diagram (figure 4.21).

Figure 4.21. Venn diagram illustrating the number of individuals with Asperger's syndrome who showed a defect in each test.

4.5. Discussion

Mean sensitivity was greater in the control group than the Asperger's group for all perimetry investigations. For pointwise deviations from age-matched controls, the FDT large stimulus examination yielded, in the Asperger's group, a generalised depression over the whole field, whereas the flicker and FDT small stimulus technique yielded a generalised depression of sensitivity which was slightly greater in the inferior hemifield. These differences could be explained by the greater spatial resolution of the FDT small stimuli and flicker examinations. Alternatively the small stimuli may be tuned to different aspects of the M-pathway, since there would be a lower degree of spatial summation compared to FDT using large stimuli which is tuned specifically to the M-y cells. The slightly greater loss in sensitivity found in the inferior visual field with small stimulus FDT and flicker perimetry would tend to suggest a deficit originating in the superior retina. The general ganglion cell density is greatest in superior retina (Curcio and Allen, 1990; Curcio et al., 1990; Perry and Cowey, 1985) which in turn would suggest that this region would be more resistant to damage due to a greater redundancy in function. Studies of retinal topography have found that magnocellular projecting ganglion cells are found in greater density in the

nasal retina, but there is little difference in density between the inferior and superior retinal regions (Lima et al., 1993; Lima et al., 1996; Silveira and Perry, 1991). However, these findings relate to the primate retina and do not necessarily translate to human physiology. Furthermore, the distribution of M-y cells in the retina has not been quantified. Further corroboration would be required to investigate these findings further (Chapter 10).

Fifty seven percent of the Asperger's sample yielded a diffuse magnocellular deficit. Other investigations of M-pathway function in Autism disorders using global motion and form detection and have shown similar findings (Pellicano et al., 2005; Pellicano and Gibson, 2008; Tsermentseli et al., 2008). Pellicano and Tsermentseli found that this was not correlated to age or developmental variability (Pellicano and Gibson, 2008; Tsermentseli et al., 2008). These findings suggest that there may be a sub-set of individuals with autism disorders who also have magnocellular deficits, the reasons for which are unclear.

Flicker perimetry had the longest duration of all the tests for both groups, with the Asperger's group taking slightly longer to complete. For all the techniques, the subject's reaction times influences the presentation rate for the stimuli, so these findings may indicate that the Asperger's group have a slower reaction time to the stimuli than the control group which is corroborated by the findings of Rinehart et al (2001) and Schmitz et al (2007) .

The longer duration of flicker perimetry compared to FDT examination inevitably makes it more demanding for subjects to perform due to the length of concentration time required. The longer the duration of the test, the greater the likelihood of fatigue affecting the accuracy of the results. This potentially artificially elevates the mean deviation of the field (Gonzalez de la Rosa and Pareja, 1997; Heijl et al., 1987; Hudson et al., 1994a; Johnson et al., 1988). Flicker perimetry does not give a statistical measure of fixation quality, which is another limitation of this technique. In the large stimulus FDT test there was no difference in the percentage of fixation errors made between the groups, whereas in the small stimulus test the Asperger's group showed poorer fixation. These findings could be explained by the Asperger's group becoming more fatigued in attention compared to the control group leading to a

decreased performance. This hypothesis is supported by previous studies which found attention to be diminished in the autism spectrum (Davis et al., 2006; Mann and Walker, 2003; Van der Geest et al., 2002). The false positive rate was highest in flicker perimetry which probably is due to the complexity of the test. That is, the patient has to respond to only a flickering stimulus and not just to the presence of a peripheral light stimulus.

Overall, these findings suggest that flicker perimetry is the most difficult for volunteers to perform, leading to high between and within-subject variability which confounds clinical diagnosis. Consequently, it is unlikely to be suitable for use in individuals with Asperger's syndrome or an ASD. FDT using small and large stimuli produced the same results in terms of identification of individuals with Asperger's syndrome who had a deficit. Since the variance in results was lowest for the FDT using a large stimulus, and the examination is completed faster to complete, this would be the examination of choice in a clinical setting.

4.6. Conclusions

Fifty seven percent of the group with Asperger's syndrome yielded an M-pathway deficit with FDT. The defect manifests as a generalised reduction in sensitivity which, with small stimulus FDT, may be slightly greater in the inferior hemifield. This finding supports the theory of an M-cell specific pathway deficit being present in Asperger's syndrome. These findings may help to explain some sensory issues suffered by the individual being tested. These include hyposensitivity to some stimuli or some mobility issues. If the person has decreased sensitivity peripheral objects may be harder to distinguish making, perhaps, things like crossing roads or using stairs more difficult (Bodis-Wollner et al., 1987; Owsley et al., 1995; Turano et al., 2004)

Individuals with Asperger's syndrome or an ASD presenting for an eye examination should have their visual fields assessed to measure threshold sensitivity levels. The FDT large stimulus is a suitable test to use, owing to its short test duration compared to other techniques and low levels of testing errors. Although flicker perimetry also detects the M-cell deficit, it requires a great deal of concentration and may not be particularly viable in the clinical situation.

5. Coloured Filters and Asperger's Syndrome

Abstract

Purpose: The purpose of this investigation was, firstly, to determine whether reading speeds are decreased in individuals with Asperger's syndrome compared to neurotypical controls and secondly to determine whether individuals with Asperger's syndrome are more likely than the general population to benefit from using a coloured overlay when reading. **Methods:** Subjects were divided into two groups; Asperger's syndrome including high functioning autism (n=21, mean age 22 +/- 10.9 years, range: 10-45 years), and neurotypical control group (n=20, mean age 23 +/- 8.01 years, range 10-48 years). Volunteers were assessed using the Institute of Optometry coloured overlay set and rate of reading was measured with (where appropriate) and without overlay using the Wilkins rate of reading test. **Results:** The control group read significantly faster than the Asperger's group both with and without the overlay ANOVA $P<0.05$. There was no significant difference in the increase in reading speed achieved by using a coloured overlay between the Asperger's and control group. The Asperger's group were no more likely than the control group to express a preference for a coloured overlay (chi test $p=0.37$) and there was no difference in the distribution of colour overlay chosen by the two groups (chi test $p=0.24$). **Conclusions:** The percentage of individuals who might benefit from the use of a coloured overlay is not greater in the Asperger's population. Nevertheless, coloured overlay testing and assessment for visual dyslexia should be considered when examining an individual with high functioning autism or Asperger's syndrome as some individuals do appear to benefit.

5.1. Introduction

5.1.1. Colour and autism

Colour perception is abnormal in individuals with autism (Franklin et al., 2008; NAS, 2008). Franklin found that children with autism were significantly less skilful at colour memory and search tasks than controls and were less accurate detecting coloured targets when presented on coloured backgrounds. Idiosyncratic responses to colours have also been widely reported anecdotally in autism (Ludlow et al., 2006; NAS, 2008). For example, parents have reported that their autistic children refuse to eat green food, will only drink from a brown cup or always choose red items to the exclusion of most others. An excellent example of this can be found in the novel "the curious incident of the dog in the night time" the book is about a boy with Asperger's syndrome by Mark Haddon. In this book a young boy Christopher hates the colours yellow and brown, but loves red. This extends to adding red food dye to brown- or yellow-coloured food (and being unable to eat two different kinds of food that are touching (Haddon, 2004). Another such example comes from a study that described an adult with autism who reported, how as a child he refused to look at the yellow bike given to him for Christmas because of its colour (White and White, 1987).

Howlin et al (Howlin, 1996) reported that some individuals with autism improve in their physical and emotional functioning as well as their intellectual capacity after observation of coloured lights, this treatment is 'Syntonics'. Syntonics treats a wide range of visual problems by applying visible light wavelengths to the eyes. This is a controversial method which is not widely accepted, so it will not be described in any further detail. At present, no controlled trials have been carried out to look at possible behavioural benefits which may be produced by the use of colour. Never the less it has been used in treatment of many different psychological and psychosomatic disorders. (Barber, 1999; Deppe, 1999).

5.1.2. Dyslexia

Dyslexia is a specific learning disability which manifests as a difficulty with written language, particularly with reading and spelling. It is a separate entity from reading difficulties with other causes, such as a general learning disability. The prevalence of dyslexia in the general population ranges between 2% and 15%, with varying rates reported for different countries (Katusic et al., 2001; Miles, 1991; Parliament, 2004; Plume and Warnke, 2007; Schumacher et al., 2007). There are several theories explaining the causes of dyslexia.

The phonological hypothesis

This is the theory that dyslexics have a specific impairment in the representation, storage and/or retrieval of speech sounds (Ramus et al., 2003). Learning to read an alphabetic system requires learning the correspondence between letters and constituent sounds of speech. If these sounds are poorly represented, stored or retrieved, the learning of correspondences, the foundation of reading by phonic methods for alphabetic systems, will be affected (Bradley and Bryant, 1978; Ramus et al., 2003; Snowling, 1981).

The visual theory

This alternative theory, states that dyslexia is a visual impairment giving rise to difficulties with the processing a page of text (Livingstone et al., 1991; Lovegrove et al., 1980; Stein and Walsh, 1997). This may involve unstable binocular fixations, poor vergence, or increased visual crowding. The proposed aetiology of this visual dysfunction is based on the theory that the magnocellular pathway is selectively. This disruption leads to deficiencies in visual processing, binocular control and visuospatial attention. Evidence for this magnocellular dysfunction comes from anatomical studies showing abnormalities of the magnocellular layers of the lateral geniculate nucleus (Livingstone et al., 1991), psychophysical studies showing decreased sensitivity in the magnocellular range (i.e. low spatial frequencies and high temporal frequencies) in dyslexics and brain imaging studies (Cornelissen et al., 1997; Eden et al., 1996; Lovegrove et al., 1980).

The cerebellar theory

This theory states that the dyslexic individual's cerebellum is mildly dysfunctional (Nicholson and Fawcett, 1990; Nicholson et al., 2001; Rae et al., 1998). The cerebellum is involved in motor control and speech articulation. It is postulated that dysfunctional articulation would lead to deficient phonological representations (Ramus et al., 2003). The cerebellum also plays a role in the automatization of over learned tasks, such as driving, typing and reading. A weak capacity to automatize would influence the learning of sound/letter correspondences (Ramus et al., 2003).

The magnocellular theory

This theory suggests that magnocellular dysfunction is not restricted to the visual pathway but is spread across visual, auditory and tactile streams (Stein, 2001; Stein et al., 2001). This theory also involves the cerebellum which receives input from various magnocellular systems in the brain (Stein, 2001). Beyond the evidence pertaining to each of the theories described, evidence specifically relevant to the magnocellular theory includes magnocellular abnormalities in the medial and lateral geniculate nucleus (LGN) of dyslexics' brains, poor performance of dyslexics in the tactile domain and the co-occurrence of visual and auditory problems in certain dyslexics (Galaburda et al., 1994; Livingstone et al., 1991; Van Ingelghem et al., 2001; Witton et al., 1998).

Perceptual visual-noise exclusion hypothesis

This hypothesis attempts to explain why dyslexic individuals experience difficulty in performing visual tasks, such as motion detection in the presence of perceptual distractions but do not show the same impairment when the distracting factors are removed (Sperling et al., 2006). Sperling asked participants to identify apparent motion of dots in the presence of random other dots appearing around the stimulus (Sperling, Lu et al. 2006). Researchers assert that dyslexic symptoms arise because of an impaired ability to filter out visual distractions and to categorize information as being important sensory data or irrelevant (Ahissar, 2007; Facoetti et al., 2008; Sperling et al., 2005). This might be similar to the problems that people with ASD have with the global versus local processing of stimuli, as was discussed in previous chapters (Ahissar, 2007; Tsermentseli et al., 2008).

Physiology differences

Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) have produced evidence of differences in brain structure in children with reading difficulties. Some dyslexic individuals have a deficit in parts of the left hemisphere of the brain involved in reading. These include the inferior frontal gyrus, inferior parietal lobule, and middle and ventral temporal cortex (Casanova et al., 2002a; Casanova et al., 2005; Haslam et al., 1981; Kronbichler et al., 2008; Shaywitz et al., 2006).

5.1.3. Irlen syndrome

The term Irlen syndrome (also known as Meares Irlen or scotopic sensitivity syndrome) refers to the signs and symptoms of visual stress that are associated with discomfort when reading. It is often confused with dyslexia but, actually, describes a distinct condition. Individuals with Irlen syndrome report perceptual distortions which are reduced when text is illuminated by light of a specific colour (Bogdashina, 2004; Evans et al., 1996; Irlen, 1997; Wilkins et al., 1996). Wearing tinted spectacles or using a specifically tinted overlay placed on top of reading material reduces symptoms such as eye strain and headaches (Irlen, 1991; Irlen, 1997; Wilkins et al., 1996). Several studies have reported that reading speed can be increased by using an optimally tinted overlay which may be selected using the intuitive colorimeter (Jeanes et al., 1997; Kriss, 2002; Wilkins, 2003).

5.1.4. Coloured overlays

Coloured overlays are transparent coloured plastic sheets that can be placed over printed texts without interfering with their clarity. Participants select the overlay which they perceive to best improve the clarity of the printed text. The overlay set used in this study was the Institute of optometry (IOO) Wilkins overlay set. The IOO Wilkins set has placebo controlled research to support its benefits (Bouldoukian et al., 2002; Mitchell et al., 2008; Wilkins et al., 1994). The chosen overlay can be any one from two sets of 10 identical (9 coloured and 1 grey) overlays provided in the selection pack. Participants can either use a single overlay or they can use stronger colours when overlays are combined. A record sheet and pie chart are filled out with the test results in order to accurately select the optimal combination of overlays. Visual material used during the test consists of two passages of random letters which

are arranged to resemble a paragraph (figure 5.1); they are not sentences so as to cause the reader to concentrate on the appearance rather than the meaning of the words.

come see the play look up is cat not my and dog for you to
the cat up dog and is play come you see for not to look my
you for the and not see my play come is look dog cat to up
dog to you and play cat up is my not come for the look see
play come cat see not look dog is my up the for to and you
to not cat for look is my and up come play you see the dog
my play see to for you is the look up cat not dog come and
look to for my come play the dog see you not cat up and is
up come look for the not dog cat you to see is and my play

Figure 5.1 Example of the text used in the Wilkins rate of reading test.

There are two letter sizes available; a large (font size12) and small (size 9). The smaller letters are closer spaced and create a more stressful text to view. The larger letters may be required for some readers, possibly younger children. It should then be ascertained whether the person is experiencing any visual discomfort or distortions; though this can be difficult without using leading questions. Usually, the examiner will start with a question such as “do the letters seem to do anything strange?”, “Do the letters seem to move?”, and “is the page uncomfortable to view?” The subject is then asked to describe, in their own words, how the page appears and what happens to the letters. The responses are recorded on the response sheet. Most people will prefer the overlay sheet with the matt coating uppermost, but preference for this should also be checked. The lighting used should as closely as possible resemble the lighting conditions experienced by the volunteer in their own environment. Overlays are shown in an order recommended by the manufacturer. This is as follows; (1) rose, (2) purple, (3) aqua, (4) lime-green, (5) orange, (6) grey, (7) yellow, (8) mint-green, (9) blue, (10) pink.

When the first overlay is placed on the test chart, the subject is asked what effect the colour has. It may improve things, make them worse or make no difference. The next

colour overlay is then presented along side the first or replaces the first overlay depending on the subjects initial response (if the colour was better both are presented, if worse the first overlay is removed). The subject is then asked which side is best/most comfortable; this process is repeated until all colours have been presented. Combinations of colours are then presented, as per 'intuitive overlays' instructions booklet, as well as double layer of the chosen colour.

Wilkins et al (2001) carried out this test on children in mainstream schools. Some (5%) of the 68 children (aged 7-11) read more than 25% faster with an overlay, while others (20%) read more than 5% faster with a coloured overlay (Wilkins et al., 2001). Similar results have been shown in an adult student population (Evans and Joseph, 2002). There, 113 university students were tested of which 100 stated that they felt a subjective improvement in viewing text when using an overlay. Of these 100 subjects, 3.8% read faster with a chosen overlay than without ($p < 0.00001$), while the 13 subjects who did not choose an overlay read 1.7% slower with a placebo overlay (an overlay of similar but slightly different colour to the optimal) than without ($p = 0.37$). Of those subjects who chose an overlay, 38% read more than 5% faster with the overlay and 2% read more than 25% faster.

The colour of overlay chosen tends to be consistent over testing sessions. Wilkins et al, found that on two separate testing sessions, three days apart, 19 children attended for a repeat testing visit. Of these children, 47% chose the same colour and 21% chose an overlay of neighbouring chromaticity to their initial selection (Wilkins et al., 2001). In another study, children were given a random rather than self-selected overlay in the classroom. Those who were given their chosen overlay or one that was of similar colour elected to use the overlays for a longer period than the children who had been given random ones (Wilkins et al., 2001). Nevertheless, one study has shown inconsistent results in a controlled trial (Mitchell et al., 2008). This study used only a choice of 3 coloured lenses and not the full range of overlays available. This could account for the inconsistent results. Most studies have shown however that the benefit of overlays is not simply due to placebo effects. Controlled trials have shown improvements in reading occur only in those who choose a coloured overlay and only with the colour they chose, showing that the colour of the overlay used is specific to

the individual (Bouldoukian et al., 2002; Jeanes et al., 1997; Robinson and Foreman, 1999; Wilkins and Lewis, 1999).

5.1.5. Rate of reading test

Passages of text are widely used by optometrists for routine tasks such establishing the additional refractive power for reading in presbyopic individuals. Most texts used are suitable only for fluent readers, although the McClure reading passages (Clement Clarke International) provide material suitable for the qualitative assessment of reading in young children. Quantitative assessment is possible using the Bailey-Lovie chart which comprises a set of random words of decreasing size but these are not suitable for children (Wilkins et al., 1996). Reading speed may be assessed by the MNREAD test (Ahn et al., 1995; Legge et al., 1989). This test provides a standard set of simple sentences with equal numbers of lines, characters, and contextual difficulty. The MNREAD can be used to determine the smallest print size that yields maximum reading speed, and so is of particular use in patients with low vision. Both the MNREAD and the Bailey-Lovie tests have been validated in optometric settings but neither is suitable for use with individuals who have a very limited reading vocabulary.

In the investigation described in this chapter the Wilkins rate of reading test was employed. Test subjects are asked to read aloud a passage of randomly ordered words as rapidly as possible within one minute and errors are noted. The passage is designed to be visually stressful, making this a particularly suitable test when investigating visual stress in dyslexia or Irlen syndrome. The text is made to resemble horizontal stripes by reducing the horizontal spacing between words and thus, induce visual stress (Wilkins, 1995; Wilkins, 2003; Wilkins et al., 1996). The text is printed in a small typeface so the ‘stripes’ created have spatial parameters close to those optimal for perceptual distortion. In other respects, the appearance of the text is conventional. The test is printed in ‘Times New Roman’ font, 9 point, and is ‘single spaced’. The same 15 common words are used in each line in a random order. All the words used in the test are selected from the 110 most frequent words in a count of words in children’s reading books (Wilkins et al., 1996). The passage can therefore be undertaken by adults and children who have only a modest reading vocabulary. The test should only be carried out if subjects can correctly identify all the words used. This is confirmed before the test begins by asking the subject to read out the 15 words

used in the passage printed in large type at the front of the test. The test is scored by noting the errors on a score sheet comprised of an enlarged version of the text, by measuring the total time taken to read the passage. Alternatively, the numbers of words read in one minute minus any errors are recorded. Errors typically consist of omissions, substitutions and reversals. Reading speed is calculated as the number of words correctly read per minute. The subject reads the four passages of text during the test, as per the instructions provided by the manufacturer. The first passage is read (1) with the chosen overlay, (2) without overlay, (3) without overlay (4) with the overlay again. This is carried out to account for effects of learning and fatigue when calculating the average number of words read across all four conditions.

5.1.6. Dyslexia, Irlen syndrome and ASD

Dyslexia is often mentioned anecdotally as being co-morbid with ASD (and ADHD) (Hale, 2005; Pellicano and Gibson, 2008; Rumsey and Hamburger, 1990; Terrell and Passenger, 2006; Williams, 1999). However. there is very little literature concerning this and according to the national autistic society of the UK there are no official figures for the percentage of people with ASD who are also diagnosed with dyslexia (NAS, 2006a). The two conditions do share many characteristics and theorised causes (Casanova et al., 2002a; Casanova et al., 2002b; Richardson, 2000a; Rumsey and Hamburger, 1990), as discussed in chapter 1. These include pregnancy and birth complications (Baron-Cohen, 1993), developmental delay in reaching milestones for motor, visuomotor and/or language development (Baron-Cohen, 1993). Abnormal cerebellar function has been suggested in both conditions (Kemper and Bauman, 1998; Kronbichler et al., 2008; Nicholson et al., 2001; Nowinski et al., 2005; Takarae et al., 2004b). A possible magnocellular defect may occur in both (Livingstone et al., 1991; McCleery et al., 2007; Pellicano and Gibson, 2008; Tsermentseli et al., 2008). There is also evidence for motion detection deficits (Pellicano and Gibson, 2008; Tsermentseli et al., 2008). There is an increased frequency of allergic or autoimmune disorders in the individual and their relatives (Richardson and Ross, 2000). There is a large male bias in numbers affected in both autism and dyslexia and both conditions may be associated with attentional difficulties (Richardson, 2000a; Rumsey and Hamburger, 1990; Terrell and Passenger, 2006).

Claims have been made that the use of coloured lenses can improve symptoms in both dyslexia and autism. Donna Williams, a well known Autistic author and artist, was

one of the first people to report a benefit from using coloured lenses (Williams, 1999). She described hyper-acute vision that resulted in a tendency for her to focus on minute details, reporting that tinted lenses enable her to view the world clearly and holistically. She proposed that many other individuals with autism would also benefit from coloured lenses. Benefits may include improvement in behaviours from motor control to eye contact. There is no evidence from placebo controlled trials to confirm these benefits.

At the present time only two studies have been carried out which investigate ASD and the influence of coloured overlays on reading (Ludlow et al., 2006; Ludlow et al., 2008). The first study looked at the effect of coloured overlays on reading ability in children with autism (Ludlow et al., 2006). They reported that 15 out of 19 (79%) children with autism showed an improvement of at least 5% in reading speed when using a coloured overlay compared to only 3 of 19 (16%) of the control group. The authors suggested that the link between autism and benefits from colour may originate from cortical hyper excitability. This is suggested because, children who have been found to benefit from coloured overlays are twice as likely to have a family history of migraine (Maclachlan et al., 1993). The cortex in migraine sufferers is hyper excitable (Aurora and Welch, 1998; Huang et al., 2003). Visual stimuli which provoke visual stress responses are similar to those which cause seizures in photosensitive epilepsy (Wilkins, 1995). Individuals who are migraine sufferers are particularly susceptible to perceptual distortions (Chronicle and Wilkins, 1991; Chronicle et al., 1995; Marcus and Soso, 1989). Wilkins has proposed that these distortions result from the spread of anomalous activation within the cortex which causes cells to fire inappropriately (Wilkins, 2003). This spread of activation reflects cortical hyper excitability in a similar way to that which occurs in epilepsy but in a less extreme way, in epilepsy this hyper excitability can by diffuse but not uniform and may only involve a few cortical orientation columns (Wilkins, 1995). Xiao et al (Xiao et al., 2003) found that in visual area V2, colour sensitive cells are distributed according to chromaticity. Hence, Wilkins has proposed that an appropriately coloured filter may change the distribution of firing within the cortex in this area, so reducing the excitation in this region (Wilkins, 2003). FMRI studies into hyper excitability in migraine have shown support for this suggestion (Huang et al., 2003).

Many studies, which support this theory of cortical hyper excitability, concern photosensitive epilepsy (Wilkins and Lewis, 1999) migraine (Evans and Joseph, 2002; Wilkins et al., 2002) and head injury (Jakobson et al., 2008). Individuals with autism are more prone to epileptic seizures (Bryson et al., 1988; Cialdella and Mamelle, 1989; Deykin and MacMahon, 1979; Steffenburg and Gillberg, 1986b; Tanoue et al., 1988; Wing, 1979; WING L, 1979; Wing and Gould, 1979). If perceptual distortions experienced by individuals reflect cortical hyper excitability, it is possible that coloured filters may alleviate the distortions and exert beneficial effects.

Ludlow et al's second paper (2008) stated similar findings to their first study. A large percentage (74%) of the children with autism tested showed a significant improvement in reading speed. This study looked at children with autism and intellectual disability aged up to 15 years, and confirmed that overlay colour must be specific to the individual to prove of benefit.

5.2. Aims

The aims of this investigation were (1) to determine whether reading speeds are decreased in individuals with Asperger's syndrome and high functioning autism compared to typically developing controls and (2) to investigate whether people with an ASD are more likely than the general population to benefit from using a coloured overlay when reading. These findings would determine whether individuals with an ASD might benefit from assessment for coloured overlays as part of a routine examination or as part of the diagnostic test battery.

5.3. Methods

5.3.1. Sample

None of these volunteers were diagnosed with a learning disability. Control volunteers were matched for educational level and age as explained in chapter 2.

	Subjects	Mean age (years)	Age range	Previously diagnosed with dyslexia or Irlen syndrome
Asperger's	21	22 ± 10.9	10-45	1
Control	20	23 ± 8.01	10-48	1

Table 5.1 Volunteer details

5.3.2. Ethical approval and informed consent

The Aston University Ethics Committee approved the project and all participants were asked for their written informed consent prior to taking part.

5.3.3. Procedures carried out

Intuitive Coloured overlays

The Institute of Optometry coloured overlay set was used and testing was performed as described in the introduction, according to the manufacturer's guidelines.

Coloured overlay characteristics

Light transmission characteristics of the overlays used are shown in table 5.2 and figures 5.2 and 5.3.

Rate of reading test

The Wilkins rate of reading test was performed after the overlay assessment, again as described in the introduction and according to manufacturer's instructions.

Colour of overlay or combination	Peak(s) transmission wavelength (nm)
Aqua	495-503
Blue	467-473
Grey	462-663
Lime Green	389-395 and 545-554
Mint Green	524-534
Orange	384-385 and >574
Pink	444-460
Purple	444-446
Rose	396-397 and >595
Yellow	360-367 and 520
Blue Aqua	470-478
Blue purple	448-459
Mint green lime green	543-547
Orange Rose	700+

Table 5.2 Peak Transmission wavelength for each overlay.

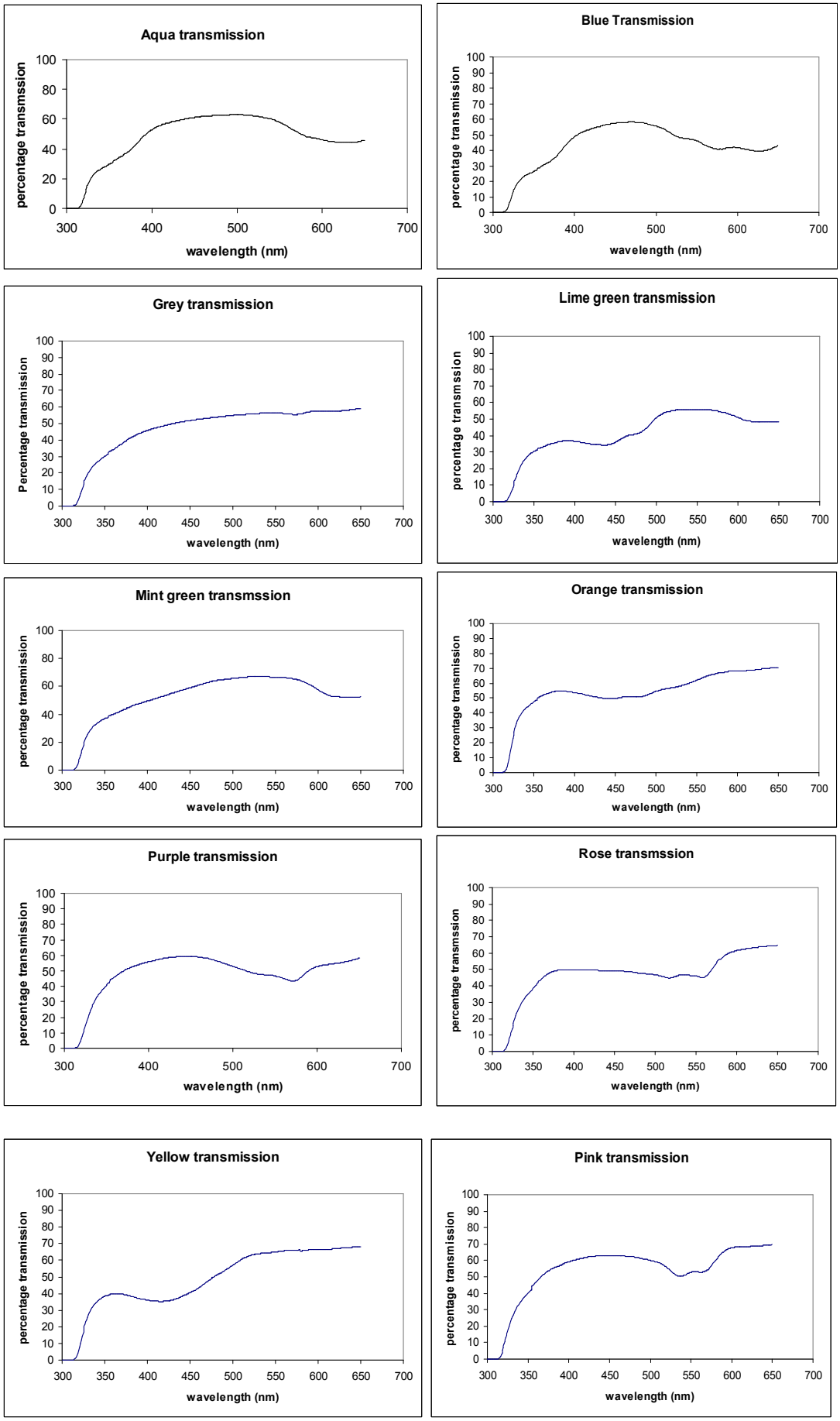


Figure 5.2 Light transmission curve for each overlay.

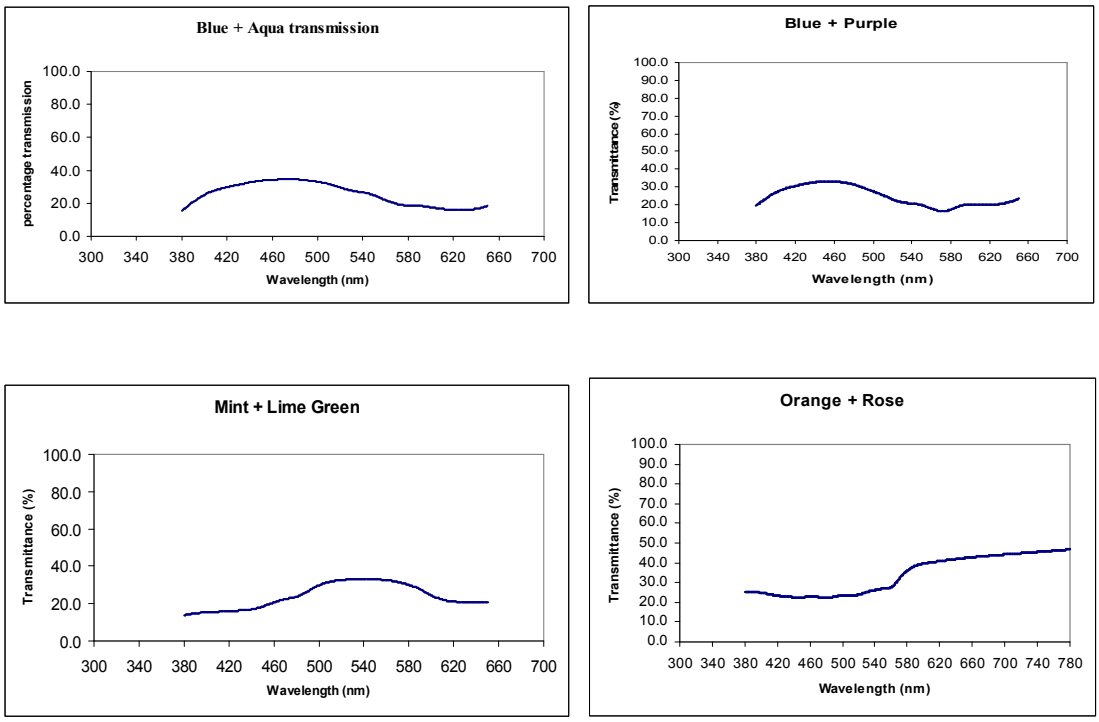


Figure 5.3 Light transmission curves for chosen combinations of overlays.

5.4. Analysis

The number of individuals who chose an overlay from each group was noted along with their preferred colour. Rate of reading measures without and with the chosen overlay (where appropriate) were recorded and any increase or decrease in reading speed was established.

5.5. Results

5.5.1. Colour of overlay chosen

There was no statistically significant difference between the two groups with respect to showing a preference for a coloured overlay (chi test for frequencies p=0.37). Twelve of the 21 (57%) volunteers with an ASD showed a preference for a coloured overlay compared with 8/20 (40%) of the control group. For the individuals who did show a preference for a coloured overlay, Chi squared testing was used to investigate the distribution of the frequency of colour choice. There was no statistically

significant difference in distribution (Chi square p=0.8). The frequencies of specific colour overlay chosen by the 2 groups are shown in Table 5.3 and figures 5.4 and 5.5.

Coloured overlay	Frequency chosen ASD (n=21)	Frequency chosen control (n=20)
Yellow	1	1
Orange	0	2
Rose	0	0
Pink	0	1
Purple	3	0
Blue	2	0
Aqua	0	0
Mint green	1	1
Lime green	1	1
Combination blue aqua	2	0
Combination blue purple	1	0
Combination orange rose	1	0
Combination lime mint green	0	2
Total combination	4	2

Table 5.3 Frequency of colour choices in each group

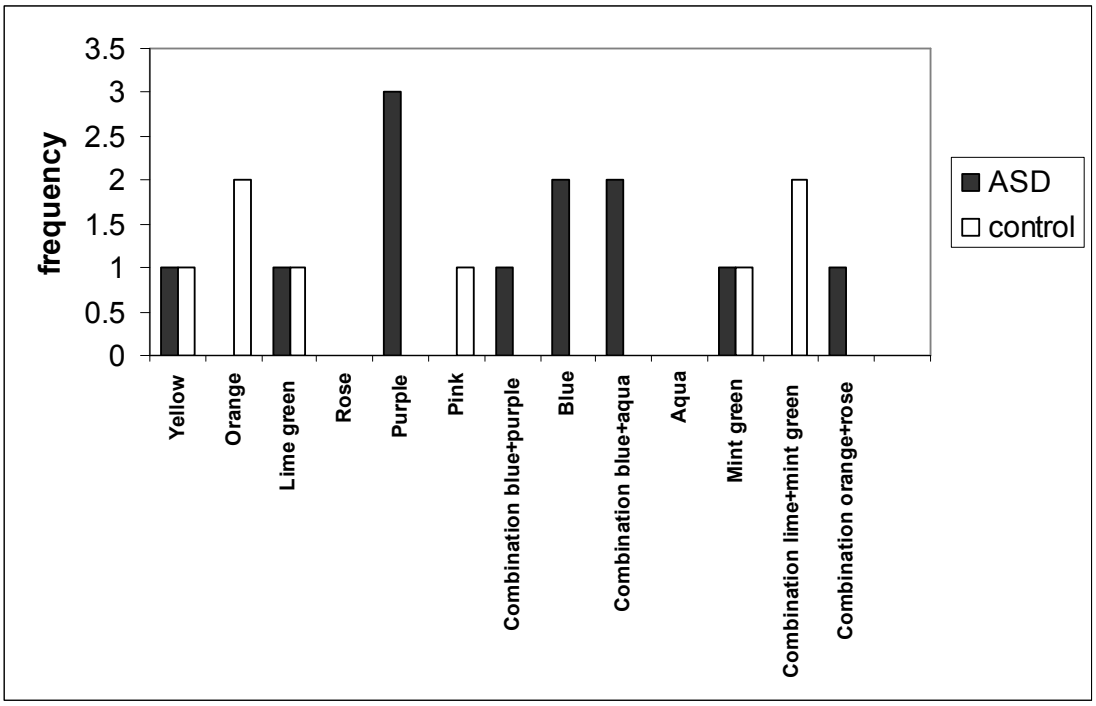


Figure 5.4 Colour of overlay chosen including combinations of overlay colours, colours in order of peak transmission wavelength.

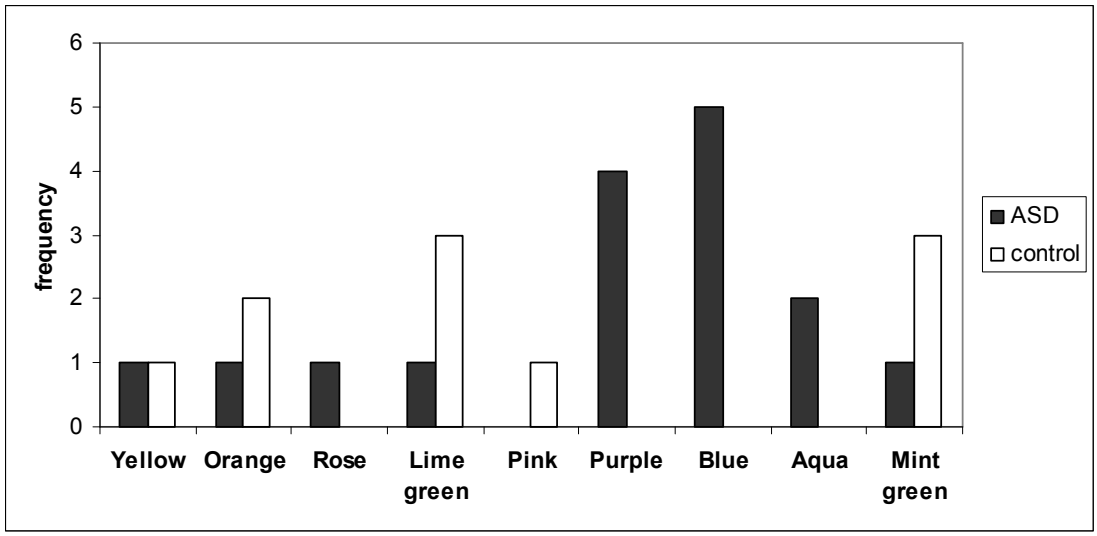


Figure 5.5 Overlay colour chosen with combination colours added to the totals for both groups.

5.5.2. Reading speeds

Without an overlay, the mean reading speed in the Asperger's group was 111 words per minute (WPM) (standard deviation SD=26, range 52-145) compared to 151 wpm (SD=37, range=115-225) for the control group. In the Asperger's group, 8 of the 21 (38%) subjects showed an increased reading speed with an overlay, 5 of these were greater than 5% increase (24%) and the largest increase in words per minute was 15.5%. This means that 8/12 (67%) of the Asperger's group who chose an overlay read faster, 5/12 (42%) increased rate of reading by >5%. In the control group, 7 of the 20 (35%) showed an increase in words per minute, 4 of these were greater than 5% improvements (20%) and the largest improvement in this group was 8.3%. The mean reading speed was greater with overlays in both groups but the difference was not (paired t-test, $p=0.5$ for both groups). The control group read faster than the Asperger's group both with (unpaired t-test $p<0.001$) and without the overlay (unpaired t-test $p<0.001$) (figure 5.6).

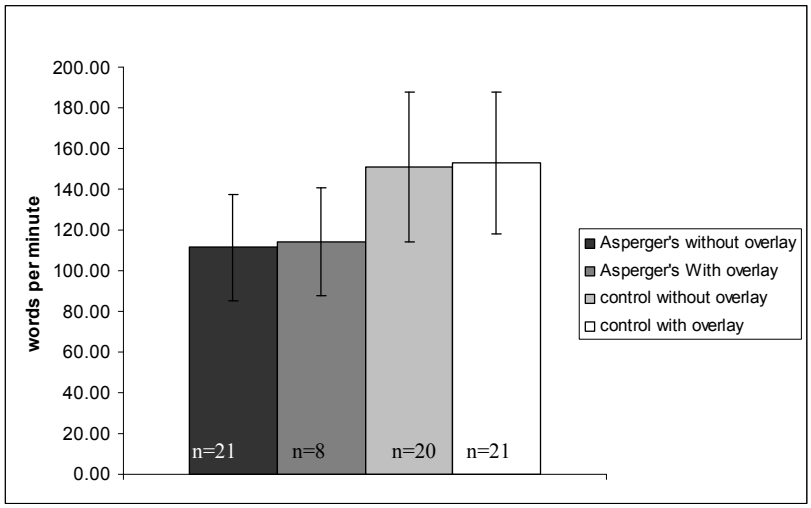


Figure 5.6 Average reading speeds with and without overlay for each group.

5.6. Discussion

Colour of overlay chosen

Other conditions which benefit from the use of tinted lenses may show a leaning towards a particular spectral range of tint, such as epilepsy or migraine (blue and rose lenses respectively) (Good et al., 1991; Takahashi and Tsukahara, 1992; Wilkins et al., 1999). In this investigation, there was no trend in the preferred colour of overlay in Asperger's syndrome. Both the control and Asperger's group had a similar distribution of chosen overlays and, although it seemed as though the Asperger's group had a bias for blue based colours, this distribution was not statistically significant. The preference for blue based colours may be an artefact caused by the relatively small sample size. However, these findings are supported by those of Ludlow et al who also showed no preference for a particular coloured overlay (Ludlow et al., 2006). The findings also agree with previous research in the neurotypical population by Wilkins et al who have found no preference (Wilkins, 2002).

Although it seemed as though a greater number of individuals in the Asperger's group (12/21) elicited a preference for an overlay compared to the control group (8/20), this was also not statistically significant. The control group did, however, show a higher than expected tendency to show a preference for an overlay, this may be however because our control group for this study was not screened for visual stress which may

affect the results. In the general population, it has been shown that around 5-15 % of individuals benefit form a coloured overlay (Wilkins, 2002; Wilkins, 2003). In the present study 40% of the control group stated a preference for a coloured overlay. This does, however, compare well with a previous study by Jeanes et al. who found that initially 50% of children tested reported perceptual benefit from use of an overlay but only 20% maintained use after 3 months (Jeanes et al., 1997). Of the individuals who expressed a preference for a coloured overlay 87% showed an increase in reading speed, 50% had an increase of greater than 5% and this value is considered to be of significant benefit to the individual (this is 20% of the control group as a whole). In the Asperger's group, of the 12 of subjects who expressed a preference for an overlay, 66% showed an increase in words per minute read and 42% an increase greater than 5% (this is 24% of the total group). In comparison with the study carried out by Ludlow et al (Ludlow et al., 2006), the present study showed much less dramatic results. The study of Ludlow et al reported that 79% of the autistic group tested showed an improvement of greater than 5%, compared to 24% in the present study. A finding of 24% showing a significant improvement is still much higher than previous studies have found in the general population (see introduction section 5.1.2). The Ludlow study did have a similar number of participants, but the age range used was quite different. In the present study the mean age of participants was 22 years with a range from 10-45 years while Ludlow et al's study was based on a sample with a mean age of 11 years ranging from 8 to 15 years. The group tested by Ludlow also had formal diagnoses of autism rather than Asperger's syndrome and ranged from normal intelligence to learning disabled, with no separation of the two groups.

An interesting observation was that the ASD group did read, on average, more slowly than the control groups both with (27% slower) and without (26% slower) overlays, despite the two groups being educationally matched. Further research is needed to investigate the basis for this finding, using a different type of rate of reading test or simply repeating the original tests on a further occasion.

5.7. Conclusions

The percentage of individuals who might benefit from the use of coloured overlays, in reading, was no higher in the Asperger's syndrome population, than normal. However, coloured overlay testing could be considered when examining an individual with high functioning autism or Asperger's syndrome as some individuals do appear to benefit. Further study would be useful in this area in order to establish whether these findings are repeatable in a wider population. Expansion of the study would be useful to include a larger sample of the neurotypical participants and to gain a truer comparison group. The current advice from Aston University's Disability advisor service (DANU) is that students with Asperger's syndrome be assessed individually in order to investigate their strengths and weaknesses. These results would suggest that assessment of reading speed with and without coloured overlays would be a useful addition to their assessment.

6. Eye movements and reading in individuals with Asperger's syndrome

Abstract

Purpose: To determine whether the eye movements of individuals with high functioning autism including Asperger's syndrome are abnormal when reading. Any eye tracking abnormalities could help to explain why reading speed is reduced in people with Asperger's syndrome. The influence of font type and colour on reading strategy was also investigated in order to determine how reading strategies could be improved and tailoring advice to individuals, both with and without Autism, on improving their reading comfort and ease. **Methods:** Subjects were divided into two groups; Asperger's syndrome including high functioning autism (n=20, mean age 23 +/- 12 years, range: 10-45 years) and a control group (n=19, mean age 23 +/- 8 years, range 10-48 years). Each subject was instructed to read six passages of sans serif font text (Arial) of different colours (black, white, red, blue and green) plus one serifed font (Times New Roman). Eye movements were recorded using the digital eye trace and the number of fixations, number of saccades and direction of saccades was recorded. **Results:** The colour and font of text did not influence the number of saccades and fixations made by either group when reading. The group with Asperger's syndrome made more positive and negative saccades than the control group ($P<0.05$), except for when viewing blue text which yielded high variance in the results. The percentage of saccades which were recessive was greater in the Asperger's group than the control group ($P<0.05$). **Conclusions:** Individuals with an ASD use a greater number of saccades when reading than non-ASD individuals. This finding may indicate a motor or visual attentional deficit. Individuals with an ASD make more regressive saccades when reading, possibly reflecting initial saccadic inaccuracy. These factors influence reading speed.

6.1. Introduction

6.1.1. Eye movements basics

Eye movements are used in order to acquire, fixate or track a target in the visual field; they may be voluntary or involuntary. Human subjects use two types of voluntary eye movement to track objects of interest; saccades and smooth pursuits.

Saccades

The saccade is the fastest movement of an external part of the human body. The peak angular speed of the eye during a saccade reaches up to 1000 degrees per second and in an average day a human will make around 2 million saccades (Boothe, 2002; Evans, 2002; Snowden, 2006). Saccades are used to bring an object of interest onto the foveal region in order to get the best possible resolution in the interests of object identification. This is done by using a quick jumping eye movement with both eyes moving simultaneously in the same direction. In addition to saccades that bring an object to fixation, bothy eyes are constantly in a state of vibration, oscillating back and forth at a rate of about 60 times per second. These movements are known as "microsaccades". Microsaccades are approximately 20 arc seconds in excursion and are completely imperceptible under normal circumstances (Ciuffreda and Tannen, 1995; Millodot, 1997). They refresh the image being cast onto the photoreceptors at the back of the eye. Without microsaccades, staring at an object would cause vision to cease after a few seconds since rods and cones only respond to a change in luminance. The saccadic system goes through significant development during the first 3 months of postnatal life. Efficient 'adult-like' saccades are only found during or after around 5 months (Grounds, 1996).

Pursuit movements

A pursuit movement is the ability of the eyes to smoothly follow a moving object. Pursuits can be divided into two stages: open loop pursuit and closed loop pursuit. Open loop pursuit is the visual system's first response to a moving object it wishes to track and typically lasts approximately 100ms. In this stage of pursuit, the visual signals have not yet had time to travel through the visual system and correct the ongoing pursuit velocity (Krauzlis and Lisberger, 1994). The second stage of pursuit is called closed-loop pursuit. This stage lasts from 100ms after the initiation of pursuit until the pursuit movement has ceased. This stage is characterized by the online

correction of pursuit velocity to compensate for retinal slip. In other words, when trying to pursue a target, that is getting farther and farther away from the fovea, closed loop pursuit increases the gain of pursuit until you stabilize the image. Smooth pursuit requires the coordination of many brain regions that are far away from each other (primary visual cortex, middle temporal visual cortex, superior colliculus, dorsolateral pontine nuclei, nucleus reticularis tegmenti pontis and cerebellum) (Krauzlis, 2003; Leigh and Zee, 2006; Newsome et al., 1985; Tian and Lynch, 1996). This makes it particularly susceptible to impairment from a variety of disorders and conditions such as autism, schizophrenia, traumatic disorders and Parkinson's disease (Armstrong, 2008; Cegalis and Sweeney, 1979; Cerbone et al., 2003; Hong et al., 2005; Irwin et al., 1999; Ladda et al., 2008; Levin et al., 1982; Lindsey et al., 1978; Marino et al., 2007; Shibasaki et al., 1979; Waterston et al., 1996) .

Dylexia- Defects in pursuits are evident in individuals with dyslexia (Adlergrinberg and Stark, 1978; Biscaldi et al., 1998; Black et al., 1984; Bogacz et al., 1974; Bucci et al., 2007; Eden et al., 1994; Fischer and Hartnegg, 2000; Pavlidis, 1985). This research indictates saccadation of pursuits and Eden et al (Eden et al., 1994) found poor smooth pursuit movements in their dyslexic group, particularly when pursuing a target moving from left to right. It has been suggested, however, that pursuit deficits in dyslexia are most likely to be due to attentional problems, such as attention deficit disorder (ADD) rather than solely dyslexia (Colby, 1991; Evans, 2002). This may explain why some studies have found little difference between eye movements of control and dyslexic populations (Hutzler et al., 2006; Olson et al., 1983).

Neural pathways for pursuits and saccades

The neural pathways for pursuit and saccades show some overlap. Both systems involve a similar set of areas in the cerebral cortex. For saccades, the cortical areas evaluate and update the locations of potential targets and provide motor commands for the saccades. Areas include the lateral intra-parietal area (LIP), the frontal eye fields (FEF's), and the supplementary eye fields (SEF's) (Boothe, 2002; Leigh and Zee, 2006). For pursuit movements, cortical areas are involved in processing visual motion and other control signals necessary for pursuit. Areas include the middle temporal (MT) and medial superior temporal (MST) areas and sub-regions of LIP, FEF, and SEF areas (Boothe, 2002; Leigh and Zee, 2006). Thus, many of the same cortical areas are involved in the control of both pursuit and saccades but each area contains

separate sub-regions for the two types of movements. Oculomotor regions of the cerebellum appear to expertly tweak the commands for pursuit and saccades to compensate for mechanical constraints and to adapt the movements to changing circumstances (Krauzlis, 2005).

6.1.2. Eye movements and reading

When reading a passage of text, our eyes don't simply move smoothly along the line of text and then down to the next line. While reading, the eyes move forward in series of short saccades between fixations; each necessitated by the rapid decline in resolution away from the fovea. Within the text, readers tend to fixate content words i.e. nouns, verbs, adjectives, and most adverbs, which are usually quite long, whilst skipping function words, which tend to be quite short (Rayner and Duffy, 1988). Along the line the eyes occasionally make backwards jumps (regression saccades) in order to re-read the previous text, perhaps to increase comprehension**.** The more difficult the comprehension of the text the more regressions are made (Evans, 2002; Murray and Kennedy, 1988; Rayner, 1998). In normal reading, around 10-15% of all saccades are regressive (Ciuffreda and Tannen, 1995; Rayner, 1998; Solan, 1985). Each saccade is usually around 8 characters in length, regardless of the size of the font, ranging from 1-18 characters. This usually equates to approximately 1 to 2 degrees (min 0.5, max 4). Most of our time reading is spent on interfixation movements rather than the fixations themselves, with over 90% of reading time spent in saccadic movement (Ciuffreda and Tannen, 1995). It takes approximately 200ms to generate a new saccade to re-fixate. The average velocity of this saccade is 800 degrees per second and the average duration of the saccade is 20-50ms (Boothe, 2002). At the end of the line of text, a return is made to the beginning of the next line. This is usually accomplished by a large sweeping right to left saccade, beginning at around 6 characters from the end of the line to the 6th character of the next line, taking around 40-54msecs to complete (Tinker, 1951).

6.1.3. Autism, pursuits and saccades

A detailed review of saccade and pursuit movements in the autistic population can be found in sections 1.7.4.1 and 1.7.4.2. Deficits in saccades implicate a developmental delay, since infant saccadic responses to a single peripheral target have long latency and are frequently in the wrong direction, with a succession of corrective saccades

needed in order to turn the eyes in the correct direction (Duckman, 2006b). Duckman suggests that because the processes underlying attention and perception of the location of objects and decision making are located in cortical areas of the brain, the characteristics of saccades in infants may be the result of immature cortical mechanisms.

6.1.4. Autism, dyslexia and reading eye movements

The link between autism and dyslexia is described in section 5.1.5

6.1.5. Text, colour and readability

It has been shown by several studies that colour can affect reading when an overlay, or lens, is used to alter the colour of the entire field of view, this has been found to be so in groups with ASD (Ludlow et al., 2006; Ludlow et al., 2008) and also those with magnocellular deficits (Chase et al., 2003; Ray et al., 2005). The effect shown by changing the colour of text has been contradictory, some research shows that colour has a significant affect on subjective reading experience (Hall and Hanna, 2004; Humar et al., 2008), whilst other studies have shown text to have little effect on reading (Lin, 2005). A study by Imhof showed that individuals with ADHD benefited from reading text printed onto coloured paper. She suggested that a decrease in visual stress may be an underlying basis for this improvement (Imhof, 2004). It has been stated previously in this thesis that ADHD and autism spectrum disorders share many similarities, therefore it may follow that visual stress cause's abnormal reading performance in ASDs, and individuals might benefit from changing the qualities of text read. No studies have thus far investigated whether colour of text might have an effect on reading in Asperger's syndrome.

6.2. Aims

The first aim of this investigation was to examine the eye movements of individuals with high functioning autism including Asperger's syndrome in order to establish whether or not they are abnormal when reading. By looking at eye movements it can be established whether there are any similarities in eye movement abnormalities which may be common with dyslexia. Any eye tracking problems found may help to explain the findings of the previous chapter, that reading speed is reduced in people with Asperger's syndrome compared to the neurotypical population. The second aim

was to investigate whether different colours or fonts of text could influence the eye tracking strategy used to read. If a specific colour or font of text can improve reading strategy this could be used to give advice to individuals both with and without autism on improving their reading comfort and ease.

6.3. Methods

6.3.1. Sample

Twenty individuals with Asperger's syndrome were recruited for this study control volunteers were matched for educational level and age as explained in chapter 2 (Figure 6.1). The subjects were the same individuals who took part in chapter 5, only one of these individuals was unable to continue onto this study.

	Subjects	Mean age (years)	Age range	Previously diagnosed with dyslexia
Asperger's	20	22 ± 11	10-45	2
Control	19	23 ± 8.01	10-48	1

Table 6.1 Volunteer details

6.3.2. Ethical approval and informed consent

The Aston University Ethics Committee approved the project and all patients were asked for their written informed consent prior to taking part.

6.3.3. Procedures carried out

Eye movements were recorded by a Video Eyetracker Toolbox (Cambridge Research Systems) (figure 6.1). In order to establish that the volunteer was able to read a passage of text at the required distance and difficulty, the volunteer was given an extract of the reading material to view at 40 cm and asked to read this aloud. Children were given a passage of text taken from a children's website and adults a passage from a newspaper (figure 6.4 and 6.5). The subject was then positioned at the eye tracker head rest and lined up for comfort and optimal screen viewing. This position maintained a 40cm working distance from the eye tracker monitor.

Figure 6.1- The digital eye tracker and set up.

Digital eye tracker

An infrared sensitive video camera was used by the digital eye tracker. This imaged the eye, while remaining outside the subject's field of view, using a mirrored glass plate, (see figure 6.1). By measuring the movement of the corneal Purkinje reflections relative to the pupil (figure 6.2) the eye tracker calculates head movement, eye rotation and consequently the direction of gaze. In order to track eye movements accurately, the equipment must be calibrated before recording is initiated. The calibration procedure involved image measurements recorded at a set of known target positions presented on the stimulus display. In the case of the eye tracker this is a series of red spots appearing in 9 locations on a white background. The eye tracker can then accurately monitor where the subject is looking from subsequent measures of pupil and Purkinje image centres while accommodating both eye and head movement's. The eye tracker capture data at a rate of 50Hz and directions of gaze was given relative to the centre of the screen. Results were provided in graphical form (figure 6.3).

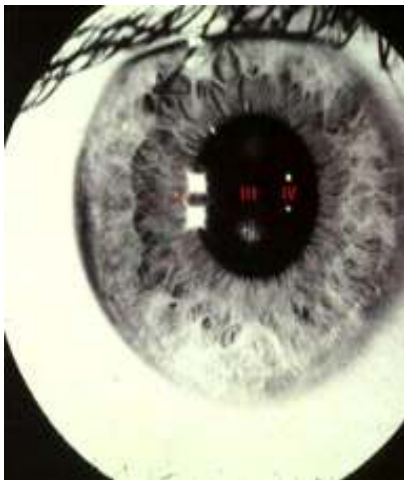


Figure 6.2 Purkinje reflections, from the cornea (I) and crystalline lens (III and IV). Digital eye trace made use of the corneal image only.

After calibration of the equipment, volunteers were shown six sections of text all of equal size, for a period of 20 seconds only. They were instructed to read the text silently as jaw movement could influence the results. Each of the texts was presented in random order to each volunteer and a rest period of 2 minutes was given between presentations.

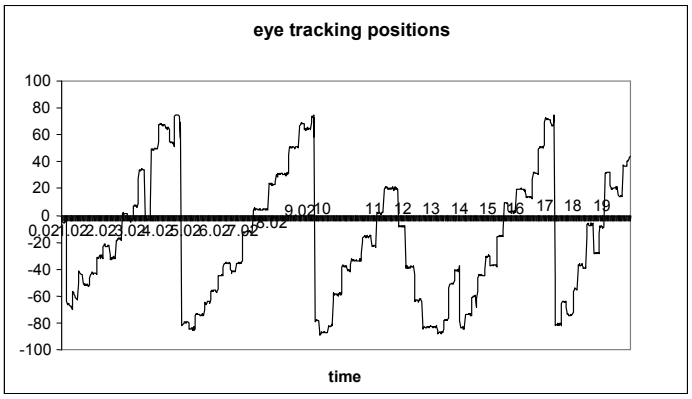


Figure 6.3 Eye trace results for reading in graphical form.

Reading Text

The text size was equivalent to size 13 Arial and 14 Times New Roman in Microsoft "Word" word processing software. The lower case letter width was 2mm and line spacing of 1.5 was adopted. Six samples of text were used (tables 6.2 and 6.3). A serif and sans serif font were chosen since some research has found sans serif fonts are more easily read than serif fonts (Mansfield et al., 1996; Sheedy et al., 2005; Yager et

al., 1998). Wilkins et al. found that, in a study considering autocorrelation of shape within a word, that more "striped" appearing fonts were read more slowly. Fonts which were found to be more striped had a greater level of autocorrelation (put very simply the letters within the word appear more similar to each other), fonts with a serif, such as Times New Roman, had greater autocorrelation and so were read more slowly, although they were preferred subjectively by the study participants (Wilkins et al., 2007). Other studies, however, have found little difference, Arditi and Cho showed that adding or removing serifs from text made no significant difference to reading speeds (Arditi and Cho, 2005; Bernard et al., 2002).

Text colour	Lines of text	Words	Characters
Black	13	179	944
White	7	90	464
Blue	12	166	800
Green	7	90	464
Red	13	179	944
Times new Roman Black	12	166	800

Table 6.2 Adult's text properties

Text colour	Lines of text	Words	Characters
Black	8	87	464
White	8	93	479
Blue	8	87	464
Green	8	93	479
Red	10	104	563
Times new Roman Black	10	104	563

Table 6.3 Children's text properties

Black and coloured text samples were shown against a white background. White text was shown on a black ground. For adults, text used contained paragraphs taken from an article in The Times newspaper feature called "a rich source of health". It was first published on January 7th 2006 (Figure 6.4). For children (under 16) text was taken from the "News round" website accessed October 2006 (Figure 6.5). The same text was used for each subject. The six versions of the text were presented in random order to each volunteer in order to reduce possible effect of practice or length of reading time on eye movements. Text was chosen as an example of reading material found in real life situations. Some studies have controlled the words used in reading tasks on the basis of the shapes created by letter combinations within the words (Wilkins et al. 2007), however in an everyday reading task the content of the subject determines the combination of words and so letters. This study aimed to investigate patterns of eye movement in reading in a more natural setting.

Who'd have thought it? Ten years ago, cod liver oil, herrings and pilchards were all a bit of a nasty, smelly, fish joke. How all that's changed. Oily fish and the omega 3 oils they contain have become the biggest thing in the health-food industry. We have smartly packaged capsules for adults, and fruity omega oil sweeties for children. Omega 3 has been added to all sorts of foodstuffs, including milk, yoghurt and eggs. And as stocks of other fish fall, the humble sardine and mackerel are becoming the darlings of the trendy restaurateur. What has brought about this remarkable turnaround? The answer, for once, is not marketing but a sudden, large amount of good scientific evidence that omega-3 oils, particularly those found naturally in oily fish (also vegetarian equivalents found in flaxseed and rape seed) really do you a lot of good. In three areas in particular, omega 3 seems to make a unique impact: heart disease, joint pain and brain performance.

Figure 6.4 Adult's text

Scientists are buzzing over what they think is the oldest bee ever. The tiny 100-million year old bee was found by the scientists in a piece of something called amber. Amber is what the sticky stuff that comes from trees- called sap- turns into after millions of years. The bee got stuck in the tree sap when it was alive and then died when it couldn't escape. When the sap turned into amber the bee was left inside it. The scientists are really excited about their find because it shows them a lot about how bees have developed over the years. It is thought that millions of years ago there were only wasps but over time some of them turned into bees. This new bee fossil has bits of both buzzing bugs. One of the scientists working on the project said. "This is the oldest known bee we've ever been able to identify, and it shares some of the features of wasps. "But overall it's more bee than wasp and gives us a pretty good idea of when these two types of insects were separating on their evolutionary paths." Bees are able to find their way home to their hive from more than 13Km (eight miles) away, a research team has shown. Researchers took 20,000 bees away room their hive at Newcastle University and then let them loose at other locations to see The scientists put tiny tags on the bees' backs and used a webcam in their hive to record them returning home Bees are really important as they help plants grow but there are fewer of them in the UK than there used to be.

Figure 6.5 Children's text.

6.4. Analysis

The eye movement data were analysed for (1) number of positive and regressive saccades per 100 words, (2) the percentage of saccades which were regressive and (3) the number of fixations per 100 words. Two millimetres was chosen to differentiate saccades from fixation eye movements as this matched the size of each individual character (table 6.4).

Eye Movement Type	Magnitude of Eye Movement
Positive saccade	>2mm
Fixation	>-2mm to <2mm
Negative saccade	<-2mm

Table 6.4 Movement classifications (+ indicates to the right, - indicates to the left).

6.5. Results

Usable data was collected from only 17 of the Asperger's group due to poor concentration and refractive error. Refractive error was a factor since the eye tracker does not track effectively when the subject is wearing spectacles. This meant that each volunteer had to be able to see the text size chosen at the correct distance, uncorrected to take part in the study. This difficulty has been encountered in previous research studies (Kemper and Liu, 2007).

	Successful data collection	Mean age (years)	Age range	Previously diagnosed with dyslexia
Asperger's	17	23 ± 11	10-45	2
Control	19	23 ± 8	10-48	1

Table 6.5 Volunteer details

6.5.1. Positive saccades

In both the control and Asperger's groups there was no statistically significant difference in the number of positive saccades made per 100 words, with differing colour of text and font; P=0.7 (repeated measures ANOVA for each group). The Asperger's group made significantly more saccadic movements than the control group p=0.001, two way repeated measure ANOVA (figure 6.6).

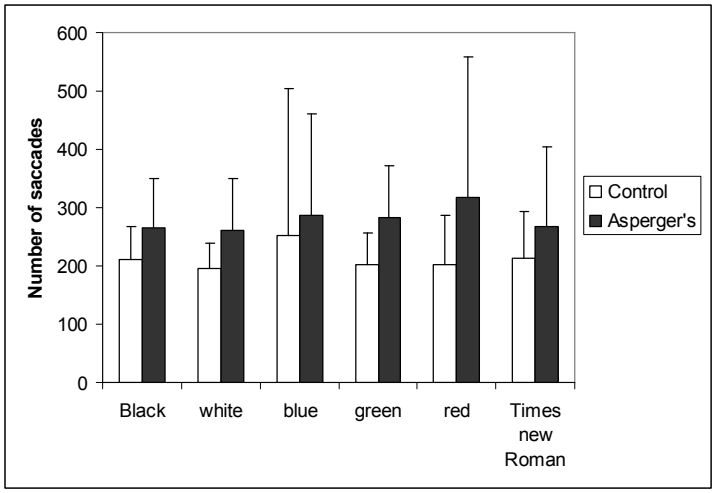


Figure 6.6 Comparison of positive saccades, per 100 words, made by both groups for all conditions, error bars represent ± one standard deviation.

The number of positive saccades per minute was not statistically different between the two groups for any of the colours figure 6.7.

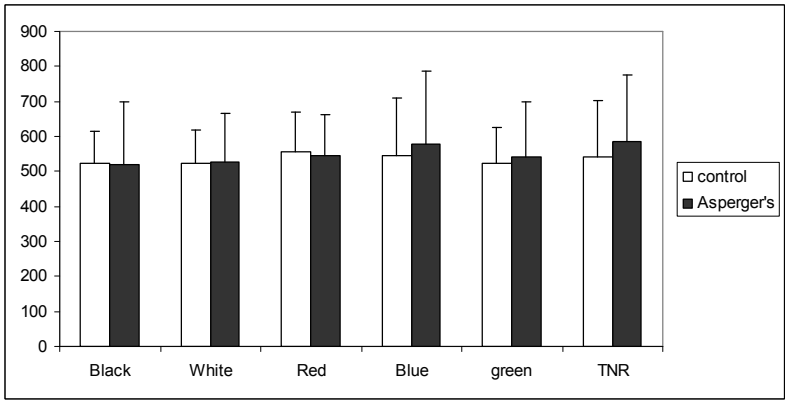


Figure 6.7 Positive saccades per minute.

6.5.2. Negative saccades

The Asperger's group made more negative saccades than the control group for all colours (repeated measures two way ANOVA testing $p<0.001$) (figure 6.8). In common with positive saccades, there was no significant difference in saccades made per 100 words between the text conditions (intra-group) (two way ANOVA $p=0.8$) (Table 6.7).

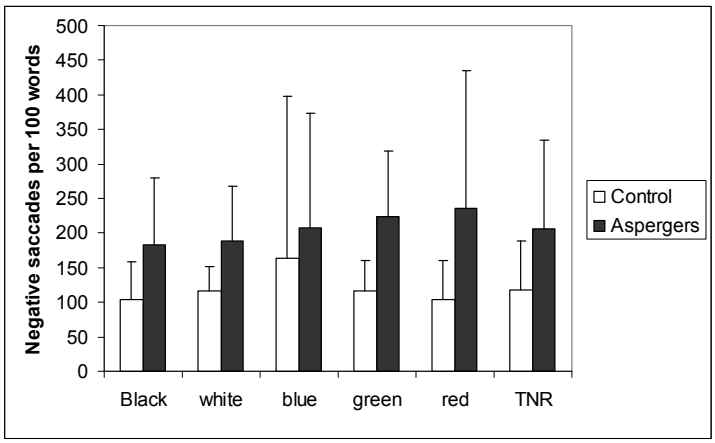


Figure 6.8 Negative saccades per 100 words.

The number of regressive (negative) saccades made per minute was greater in the Asperger's group than the controls as for the number of saccades per 100 words, figure 6.9 (two way repeated measure ANOVA).

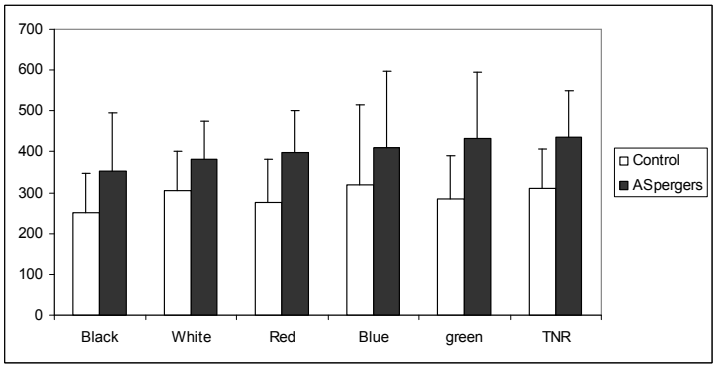


Figure 6.9 Regressive saccades per minute

6.5.3. Percentage saccades which are regressive

The percentage of saccades made which were regressive was higher in the Asperger's group than the control group figure 6.10 (two way repeated measures ANOVA $p<0.001$). The percentage of saccades which were negative was not affected by

colour. Repeated measures two way ANOVA was used to compare the results for colour p=0.1.

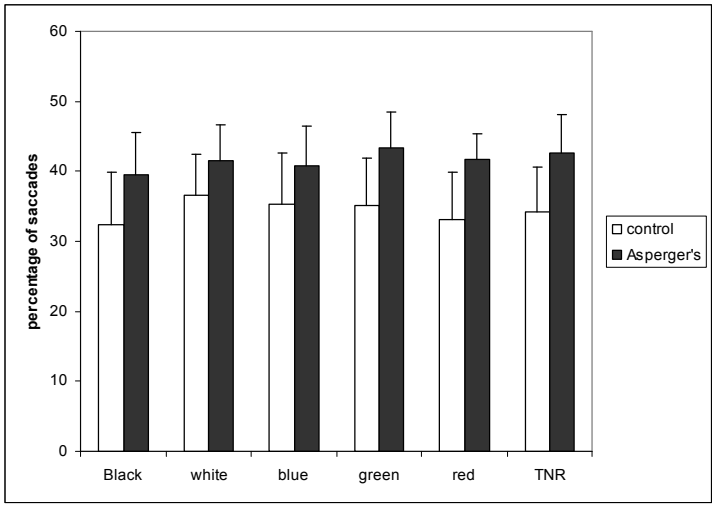


Figure 6.10 Percentage of saccades which are regressive in comparison to total number saccades made.

6.5.4. Fixations

The control group used more fixations than the Asperger's group for all text conditions (repeated measure two way ANOVA p=0.0001) (figure 6.11). Colour and font used did not appear to influence the number of fixations used per 100 words; (repeated measures ANOVA) p=0.3 for both control and Asperger's groups.

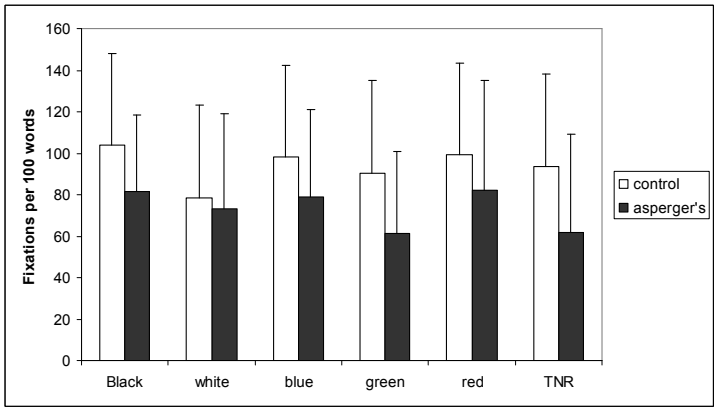


Figure 6.11 Number of fixations per 100 words, comparison for all conditions

6.6. Discussion

The ASD group made a greater number of saccadic eye movements when reading than the control group. The colour of text or presence of a serif (Time New Roman versus Arial) on the letters did not alter the reader's performance. No statistically significant differences of movements were observed between the different text stimuli in either group. This supports the idea that individuals with autism may exhibit abnormal saccadic eye movements. Kemner et al. (1998) reported that children with autism make an increased number of saccades compared to neurotypical children when observing a stimulus (Kemner et al., 1998). This supports the findings of this study. Kemner's study also found that the autism group showed an increase in the number of saccades independent of stimulus type. They suggested that this abnormal pattern of saccades may negatively influence the ability to attend to stimuli, and thereby learning processes. Thus, an increased number of saccades in individuals with an ASD might impair their reading ability/speed.

The increase in saccadic eye movements could arise because of a motor function deficit arising at the level of the cerebellum (Kemner et al., 1998; Quaia et al., 1999) or, as suggested by other authors, a neocortical defect (Minshew et al., 1999). The results of the present study do not rule out either explanation. Van der Geest et al (Van der Geest et al., 2002) argue that since there is a close link between eye movements and visual attention (a shift of visual attention is usually combined with a shift of the point of fixation), autistic children produce more saccadic eye movements than normal controls due to problems in engaging their attention. From our research this seems to be similar in the Asperger's population. This ties in with the previous research on saccades in dyslexia, where it has been suggested that saccadic pursuit deficits are most likely to be due to attentional problems rather than solely dyslexia (Colby, 1991; Evans, 2002).

The percentage of saccades which were regressive was significantly greater in the ASD group for all text stimuli. These values were higher in both groups than expected from the values given in literature (10-15%- (Ciuffreda and Tannen, 1995; Rayner, 1998; Solan, 1985). In the present study, the control group showed a mean percentage regression of 34% and the ASD group had a mean percentage of 42%. These differences could be due to a number of methodological differences. Rayner and

Ciuffreda do not state by which method eye movements were tracked for these figures or whether this is affected by reading silently or aloud. Fixations are affected by this difference, being longer in reading out loud (Rayner, 1998). Ciuffreda and Solan used silent reading techniques but did not have computer software for data analysis. Numbers of saccades were calculated by eye in their study. Due to the way data has been analysed in the present study, some of the eye movement regressions will be very small (i.e. of only one character). They therefore may be smaller measures than those used by Ciuffreda and Tannen who do not state the magnitude of movement which classified a saccade (positive or regressive). Spacing of text is known to affect reading eye movements (Chung, 2002; Chung, 2004; Epelboim et al., 1994) and differences in reading material selections between studies will inevitably influence comparisons. Regressive saccades may be influenced by both perceptibility of words and the qualities of the saccades made during reading (Vitu et al., 1998). All subjects were able to read the words of the text, having been asked to read the text stimuli aloud prior to commencement of testing in order to confirm its legibility to the subject. Therefore the subjects should not have been affected by the perceptibility of the words in the present study. This would suggest that perhaps the increased rate of regressive saccades is related to the higher number of saccades made overall and the inaccuracy of those saccades. In other words, the saccades, if inaccurate, will lead to the need for a regression in order to continue reading. There were some limitations with the design of this study which could be improved in future tests. The perceptibility of words was not formally controlled so some words within the text would be easier to read than others. This is true in a natural reading situation but in comparing the colours of text, some colours may have been, in themselves, slightly more or less easy to read and this may have influenced the regression rate.

6.7. Conclusions

Individuals with an ASD use a greater number of saccades when reading than non-ASD individuals. This finding may indicate a motor deficit, possibly originating in the cerebellum or neocortex, or a visual attentional deficit. People with an ASD make more regressive saccades when reading, possibly reflecting initial saccadic inaccuracy. These factors may influence reading speed in people with Asperger's syndrome which has been demonstrated to be reduced in the previous chapter.

7. The Electro-Oculogram and Assessment of Eye Movements in Asperger's Syndrome

Abstract

Purpose: The aim of this study was to compare eye movements using two different methodologies: electrophysiology using the electro-oculogram (EOG) and optically using the digital eye trace (DET) tracking system. **Methods:** Six subjects who had previously taken part in the study on eye movements using the Digital Eye Trace (DET) volunteered to be tested using EOG. Their mean age was 27± 11 years; range 13-46 years. Each subject read six text stimuli, which were the same as used in the eye trace investigation, presented in random order. Eye movements were recorded using the electro-oculogram. **Results:** Neither text colour nor font influenced the number of saccades or fixations made per 100 words when reading. These findings were concordant with eye tracking using the digital eye trace. The EOG yielded statistically significantly different values from the digital eye trace ($p<0.05$) with greater variance ($P<0.05$). The only parameter where variance was greater in the eye trace was when examining the ratio of negative to total saccades, where variance was low in both techniques. **Conclusions:** Individuals with Asperger's syndrome show no significant difference in their reading eye movement characteristics between texts of the differing colours used or between the fonts of Arial and Times New Roman. The DET eye tracking system is more suitable for measuring eye movements when reading than the EOG method for people with Asperger's syndrome. Results are more precise with the DET. The set up is simpler and the technique is less invasive or discomforting to the subject.

7.1. Introduction

7.1.1. The Electro-oculogram

Emil du Bois-Reymond (1848) (Du Bois-Reymond, 1848) first observed that the cornea of the eye is electrically positive relative to the back of the eye. This potential difference is mainly derived from the activity of the retinal pigment epithelium (RPE) and its responses to retinal illumination. The eye, therefore, behaves as a dipole oriented from the cornea to the retina Corneo-retinal potentials are well established and are in the range of 0.4 - 1.0 mV (E-advisor, 2006; Lam, 2005). It may be assumed that, in constant lighting conditions the corneo-retinal potential is constant. Consequently, it can be used to monitor eye movements since eye movements generate potential differences in voltage which may be monitored from a periorbital electrode. The electrical signal is then amplified and can be displayed on a computer monitor. Horizontal eye movements are recorded from electrodes placed at the lateral canthi (figure 7.1), with a second pair of electrodes placed at the superior and inferior orbital rims to monitor vertical movements and blinks. With the eye at rest, in the primary position, the electrodes are effectively at the same potential and no voltage is recorded. Rotation of the eye to the right causes a difference of potential. Consequently, the electrode in the direction of movement (i.e. the right canthus) becomes positive relative to the second electrode. The change in potential can be displayed against time as shown in Figure 7.2. Typical signal magnitudes range from 5-20 μV/°. When the eyes rotate to the left, a negative potential arises. These changes in electrical potential which arise due to horizontal eye movements constitute the electro-oculogram (EOG).

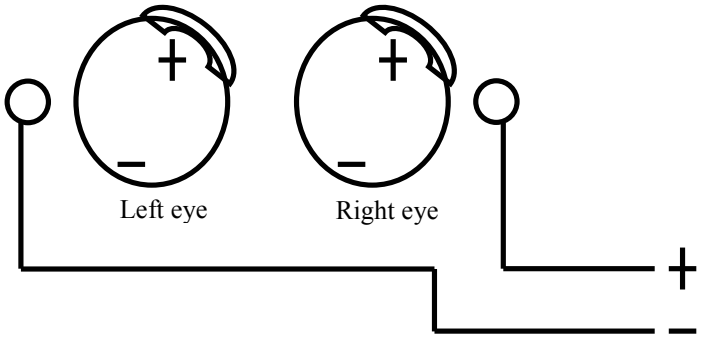


Figure 7.1 Eyes rotate to the right. Right electrode picks up a relative positive signal, the left a negative.

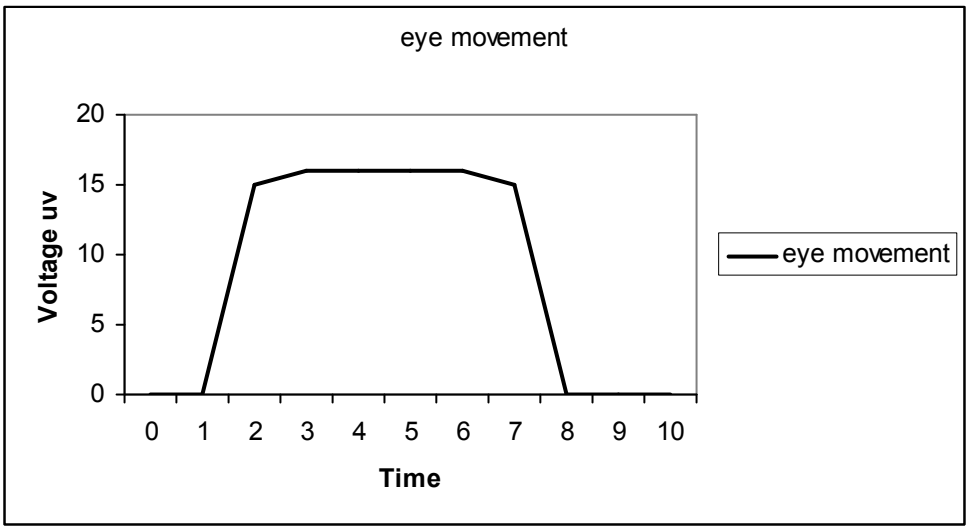


Figure 7.2 The movement shown in figure 7.1 produces a positive trace as above. An equal leftwards movement will produce an equal but inverted (negative) trace.

The signal is calibrated by asking the patient look consecutively at two different fixation points positioned a known angle apart and recording the concomitant electro-oculograms. Clinically achievable accuracies in measurement are in the order of ±2° and maximum ocular rotation of ±70°. Linearity in the response becomes progressively worse for angles beyond 30° (Young and Sheena, 1988). Eye movements measured by EOG are assumed to be conjugate i.e. the visual axes of the eyes remain parallel.

Advantages of EOG

The EOG is an indirect and objective method of recording eye movements. It may be employed when the eyes are open or closed to assess both horizontal and vertical eye movements under any ambient lighting condition. It is relatively easy to set up and does not require bulky instrumentation to be attached to the patients head or in front of the patient, obstructing their field of view. A normal head posture for the patient can be maintained through the testing. Unlike digital camera eye tracking methods, there is no dependence upon the intensity of corneal reflexes which enables spectacles to be used. Indeed, many EOG studies in non-compliant patient groups, such as those with psychiatric problems, have used the EOG in preference to reflection eye tracking techniques (Cegalis and Sweeney, 1979; Iacono, 1988; Levin et al., 1982). Additionally, since no limiting external landmark is used, such as a purkinje image, movements of up to 70º may be assessed, although movements greater than 30º reduce the accuracy of EOG (Ciuffreda and Tannen, 1995).

Disadvantages EOG

Some patients may find the attachment of the electrodes uncomfortable but this should be relatively easily overcome with good preparation and technique. The main disadvantage of the EOG technique stems from the electrodes and their leads which are susceptible to artefact and "noise" arising within the signal from endogenous (facial muscles and blinks) as well as exogenous (external electrical interference) sources. A further disadvantage of the EOG is that the signal strength may be influenced by the eyes adaptation to light intensity which occurs when room illumination changes during the test.

Three studies have shown that the results of digital eye tracking using corneal and electro-oculographic techniques compare favourably, with a correlation of around 0.95 between the techniques (Iacono and Lykken, 1981; Lindsey et al., 1978; Ong and Harman, 1979). However, the close correlations were based on gross indices of tracking performance. Closer inspection reveals events which are evident in the EOG trace but are missing from the reflective trace (Iacono, 1988). These differences may arise from the bioelectric nature of the EOG leading to interference and possible artefacts in the signals.

7.1.2. The Electro oculogram and digital eye tracking in Asperger's syndrome

Abnormal eye movements are found in autism, as described in the previous chapter. The digital eye tracker is a relatively new technology; electro-oculography has been used to look at eye movements for over 50 years (Marg, 1951; Schott, 1922). One study has previously looked at the use of eye tracking technology in comparison to electro oculography (Itoh, 1987). Itoh measured smooth pursuit eye movements and saccadic eye movements in Japanese autistic, learning disabled, and neurotypical young children using an eye camera system and an electro-oculography system. Advantages of the EOG method included high sensitivity and real time data compared to the camera system which required a large amount of time for data processing with relatively poor sensitivity. Both methods were considered appropriate for use with autistic children but selection should depend on the type of autistic child being tested (Itoh, 1987). No studies have directly compared a digital eye tracking system with electro oculography.

7.2. Aims

The aims of this study were to use the EOG to investigate eye movements made when reading a textual passage by individuals with Asperger's syndrome and then compare this method to the Digital Eye Trace tracking system.

7.3. Methods

7.3.1. Sample

	Number	Mean age (years)	Age range (years)
Individuals	6	26.8 ± 11.0	13-46

Table 7.1 Sample details

All of the volunteers with Asperger's syndrome who participated in the investigation of reading using the Digital Eye Tracer were asked to participate in this study. Only six of the participants agreed to take part. This was due to anxiety about the method, the contact electrode placement and wiring up involved. Refractive error was not used as an exclusion criterion since the volunteers were able to wear their refractive correction if needed to view the text. Prior to testing it was ensured that the volunteers were able to read the required text size at the testing distance of 40 cm when wearing their refractive correction.

7.3.2. Ethical approval and informed consent

The Aston University Ethics Committee approved the project and all patients gave their written informed consent prior to taking part, having the opportunity to ask questions and withdraw at anytime should they have chosen to do so.

7.3.3. Procedures

The electro-oculogram equipment was set up and preparation was carried out as per the International Society for Clinical Electrophysiology of Vision (ISCEV) standards and recommendations (Brown et al., 2006). The skin area which the electrode was to be applied was cleaned and dead skin removed using a mildly abrasive soap solution (omniprep). This insured that optimal electrical contact was made between the skin, conductor gel and electrode whilst minimising electrical interference. The room illumination remained constant for 10 minutes prior to and during EOG recording in

order to establish a stable level of retinal activity. Each subject was as relaxed as possible and seated comfortably with both feet on the floor to minimise signals from muscle movements within the body. Electrodes were placed close to the outer canthus of each eye and connected to a differential amplifier. An earthing electrode was placed on the forehead which served as a reference point for the recordings. The impedance between the electrodes was measured and maintained at less than 5kΩ.

Each subject was seated at a viewing distance of 40 cm from the test stimulus. This was the same text stimulus as used in the Digital Eye Trace investigation but with the addition of 2 crosses at the start and end of the text (figure 7.3). Prior to reading the text, the subject was instructed to fixate a cross in the top left corner of the stimulus page and then shift fixation to an identical cross positioned in the top right corner of the page. This movement was repeated for 10 seconds in order to produce a regular saccadic movement before the subject was instructed to begin reading the text. This movement was used to monitor saccadic accuracy and to differentiate between the trace for each text stimulus. At the end of the text, a similar procedure was followed to the start, wherein the subject was requested to initially fixate a cross on the bottom left of the page before moving fixation to a cross on the bottom right.

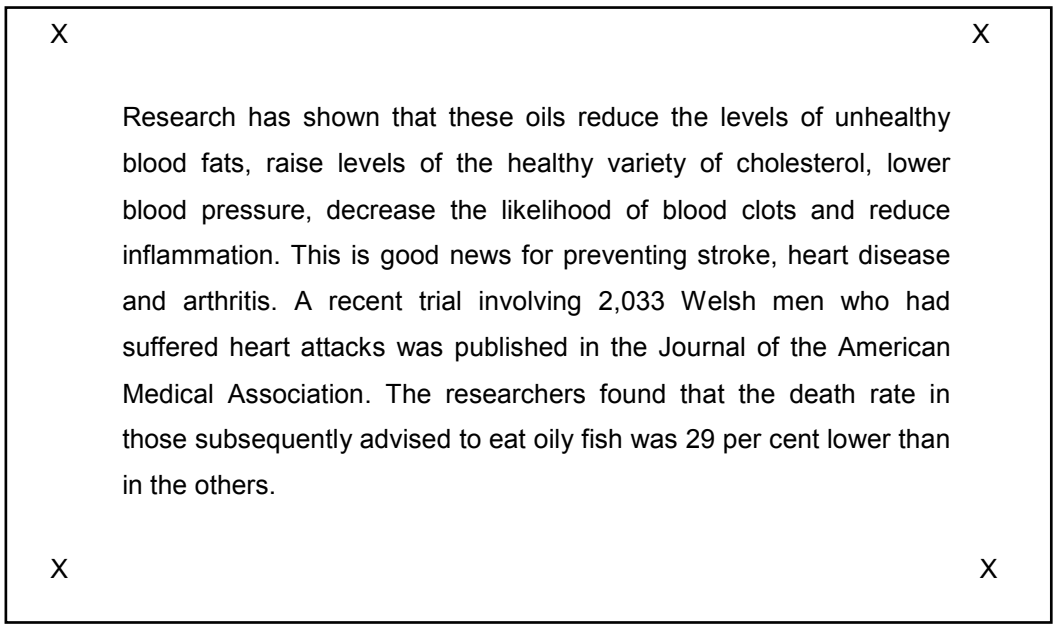


Figure 7.3. Text stimulus used for EOG measurement.

EOG's were recorded for the six text conditions used in the digital eye tracking study (Chapter 6):

- Arial font black
- Arial font green
- Arial font blue
- Arial font red
- Arial font White on black ground
- Times New Roman (TNR) font of equivalent size to the Arial fonts in black.

7.4. Analysis

In common with the digital eye tracking study, the number of positive and negative saccades, the ratio of negative to positive saccades, total number of saccades and the number of fixations were quantified. Saccades were defined in the same way as for the DET analysis (see table 6.4). The EOG data were compared with the outcomes from the digital eye tracking study (Chapter 6)

7.5. Results

There was visibly more "noise" on the trace from the EOG than the Eye tracker (figure 7.4). The noise could have arisen from the preparation itself, the electrodes, the electronic instrumentation (e.g., amplifier) or external sources (50 or 60 Hz power lines, fluorescent lights, video monitors, acoustic noise, and mechanical vibrations

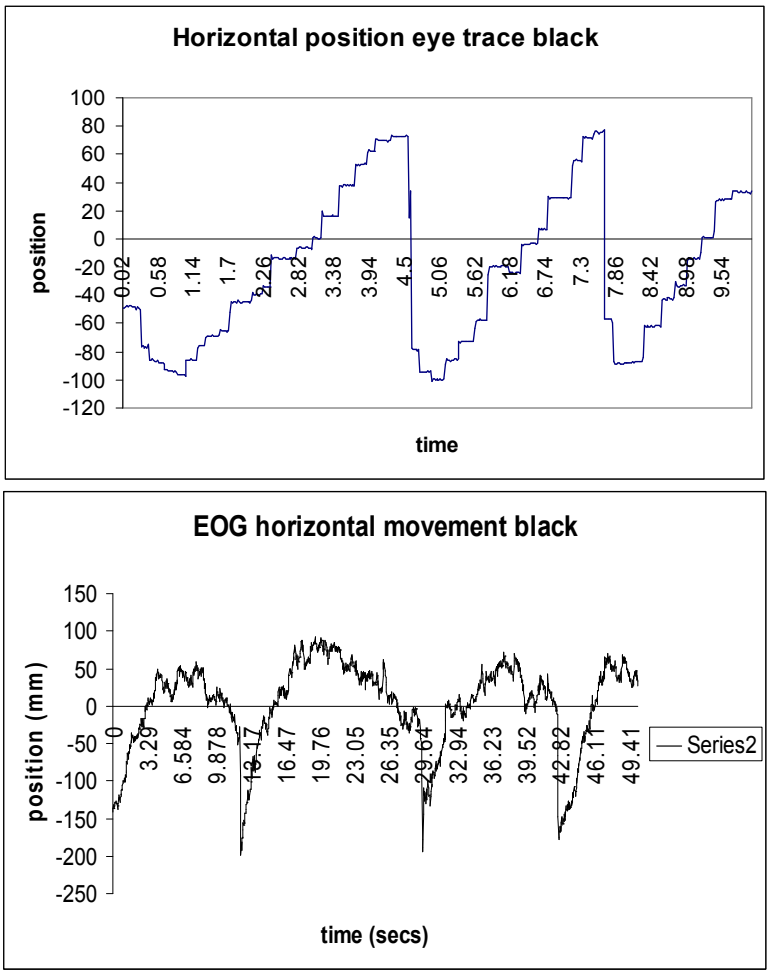


Figure 7.4 Example of trace produced by the different methods in the same volunteer.

Figure 7.5 illustrates a limitation of the digital eye trace method. If the patient is not correctly positioned, the Purkinje images are not picked up by the equipment and the position of the eye cannot be tracked until the reflection is once again picked up. This problem was particularly troublesome when the user was wearing spectacle refractive correction. It is suggested that if the user requires a correction for ametropia or presbyopia then contact lens correction may be more appropriate when using this testing method in order to improve the recording efficiency.

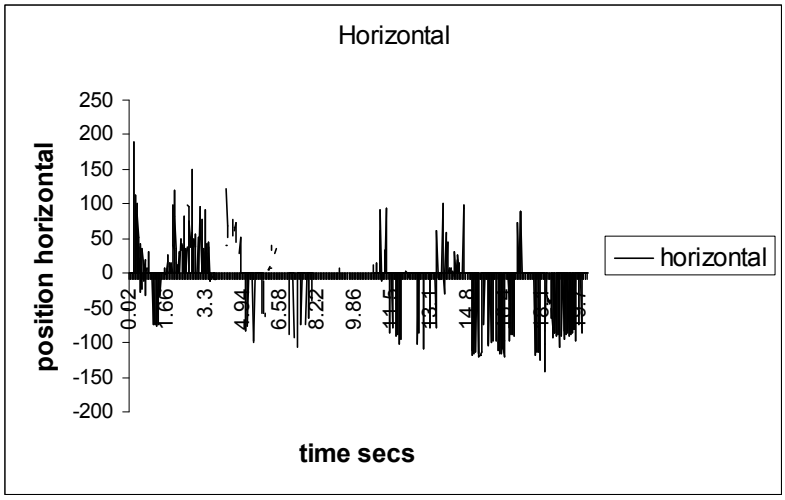


Figure 7.5 Poor trace results from DET, resulting from initial poor set up/calibration, and possibly some lack of compliance.

Figure 7.6 shows a poor trace from the EOG test. This shows the need for accuracy in electrode placement to gain a reliable signal.

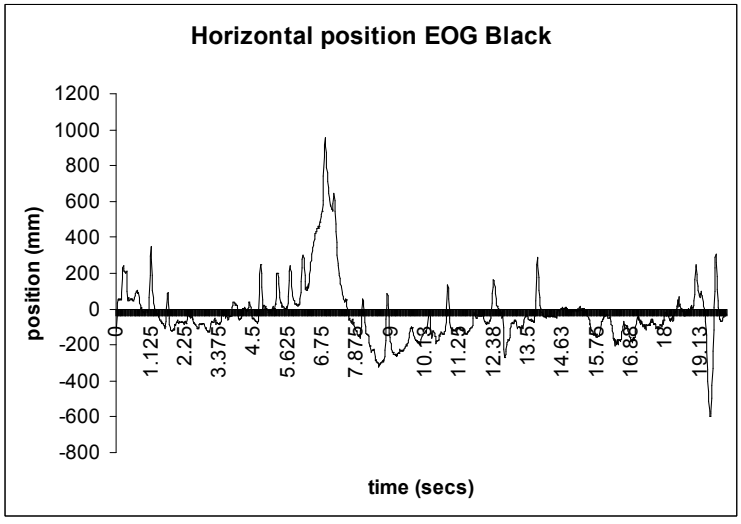


Figure 7.6 Poor recording of EOG example, due to poor electrode placement.

When poor quality data was acquired using the EOG, the patient was reassessed until good quality data was obtained.

Data was found to be normally distributed using Kolmogorov-Smirnov testing.

7.5.1. Number of saccades

There was no statistically significant difference between the number of positive or negative saccades made when reading the different text stimuli (figure 7.7 and 7.8) ANOVA p=0.7 and p=0.8 respectively.

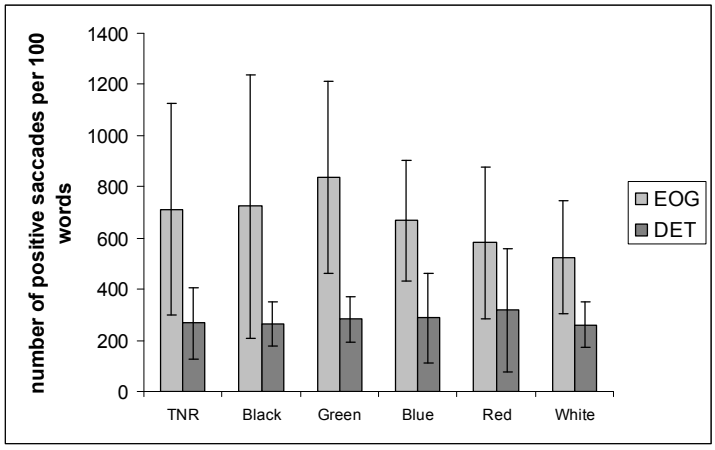


Figure 7.7 Number of positive saccades per 100 words.

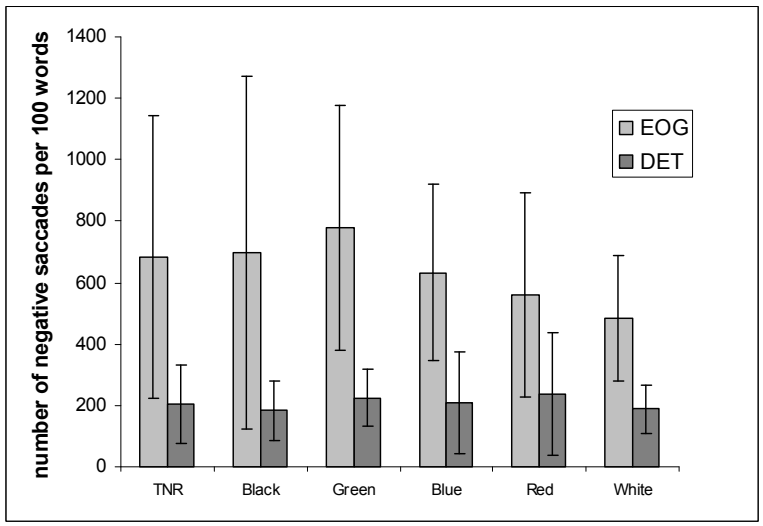


Figure 7.8 Negative saccades per 100 words

Two-way ANOVA shows that there is a statistically significant difference between the results depending on test used (positive saccades $p<0.001$, negative saccades $p<0.001$). This is result is the same whether test data is considered separately as in the two way ANOVA or if data is pooled and a paired t-test performed ($p=<0.001$).

7.5.2. Ratio of negative saccades compared to the total number

The ratio of negative saccades to the total number of saccades did not vary with the colour of text (ANOVA p=0.99), figure 7.9. Analysis of variance testing showed, again, that the EOG yielded a higher ratio compared to the digital eye tracker but followed the same trend. The quality of the text in terms of font and colour did not influence the ratio but the text colour/font did not have a statistically significant influence on variation of results. Individual t-tests of each colour confirmed that the EOG produced a significantly higher ratio of negative: total saccades than the DET method. The variance was greater for the DET when compared to the EOG ($p<0.001$, paired t-test).

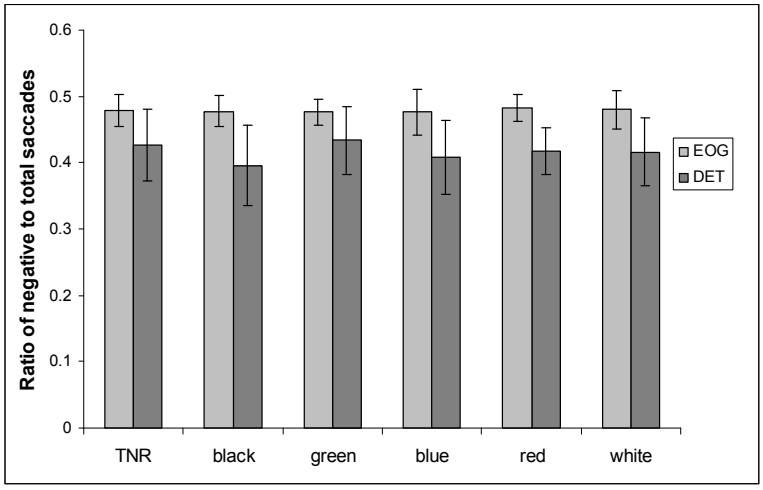


Figure 7.9 Ratio negative to total saccades.

7.5.3. Fixations made

The number of fixations calculated was statistically significantly greater for the EOG compared to the DET, for all colours (two-way ANOVA $p<0.05$) (figure 7.10). There was no significant difference between the number of fixations made for the different colours or font of text (ANOVA $p=0.7$).

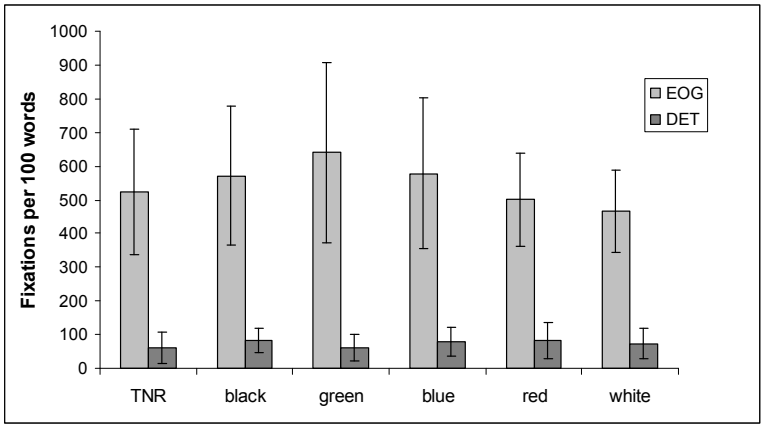


Figure 7.10 Number fixations per 100 words

7.6. Discussion

Although the number of positive and negative saccades recorded using the EOG was greater than that recorded using the digital eye tracking system, the trend in EOG findings was concordant with the digital eye tracker system. There was no difference in the number of saccades or fixations made when reading text of different colours or front. These data suggest that the colour or font of text used does not influence the number of saccades a person makes when reading or the percentage of saccades which are regressive (negative). Since the percentage of negative saccades can be regarded as an indicator of reading ease or difficulty (Ciuffreda and Tannen, 1995; Rayner, 1998; Rayner and Pollattsek, 1989; Stein, 1990), these results show that neither the colour not the font of text influence its readability. This finding is at variance with those of Bernard et al (2003) who reported that the Arial font is subjectively preferable to read than Times New Roman. The present study measured eye movements by objective methods and may explain the difference in findings

There was a discrepancy between the numbers of saccades made per 100 words for EOG compared to digital eye tracking. This could have been due to a number of reasons (1) the spatial resolution of digital eye tracking is greater than in EOG (0.5

and 0.1 degrees respectively) and better accepted by Asperger's patients in a clinical setting due to problems with anxiety and relative invasiveness of the technique. (2) The EOG has a greater temporal sampling frequency (64 Hz in comparison to 50Hz); (3) the text was read aloud in the EOG test and silently in the DET. A good set up for recording and giving the patient precise instructions are essential to obtain high quality recordings using both techniques. To some extent, the "noise" produced in the recording of the EOG could have been reduced by having the patient read silently. This would have eliminated some noise from facial muscle action. However this may have made it difficult to tell when the subject had reached the end of the text stimulus in the EOG method.

All of these factors considered, despite the relative insensitivity in the detection of saccades using the digital eye tracking system when compared to EOG, it is a more useful tool in recording eye movements when reading. The main limitation of digital eye tracking is a slightly decreased peripheral field of view in the eye tracker, due to the brow and chin rest, but the unobstructed field covers the entire monitor screen on which stimuli are presented and is, therefore, adequate for its purpose. The difficulty in assessing patients who wear spectacles could be overcome by fitting the patient with temporary soft contact lenses. Despite the greater sensitivity of EOG in detecting eye movements, this technique yielded a greater variance than those found using digital eye tracking for positive, negative saccades and fixation numbers. Interestingly, the ratio of negative compared to the total number of saccades produced greater variance in the digital eye trace than the EOG, although this was only small in both the normal and Asperger groups. The ratio of negative saccades was similar for all colours using the EOG with an average value of 0.48 (SD 0.02) over all the colours of text, compared to 0.41 (SD 0.05) in the digital eye tracer. These findings suggest that the EOG method may be a less reliable test for measuring eye movements when reading than the digital eye tracking method. Eggert (2007) compared the EOG with video oculography and showed greater recording accuracy using digital eye tracking (Eggert, 2007).

7.7. Conclusions

The colour of text or font used (Arial vs. Times New Roman) does not influence the eye movement characteristics of individuals with Asperger's syndrome when reading. Although the DET system appeared to be less sensitive in detecting saccadic eye movement than the EOG, it yielded results which followed the same trend and with less variance. Thus, DET can be considered as a viable clinical substitute for EOG when examining patients with Asperger's syndrome.

8. Eye Movements When Viewing an Image in Asperger's Syndrome.

Abstract

Purpose: The aim of this study was to investigate how individuals with Asperger's syndrome view static scenes. This would indicate whether there are similarities between Asperger's syndrome and other parts of the autism spectrum which have previously been documented. Any differences in gaze strategies between the normal population and Asperger's individuals could also inform the development of a diagnostic test battery. **Methods:** Subjects were divided into two groups; Asperger's syndrome including high functioning autism (n=19, mean age 22 +/- 11 years, range: 10-45 years), and control group (n=19, mean age 23 +/- 8 years, range 10-48 years). Subjects were asked to view a series of five images of varying characteristics and their eye movements recorded using the digital eye trace eye tracking equipment and software. Patterns of viewing were then assessed by analysing where they had made fixations in the images. **Results:** In the images which contained human faces or social information, the Asperger's group exhibited a statistically significantly different pattern of fixations compared to the control group. In facial viewing the Asperger's group looked less at the eyes and mouth when considered both separately and together than at the rest of the face (ANOVA $P<0.01$). Both groups looked more at the faces than the rest of the image but the control group looked more at the eyes compared to the Asperger's group (ANOVA $P<0.001$). **Conclusions:** Individuals with Asperger's syndrome show abnormal patterns of looking. Although they do look at human figures in preference to the surrounding background detail (neutral objects) there is a lack of interest in the face, in particular the eyes. Face detail viewing in Autism may be a particularly useful avenue for investigating the underlying cause of social communication difficulties in this condition. Eye tracking should be considered as a useful diagnostic tool for the assessment and quantification of the developmental processes in autism and Asperger's syndrome.

8.1. Introduction- Autism and gaze

Individuals with autism exhibit atypical gaze strategies and show reduced eye contact in comparison to the neurotypical population (Baron-Cohen et al., 1996; Boraston and Blakemore, 2007; Dalton et al., 2005; Fischer and Hartnegg, 2000; Sasson et al., 2007; Scharre and Creedon, 1992; Spezio et al., 2007; Trepagnier et al., 2002; Van der Geest et al., 2002; Volkmar et al., 1989). An understanding of how the individual with autism views the world and the strategy they use to process information about the environment around them is important to enable a better understanding of how the autistic mind and brain works. This could lead to a better understanding of communication, one of the key areas of deficit in the autistic population and ultimately how to improve it (Kasari et al., 2008; Paul, 2008). Individuals with Asperger's syndrome exhibit better communication skills than others within the autistic spectrum. Nevertheless, they still exhibit reduced eye contact (Spezio et al., 2007; Tantam et al., 1993).

8.1.1. Abnormal looking and joint attention

Abnormal looking behaviour is a characteristic of autism with a lack of gaze following becoming evident at eighteen months. This is one of the earliest detectable symptoms of an autism spectrum disorder (Baird et al., 2000; Baron-Cohen et al., 1996). Gaze following is evident in children with high functioning autism and Asperger's syndrome but its onset is delayed. (Leekam et al., 2000). Preferential attention to social stimuli in the environment is present in typically developing children from birth (Johnson et al., 1991b). In contrast, a lack of interest in the faces of others is evident in the first 6 months of life in autism spectrum disorder and is one of the best predictors of later diagnosis (Maestro et al., 2002; Osterling and Dawson, 1994; Swettenham et al., 1998).

Normally present at 6-12 months of age, joint attention describes the ability to coordinate attention between people and objects in the environment, (Carpenter et al., 1998). Joint attention is thought to be a precursor of theory of mind (Anderson et al., 2006; Baron-Cohen, 1989) which develops at around 3 years of age (Flavell, 1993; Wellman, 1994). Joint attention is impaired in autism spectrum disorder (Bruinsma et al., 2004; Naber et al., 2008; Warreyn et al., 2005). Theory of mind is one of the best known deficits in autism (Baron-Cohen et al., 1985). A theory of mind deficit means

that individuals would experience difficulty seeing things from any other perspective than their own. It has been suggested that a low level attentional or perceptual impairment may affect the ability of an autistic individual to make a response to another person's eye movements and gaze (Bruinsma et al., 2004; Swettenham et al., 2003; Trepagnier et al., 2002). The evidence for theory of mind deficits is contradictory with several studies finding no difference in response to gaze direction in autism (Okada et al., 2003; Swettenham et al., 2003).

Abnormal looking and gaze behaviour is an indication of abnormal brain development (Boraston and Blakemore, 2007; Koshino, 2005; Nowinski et al., 2005) and is consistent with the hypothesis of disruption during the critical period for typical social and cognitive development. There are important implications for the selection of appropriate interventions. For example, a relationship between the face-recognition difficulties of autism and maladaptive allocation of face gaze suggests that intervention directed at increasing attention to the informative area of the face and teaching how to interpret face borne information may be beneficial (Trepagnier et al., 2002). Abnormal looking behaviour gives important information about how an individual extracts information from a scene, and thus is clinically informative about the cognitive processing of the environment by that individual.

8.1.2. Facial viewing and social viewing

Face perception development in neurotypical populations

For social development, infants must learn to recognise faces. Newborn infants as young as 36 hours may show a preference for 'face-like patterns' (Haan et al., 2001). This recognition process begins to develop at around 3 months and by the age of 4 to 5 months infants will smile at specific faces and cease smiling at strangers (Duckman, 2006b; Frank et al., 2008; Haan et al., 2001). Face recognition undergoes prolonged development which extends into adolescence (Carey, 1981; Chance et al., 1982; Cross and Cross, 1971; Golarai et al., 2006). Recognition performance for newly learned faces improves significantly during childhood, ranging from 50% to 70% of the adult level at age 6 to 14. A dip occurs before puberty. Slower gains occur after 16 years of age. Neurotypical children and adults have developed perceptual processes which can distinguish between faces quickly and accurately, a key skill in socialising.

Face perception in autism

Face processing in autism is discussed in section 1.7.7. Children with autism are significantly less interested in the faces within a scene (Maestro et al., 2002; Osterling and Dawson, 1994; Schultz, 2005; Swettenham et al., 1998). They concentrate less on the eye region and more on the mouth or peripheral regions of face than neurotypical individuals (Chawarska and Shic, 2009; Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002; Trepagnier et al., 2002). They are slower and less accurate at experimental tasks on face perception; relying on 'feature level' i.e. local analysis instead of configural strategies (Schultz, 2005). Conversely, some studies have found little or no difference between the pattern of looking in autism versus controls (Fletcher-Watson et al., 2009; Van der Geest et al., 2002). Van der Geest (2002) investigated face scanning in participants with autism and found normal visual fixation patterns when viewing photographs of human faces. When viewing upright faces with and without emotion both groups made most of their first fixations on the eyes region (Van der Geest et al., 2002). There were also abnormalities shown in facial gaze patterns, but order of facial features observed was not different. Bar-haim et al. (2006) reported no differences in facial feature fixation between neurotypical controls and those with high functioning autism (Bar-Haim et al., 2006). Eye gaze is attended to when it is explicitly relevant to the task given. Thus, the instructions given to the test subject are of key importance in the experimental design and could explain the differences in the findings of Van der Geest, Kemner et al and Bar-Haim, Shulman et al. compared to the rest of the literature (Speer et al., 2007).

Typically developing individuals look at the eyes of others for clues about their mental state (BaronCohen et al., 1997; Kleinke, 1986; Walkersmith et al., 1977). So if individuals with autism spectrum disorders, including Asperger's syndrome use an abnormal gaze strategy when viewing a face, it can provide us with information about communication and social imagination problems experienced within this disorder. This difference in gaze strategy has previously been flagged up as a potential diagnostic tool in autism (Baron-Cohen et al., 2001; BaronCohen et al., 1997). Further investigation into gaze strategy as a whole in this condition could be used to support and develop this suggestion.

8.1.3. Abnormal gaze and hypersensitivity

It has been suggested that hyper-activation in parts of the brain associated with emotion produces an increased sensitivity to social stimuli, leading to diminished gaze fixation (Dalton et al., 2005; Klin et al., 2002; Senju and Johnson, 2009). So, instead of a lack of interest in the face and eyes, perhaps there is so much emotional interest in the eyes (almost too much) that individuals with autism avoid them. A review of literature and full discussion on mechanism of abnormal eye contact in autism was written by Senju (2009). Autistic individuals may have a heightened sensitivity to minute differences in sensory stimuli. Dakin and Frith (2005) suggested that Enhanced perceptual function and the ability of autistic individuals to avoid context may also be associated with this hypersensitivity. The stereotypical behaviours reported by Scharre and Creedon (1992) such as eye pressing, light gazing and repeated blinking during motion processing may also be coping strategies to deal with this sensory overload. Another observed coping strategy behaviour in autism may be lateral glance (this is an atypical visual exploratory behaviour for inanimate objects, looking at things out of the corner of your eye). Autistic children have been shown to exhibit lateral glances towards moving stimuli (Mottron et al., 2003; Ozonoff et al., 2008). Lateral vision is associated with the filtering of high spatial frequency information and also the facilitation of high temporal frequencies. Thus, lateral glancing may be compensatory behaviour aiming to make use of excessive amounts of local information and a deficit in motion perception (Mottron et al., 2007).

8.2. Aims

There is little literature or research which has investigated gaze strategies in individuals with Asperger's syndrome. The aim of this study was to investigate how individuals with Asperger's syndrome view scenes. This will help determine whether there are similarities with other parts of the autism spectrum which have previously documented. Additionally, any differences in gaze strategies between the normal population and Asperger's individuals inform the development of a diagnostic test battery. Digital eye-tracking allows the observation of behaviour and, through the analysis of fixation patterns can indicate which information from a scene is available to the brain. Analysis of the pattern of fixations could help further develop theories based around a local processing bias in Autistic spectrum disorder. In this study, gaze

strategy was investigated for a variety of images in individuals with Asperger's syndrome. Comparisons were made with a control group.

8.3. Methods

8.3.1. Sample

	Subjects	Mean age (years)	Age range
Asperger's	19	22±10.75	10-45
Control	19	23 ± 8.01	10-48

Table 8.1 Sample details

All volunteers (table 8.1) were diagnosed with Asperger's syndrome (including high functioning autism, without learning disability). All had visual acuity of at least 6/7.6 Snellen equivalent, a distance refractive error of less than ±6.00 dioptres of sphere or ±2.5 dioptres of astigmatism. The sample comprised the same individuals who took part in the study for chapter 6 on reading and eye tracking, with two additional volunteers for the Asperger's group who had been unable to attend for that earlier study.

8.3.2. Ethical approval

The study was approved by Aston University Ethical Committee. All volunteers were provided with information about the study in advance of taking part and were able to ask questions. Written consent was provided by all volunteers at the time of participation.

8.3.3. Procedures

Five pictorial images of different scenes were selected with varying characteristics of colour, content, social scenario and possible familiarity. Images were chosen on the basis of these differences from the digital eye tracker and optometry department image bank. The images were shown in a random order to each volunteer.

The Digital Eye Trace eye tracking equipment (described in chapter 6) was used to monitor gaze pattern and fixation for each image. The pictorial images were presented

for 10 seconds each. This was followed by a rest period of 30 seconds to 1 minute between presentations to minimise patient fatigue or discomfort.

Image 1- Painting of a Coronation Scene.

This image (figure 8.1) was chosen as an example of a non-photographic image of a social scene featuring images of people, faces and details of interest (table 8.2)

Figure 8.1 Stimulus 1- taken form the picture library of the digital Eye Trace, eye tracker

Locations of interest within the image	**Category**
faces	Human
torso's	
flags	Non Human
shields	
canopy	
stairs	
throne	
other- including floor area and unoccupied wall area	

Table 8.2 Locations within the image for fixations

Image 2- Glasgow street scene

Image 2 was chosen as a photographic social scene which contains no faces. Human figures are seen from behind and there are other objects of interest (figure 8.2 and table 8.3).

Figure 8.2 Image 2- Glasgow taken from the eye trace image library.

Locations of interest within the image	**Category**
People	Human
banner tartan length	Non Human
banner crown	
large building roof	
large building windows	
Column base	
Column statue top	
other/trees/sky	

Table 8.3 Locations within the image for fixations

Image 3- Optometry reception

This is an image of the Optometry Department reception area at Aston University showing where the volunteers who participated in the study entered the building. Thus, this image can be considered as a recognisable environment to the volunteer (figure 8.3 and table 8.4).

Figure 8.3 Optometry reception

Locations of interest within the image	**Category**
faces	Human
Torso	
blue door	Non Human
glass door	
computer	
lights	
chairs	
object on desk	
phone	
exit sign	
other	

Table 8.4 Locations within the image for fixations

Image 4- Optometry clinic dispensing area

This image was also recognisable to the volunteer. It features objects of interest in the background of the image and social interactions between people (figure 8.4 and table 8.5).

Figure 8.4 The dispensing area of the optometry department.

Locations of interest within the image
faces
torso
clock
spectacles/frames
external window display
object on desk
object outside window
Other

Table 8.5 Locations within the image for fixations

Image 5- Two women looking into a camera

This image comprises of the faces of two people looking directly into a camera thereby simulating eye contact figure (8.5 and table 8.6).

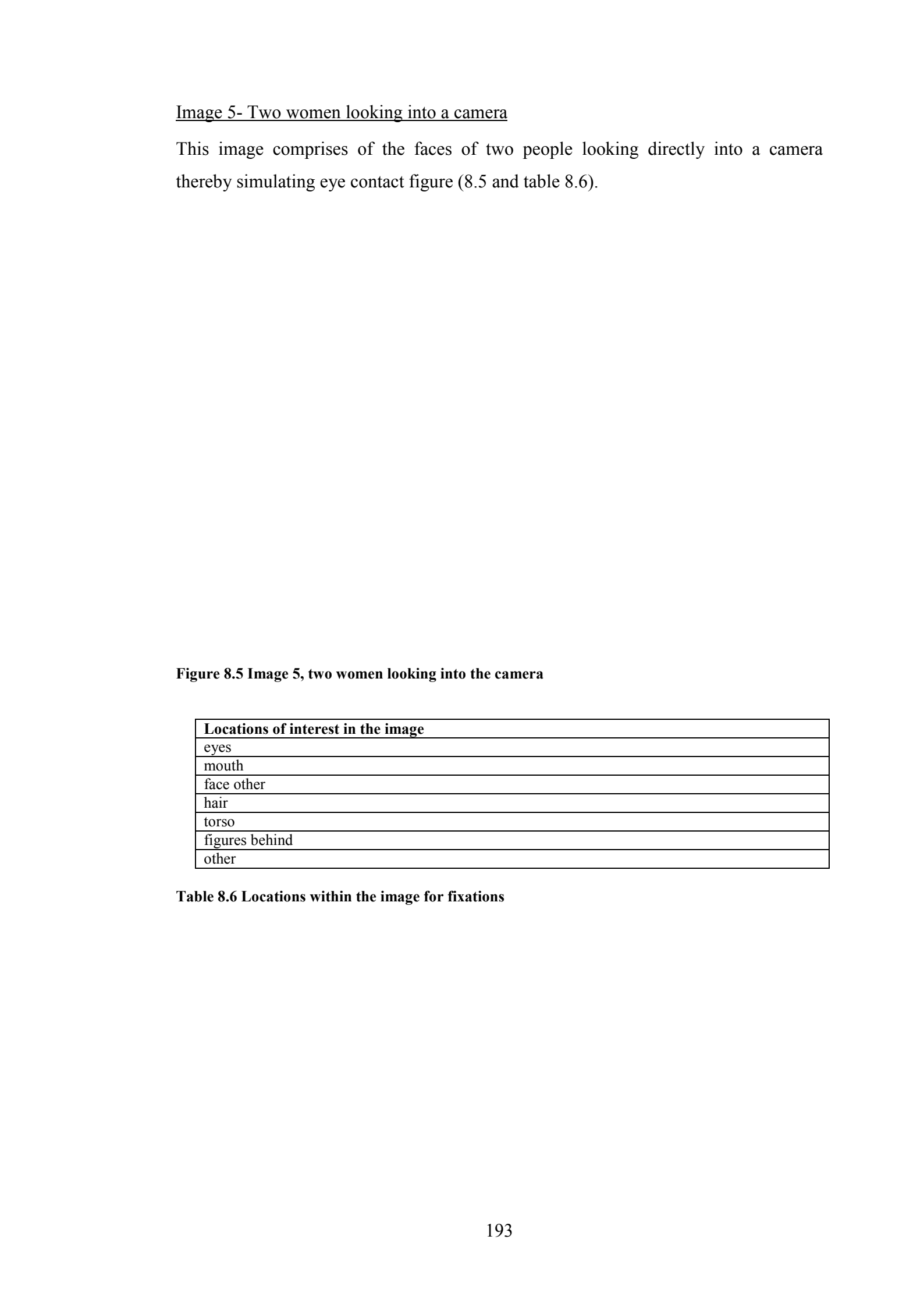


Figure 8.5 Image 5, two women looking into the camera

Locations of interest in the image
eyes
mouth
face other
hair
torso
figures behind
other

Table 8.6 Locations within the image for fixations

8.4. Analysis

The “mimic image” viewed by each participant for each of the presented images was saved for analysis. This is a minified version of the image with superimposed gaze trace and fixations represented by circles (Figure 8.6).

Figure 8.6 Mimic image of Glasgow stimulus-viewed by a normal control

For each image stimulus, a set of locations of interest in the picture were chosen. For each chosen location the number of fixations was recorded and also expressed as a percentage of the total fixations for that picture. A fixation was recorded where the point of gaze remained within 1 degree of visual angle for at least 100 milliseconds. This definition of fixation has been used previously (Van der Geest et al., 2002) and represents the median value of other measures of fixation (Dalton et al., 2005; Snowden, 2006).

8.5. Results

8.5.1. Image 1 Painting of a coronation scene.

Data was found to be normally distributed (Kolmogorov-Smirnov test). Figure 8.7 shows a sample mimic image from a normal control and an individual with Asperger's syndrome.

Figure 8.7 Example of control (left) and Asperger's (right) fixations for image 1.

The control group fixated more on the faces within the scene than any other single aspect (ANOVA $p<0.05$, with Bonferroni post-hoc testing) figures 8.8 and 8.9. They also fixated more on human figures than the background details (all non-human objects) $P<0.001$. In common with the normal control group, the Asperger's group looked at the human figures more than other aspects of the scene (ANOVA $p=0.047$). However, there was no significant difference between the percentage of fixations on faces from the rest of the body (ANOVA $p>0.1$). The control group more often looked at faces compared to the Asperger's group (ANOVA $P=0.002$). Conversely, the Asperger's group used a higher percentage of fixations looking at torsos than the control group (ANOVA $p=0.03$).

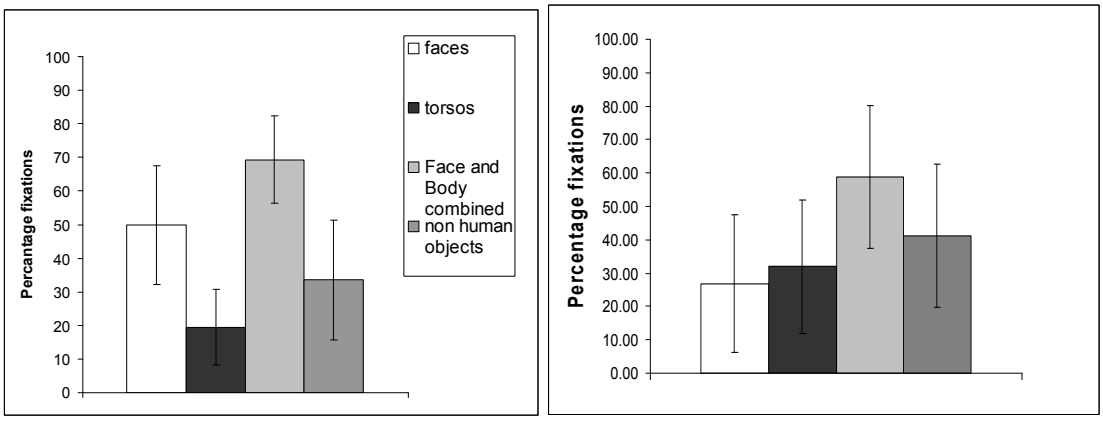


Figure 8.8 Fixations; control (left) and Asperger's (right)

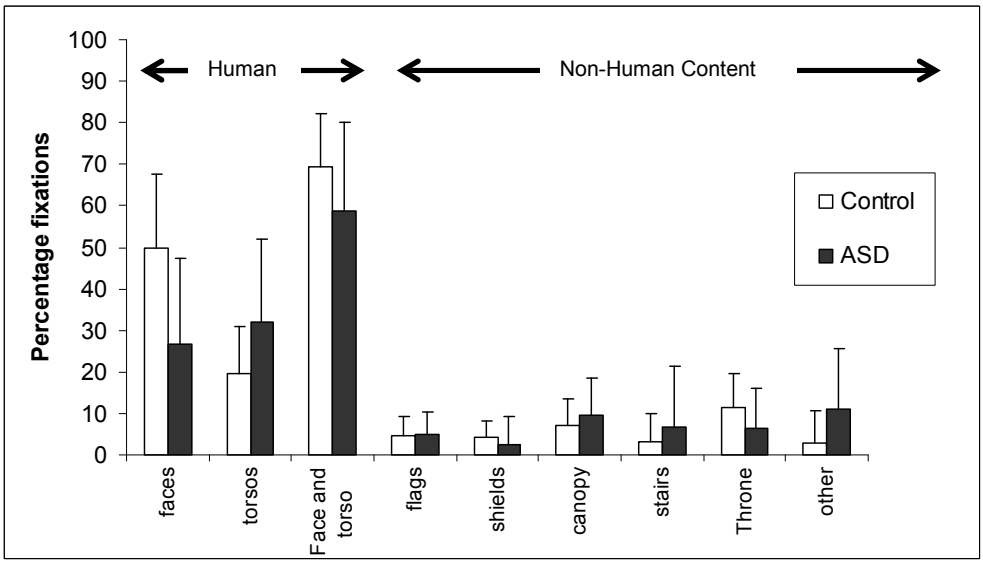


Figure 8.9 Comparison of the two groups fixation patterns

8.5.2. Image 2- Glasgow street scene

Figure 8.10 shows a sample mimic image from a normal control and an individual with Asperger's syndrome.

Figure 8.10 Example of control (left) and Asperger's (right) fixations, image 2.

Both groups spent most time fixating on the large building (mostly the windows) in the background of the image and the people within the image (ANOVA with post-hoc Bonferroni testing, $p<0.05$). The patterns of fixation for this image were very similar between groups (figure 8.11). There was no statistically significant difference in the percentage of fixations used to look at people between the two groups (ANOVA P=0.53).

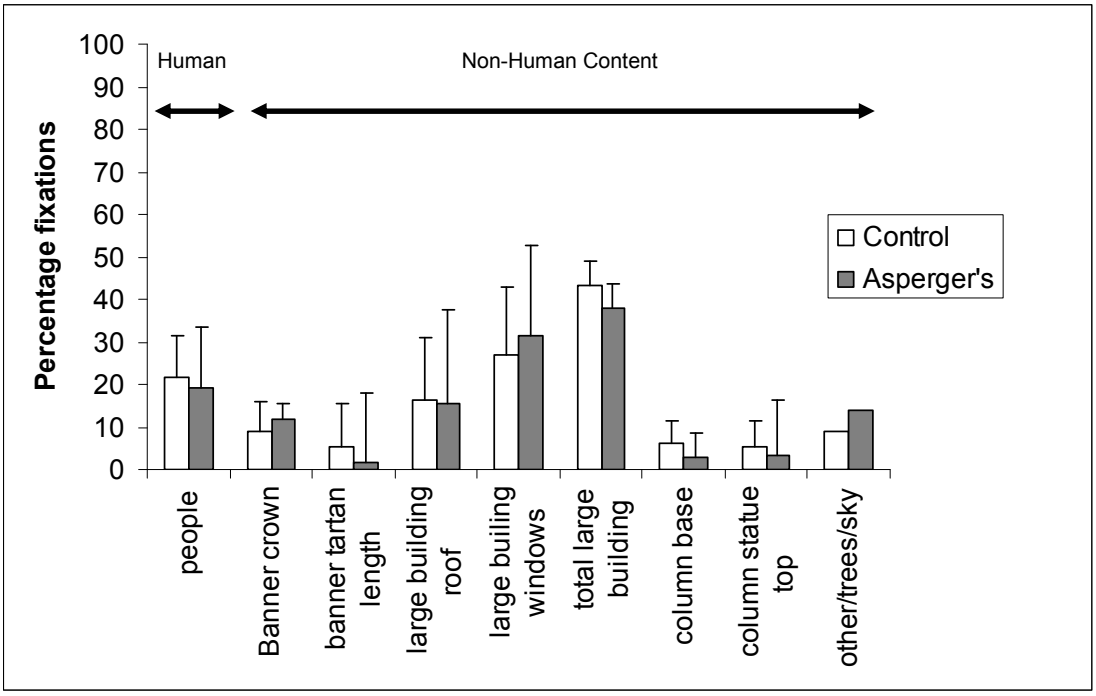


Figure 8.11 Comparison of the 2 group's viewing patterns

8.5.3. Image 3- Optometry reception

Figure 8.12 shows a sample mimic image from a normal control and an individual with Asperger's syndrome.

Figure 8.12 Example of control (left) and Asperger's (right) fixations, image 3.

The control group made a statistically significantly higher percentage of fixations on the people within the scene than other details. They also made statistically significantly more fixations on the faces than torsos (ANOVA plus post hoc analysis $p<0.05$) (figure 8.13). The control group looked significantly more at the faces of the figures within the image than at their torso's and overall looked more at human content (ANOVA testing $p<0.001$ in both cases) figure 8.14. There was a statistically significant difference between the percentage of fixations made on different features by the Asperger's group (ANOVA $p<0.001$) (figure 8.14). In this case the non face areas of the figures were looked at most. The Asperger's group used a higher percentage of fixations observing the people in the image, but used more of these fixations on the torso than the face (both ANOVA $p<0.001$). Figure 8.14 shows the average percentage of fixation spent looking at faces and bodies are almost exactly inverse between the control group and the Asperger's group.

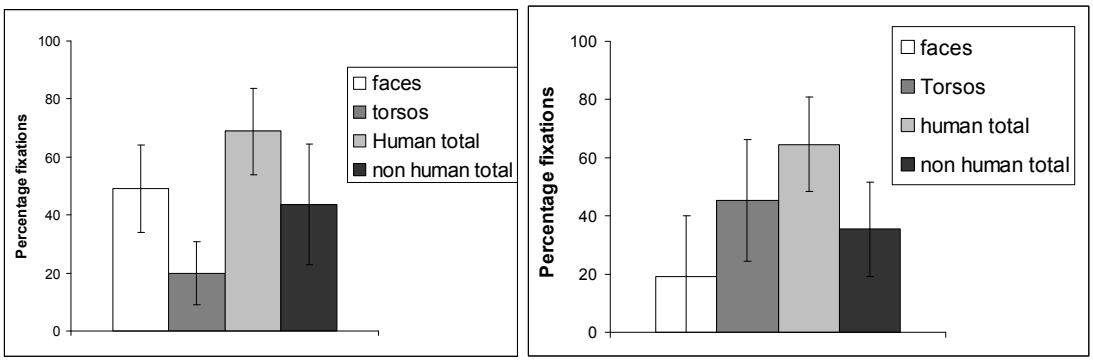


Figure 8.13 Image 3 optometry reception area control (left) and Asperger's (right)

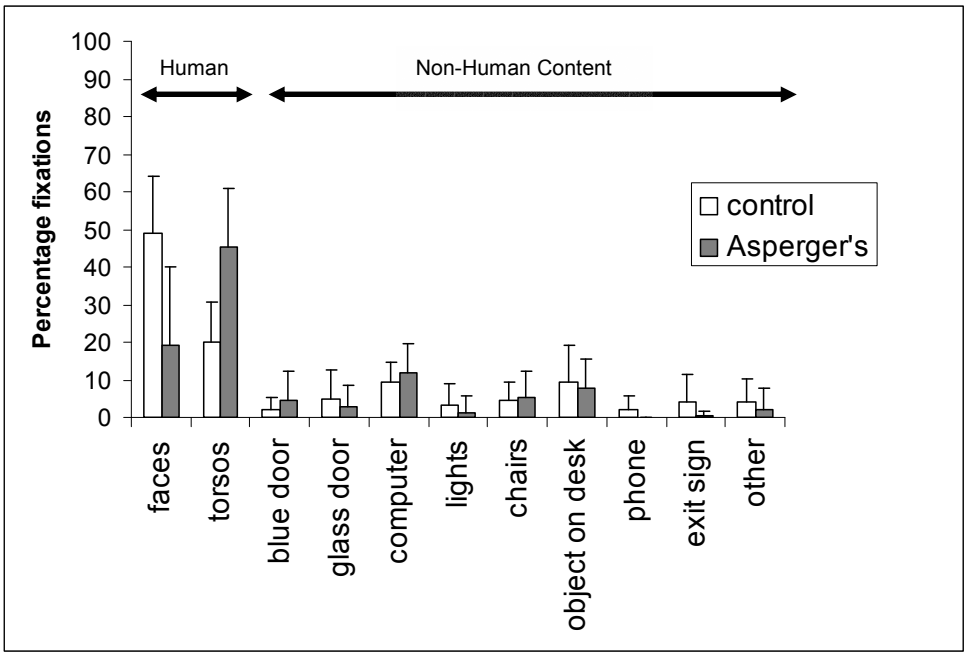


Figure 8.14 Group comparison results for image 3.

8.5.4. Image 4- Optometry clinic dispensing area

Figure 8.15 shows a sample mimic image from a normal control and an individual with Asperger's syndrome.

Figure 8.15 Example of control (left) and Asperger's (right) fixations, image 4.

The percentage of fixations were similar between torsos and faces for this image (ANOVA $p=0.95$), and the percentage of fixations made for human content was greater than the other features (ANOVA $p<0.01$) figure 8.17. The Asperger's group yielded a statistically significantly lower percentage of fixations for the faces within the image than the torso (ANOVA $p<0.001$) (figure 8.16). The control group yielded a statistically significantly higher percentage of fixations on the faces within the image

than the Asperger's group (ANOVA p=0.003), although both groups looked more at the figures in the image than the background detail (p<0.001 ANOVA) (figure 8.16).

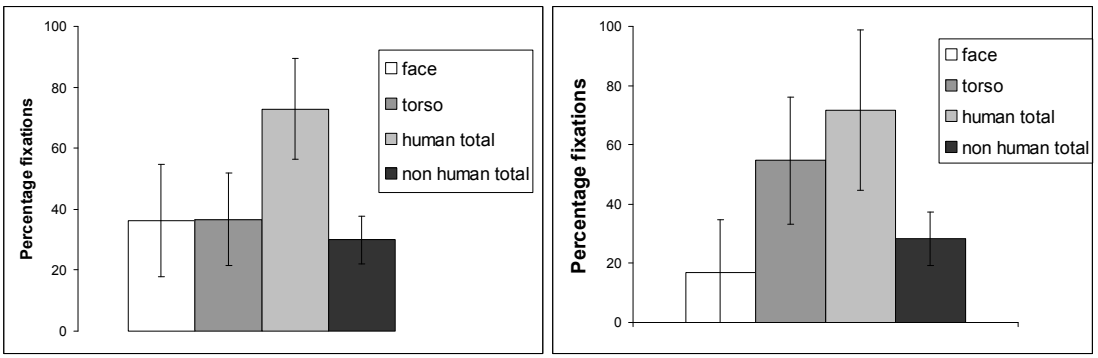


Figure 8.16 Image 4, Fixations to dispensing area; control (left) and Asperger's (right)

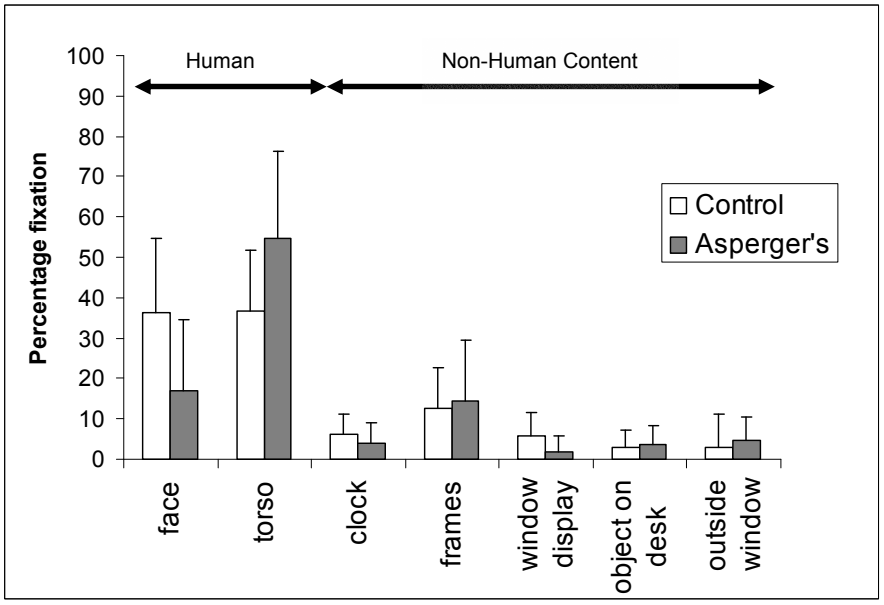


Figure 8.17 Comparison of the groups image 4

8.5.5. Image 5- Two women looking into camera

Figure 8.18 shows a sample mimic image from a normal control and an individual with Asperger's syndrome.

Figure 8.18 Example of control (left) and Asperger's (right) fixations, image 4.

In the control group, most fixations were on faces in the image (ANOVA with post hoc Bonferroni testing $p<0.05$). There was no statistically significant difference between the observations of the facial features Figure 8.19 (ANOVA $p=0.09$). The Asperger's group did not use a higher percentage of fixations on the face than other areas of the image (figure 8.19) and within face fixations were different to the control group. The Asperger's group looked less at the eyes and mouth when considered both separately and together than at the rest of the face (ANOVA $p<0.01$). The control group looked more at the eyes in comparison to the Asperger's group (ANOVA $p<0.001$). The difference in fixations on the mouth in both groups was not statistically significant. The Asperger's group fixated the torsos of the figures to a greater extent than the control group (ANOVA $p=0.002$).

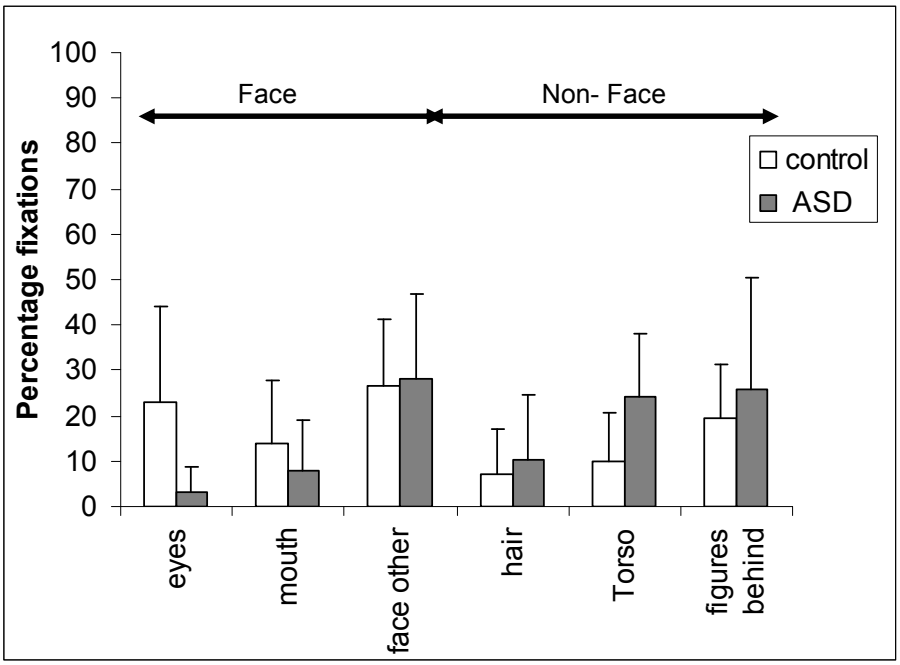


Figure 8.19 Comparison of the two groups for image 5

8.6. Discussion

These findings agree with previous research on individuals who are on the autistic spectrum (Boraston and Blakemore, 2007; Dalton et al., 2005; Pelphrey et al., 2002; Speer et al., 2007; Trepagnier et al., 2002; Van der Geest et al., 2002). This abnormal looking behaviour not only suggests an abnormal brain function and possible disrupted development but it also yields important information about how an individual draws information from a scene and how they process the world around them.

In the images selected with visible faces and social context (image 1, 3 and 4) the Asperger's group looked at the human figures more than background details. This supports previous research by Van der Geest et al (2002), who found that children with Asperger's showed a preference for social objects (human figures) within an image in the same way as neurotypical children (Van der Geest et al., 2002). These findings are still in evidence in Asperger's adults, according to the findings of the present study. Also, the group with Asperger's syndrome yielded a lower percentage of facial fixations within these images, spending more time instead on the non-facial regions of the human figures. These findings support those reported previously (Maestro et al., 2002; Osterling and Dawson, 1994; Shultz, 2005; Swettenham et al.,

1998; Trepagnier et al., 2002) that people with an autism spectrum disorder look less at faces than controls. These previous studies have mainly looked at groups of children, of varying levels of developmental delay (or lack of) rather than adults. The current study shows that this difference in attention or gaze strategy holds true in adulthood. This is supported by a smaller study by Trepagnier et al who found similar results in their 5 adult participants (Trepagnier et al., 2002).

Fixations to image two, the Glasgow scene, showed that the observers of both groups looked at the large buildings more than the people in the image. This could be due to the scale of the scene. The figures within are small and there is no particular social focus or common activity of the people. There were no faces visible within the image so less social information was to be gained form the figures. The large building dominates the scene overall. This suggests that in a scene with little social information to be gained, a group with an autism disorder will look in a similar way to a neurotypical group.

Image 5, of two people looking into the camera was selected to asses in more detail than the other images, facial viewing strategies. Results support the suggestion that people with Asperger's syndrome use less eye contact than the neurotypical population. This finding may support the suggestion that individuals with Asperger's give less eye contact due to a hypersensitivity which makes the eye contact uncomfortable for that individual (Dalton et al., 2005; Klin et al., 2002). It also supports previous research which has found differences between the looking patterns of controls and those with autism, when looking different aspects of faces, the eyes being fixated less than other facial aspects. Some research has shown that individuals with autism look less at the eyes of the figures than other regions (Dalton et al., 2005; Klin et al., 2002; Pelphrey et al., 2002). Klin *et al.* (Klin et al., 2002) found that individuals with autism looked significantly longer at the mouth region than control subjects. In contrast, the findings of the present study did not yield a greater percentage of fixations when looking at the mouth than eyes. These findings agree with studies performed by Dalton et al. (Dalton et al., 2005). Bar-Haim et al (Bar-Haim et al., 2006) found both groups (high functioning autism and control) looked more at the eyes than other facial areas initially, as did Van Der Geest et al (Van der Geest et al., 2002). They suggested that the abnormal viewing behaviour might be due

to avoidance or to lack of interest in the eyes region at later, more controlled stages of processing, which may indicate hyperactivation of the amygdala associated with an emotional response, as mentioned by Dalton *et al.* (2004).

8.7. Conclusions

Individuals with Asperger's syndrome show abnormal patterns of looking. Although they do look at human figures in preference to the surrounding background detail (neutral objects) there is a lack of interest in (or perhaps an aversion to) the face, in particular the eyes. The typically developing individual looks at the eyes of others for a source of social information and a large amount of non-verbally given communication. Abnormal gaze behaviour of people with autism and Asperger's syndrome may, therefore, contribute to the impaired ability of these individuals to process social information and non-verbal communication. Eye tracking should be considered as a useful diagnostic tool for the assessment and quantification of the developmental processes in autism and Asperger's syndrome.

The viewing of face detail viewing in Autism may be a particularly useful avenue for investigating the underlying cause of social communication difficulties in this condition. An extended study of different facial types over a larger population sample may provide further insight into interventions directed at (1) increasing attention to the informative area of the face and (2) teaching how to interpret face borne information.

9. The Electroretinogram in Asperger's: a Case Study

9.1. Introduction

9.1.1. The Electroretinogram

Electrophysiological testing of patients with retinal disease began in clinical departments in the late nineteen forties. The electroretinogram (ERG) is a technique that measures an electrical action potential recorded at or near the cornea, when retinal cells are activated by a flash of light. The recorded electrical activity reflects the complexity of the retinal network (Figure 9.1). The photoreceptors (rods and cones) are connected to bipolar cells (second-order neurones), ganglion cells (third-order neurones) and two types of inter-neurones called horizontal and amacrine cells. Surrounding these neurones are the structurally unique glial cells (Müller cells). The distribution of the bipolar cells and the ganglion cells are similar to that of the cone photoreceptor in that their density peaks at the fovea centralis. The ERG is a combination of activity of different cells within the retina but in predominantly the middle and outer layers (Rudduck, 2006).

The basic method of recording the electrical response is the global or full-field ERG. This is produced by stimulating the eye with a bright light source such as a flash. This light stimulus is produced by a Ganzfeldt stimulator where the light output reaches 2×10^{6} cdm^{-2} in order to achieve maximum response amplitudes. A full field dome stimulator (the ganzfeldt) is preferable to an ocular diffuser since with the diffuser it is difficult to measure and control the extent and intensity of retinal illumination.

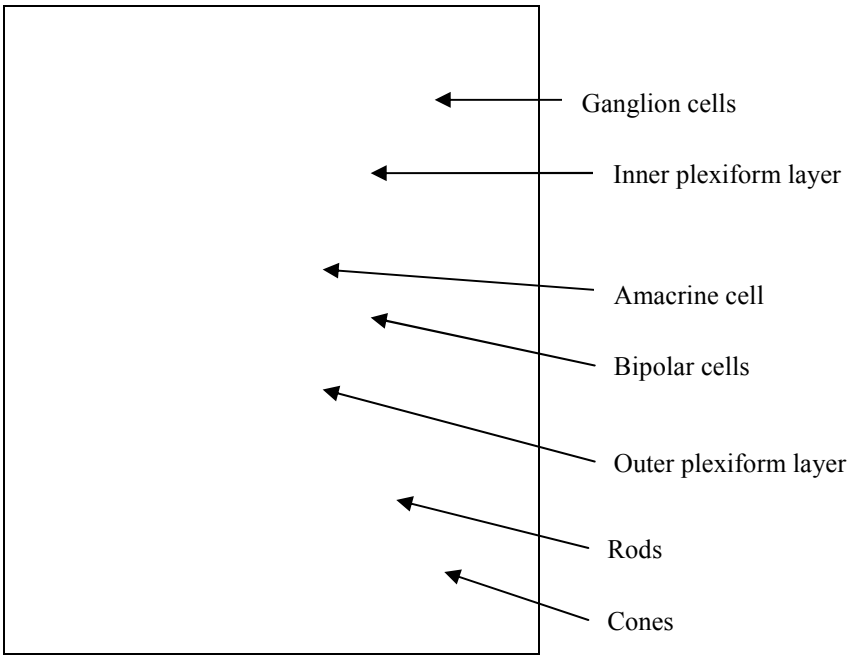


Figure 9.1 Layers of the retina- arrow indicates direction of light.

9.1.2. The Global/full field electroretinogram

The wave form

The flash of light produces a biphasic waveform similar to that illustrated in figure 9.2.

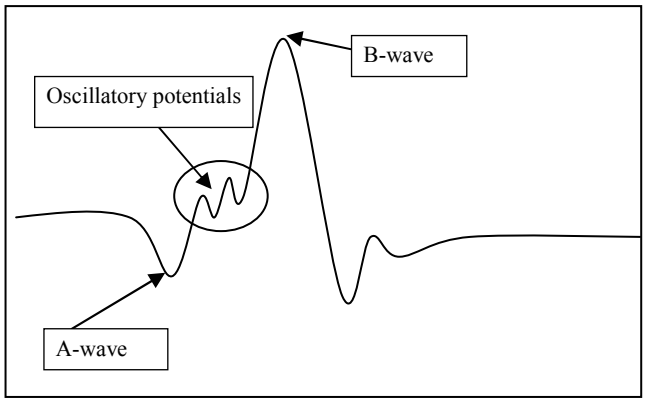


Figure 9.2 Full field ERG trace

The a-wave

The first wave of the flash ERG response is the negative a-wave. This is associated with the initial hyperpolarisation of the photoreceptors and is sometimes called the "late receptor potential" (Bornschein and Goodman, 1957; Rudduck, 2006). In the dark adapted state, the retina is very sensitive to light. The resting potential of the photoreceptors is -40 mV compared with approximately -90 mV of other central nervous system neurons. This low resting potential is due to the fact that, in darkness, the photoreceptors are 'leaky' to positively charged ions (e.g. sodium and potassium) which flow into the cell. On exposure to light, however, the cell becomes more resistant to this ion flow. This makes the cell membrane potentials relatively more negative; the cell hyperpolarises. The combined effect of numerous photoreceptors contributes to the initial a-wave in the ERG recording (Barraco et al., 2006; Rudduck, 2006).

The b-wave

The b-wave reflects the postsynaptic neuronal activity in the retina and is clinically the most important component of the ERG (Rudduck, 2006). The ERG b-wave is selectively abolished by any agent which blocks synaptic transmission. The b-wave is generated by current flow following the light evoked increase in the potassium concentration in the extra cellular space, causing the Müller cells to depolarise. The response of the Müller cells, however, is caused by the balance of neuronal activity, which involves both the outer- and inner-synaptic layers (Johnson, 1958; Rudduck, 2006).

Oscillatory potentials (OP)

The ascending limb of the b-wave contains oscillatory potentials, which are triggered by bright light stimulation. *Amacrine cells* are thought to be involved in the generation of the oscillation (Cobb and Morton, 1953; Wachtmeister and Dowling, 1978), although this is debated in the literature (La Chapelle, 2006). OPs are very sensitive to ischemia (reduced blood flow) in localised retinal areas. Therefore, in situations where the a- and b-waves remain normal in waveform and amplitude, OPs can indicate mild retinal ischemia in the inner retina (Speros and Price, 1981). For example, OP recordings have sometimes been used as an indicator of background diabetic retinopathy (Asi and Perlman, 1992; Bresnick and Palta, 1987; Larsson et al., 2005).

9.1.3. Analysis of the ERG wave form

The ERG of an infant looks similar to that of an adult. The peak amplitude is attained in adolescence and slowly declines in amplitude throughout life (Weleber, 1981). Implicit times (see below) slow gradually from adolescence through old age.

To reduce either the a or b waves, a disorder needs to affect a large area of retinal tissue. So a flash ERG is not affected by a focal lesion but (Giltrow-Tyler et al., 1978) a 50% loss of the retina leads to a 50% reduction in amplitude. The b-wave of the ERG is dependent on electrochemical events producing the a-wave and therefore any disorder affecting the a-wave will also affect the b-wave (Rudduck, 2006)
There are two principal measures of the ERG waveform:

1) **The amplitude (a)** from the baseline to the negative trough of the a-wave, and the amplitude of the b-wave measured from the trough of the a-wave to the following peak of the b-wave.
2) **The time (t)** from flash onset to the trough of the a-wave and the time (t) from flash onset to the peak of the b-wave.

These times, reflecting peak latency, are referred to as "implicit times".

Peak latencies.

Each laboratory that measures ERG needs to establish its own normal values and confidence intervals due to the influence of the equipment used and testing conditions. Some ERG parameters such as the b-wave are not normally distributed. Therefore, to describe limits of normality, the median value is of greater importance as are its associated 95% confidence intervals (Marmor and Zrenner, 1998).

B-wave latency

The b-wave latency is the time from the onset of the flash stimulus to the peak of the b-wave. The normal time for the b-wave to appear in the dark adapted eye is approximately 40-50 msec (Rudduck, 2006). Early changes in retinal disease often manifest as a reduction in the speed of the b-wave. For example in early retinitis pigmentosa, the b-wave latency is increased significantly, it often presents before any attenuation in the b-wave becomes manifest (Birch and Sandberg, 1987; Schoon and Harris, 1982).

Amplitudes

In order to compare pre-synaptic retinal activity (the a-wave in the signal), and post-synaptic activity (the b-wave), the b-wave: a-wave ratio is used (Perlman, 1983). In healthy subjects, the b-wave should be at least twice the size of the a-wave at the highest intensity. The ratio may be reduced in cases of drug induced visual defects or retinal vascular disease not involving the choroidal circulation (Rudduck, 2006). An example of this would be a case of central retinal artery occlusion, where there is a selective loss in b-wave amplitude. The pathogenesis is that the choroidal circulation that gives nutritional supply to the photoreceptors is intact, whilst the central retinal artery that supplies the amacrine, bipolar, and ganglion cells is blocked. This results in electrical inactivity of the post-receptoral cells (Rudduck, 2006).

Oscillatory potentials

These are described as 3 major peaks followed by a smaller one. They can be seen on an ERG recording by raising the low band pass (lower limit for measurement) from the usual <1 Hz up to around 100 Hz (Rudduck, 2006). This filters out the slower a- and b-wave components leaving a burst of cone oscillatory potentials following a bright white flash between about 15 and 40 msec. Oscillatory potentials are significantly attenuated in various retinal degenerations. Amongst them are the following: retinitis pigmentosa, diabetic retinopathy, hypertensive retinopathy, central retinal vein occlusion and central retinal artery occlusion (Bellini et al., 1994; Johnson et al., 1991a; Kizawa et al., 2006; La Chapelle, 2006; Movasat et al., 2008; Stepien et al., 2006).

9.1.4. ERG Responses

Separating rod and cone ERGs

Implicit times and amplitudes vary depending upon whether the eye is dark adapted or not in addition to brightness and colour of the light stimulus. Thus changing the parameters of the stimulus will allow separation of rod and cone activity. Because of their numerical preponderance, rods dominate the ERG following a white flash. Using different rates of stimulus presentation (flicker) also allows rod and cone contributions to the ERG to be separated. Rods cannot follow a flickering light above 20 per second whereas cones can easily follow a 30 Hz flicker, which is the rate

routinely used to test if a retina has good cone physiology therefore this rate of flicker is used to test cone function.

Rod response

In order to produce a rod dominated response, the patient should be dark adapted for 20mins. The rod response is the first signal measured after this adaptation. Standard stimulus is a dim white flash with a gap of 2 seconds should be given between flashes. (Alternatively a blue stimulus can be used)

Maximal combined response

This response is produced by a standard white illumination. Flash in the dark adapted eye requires a gap of 10 secs between stimuli and is a measure of the combined response of rods and cones.

9.1.5. Pattern electroretinogram

The pattern ERG (PERG) is evoked by stimulation of the retina as a response to a patterned stimulus, such as a chequerboard pattern. In clinical terms it produces valuable information about retinal macular function. It is a measure of retinal ganglion cell function and reflects macula function, mainly because of the high density of photoreceptors and ganglion cells dedicated to this region (Lam, 2005). Compared with the flash-evoked ERGs, described earlier which are in the order of 100-200 V, PERGs are much smaller, in the order of 0.5-8 V.

The PERG is maximally stimulated when the black and white chequerboard stimulus projects on to the macula and para-macular areas. The stimulus is defined by the size (the angular subtense at the eye) of a single check. The checks change phase rapidly at a specific rate (pattern reversal). Using this pattern reversal method, there is no overall change in luminance. At low rates of reversal (e.g. 2 to 6 per second), the resultant waveform is characterised by a small initial negative component at approximately 35 ms; although this is not always visible. This is followed by a positive inflection at 50 ms (P50), and a large negative component (N95) at the corresponding time of 95 ms post stimulation (figure 9.3).

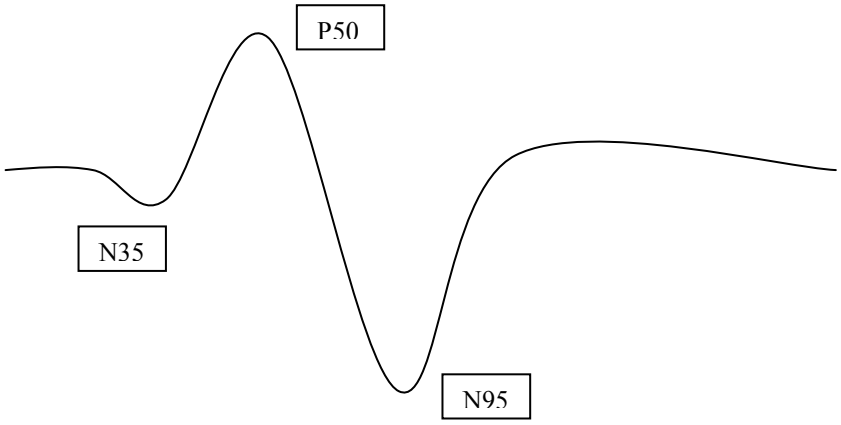


Figure 9.3 PERG trace

Perception of a patterned stimulus depends upon the spatial contrast discrimination rather than the detection of gross luminance changes. The neuronal ability to discriminate spatial contrast in the retina begins at the level of the bipolar cell. Importantly, there are two types of bipolar cells: those which depolarise with light as well as those which hyperpolarise with light. The depolarising bipolar cells hyperpolarise when the surround is stimulated by light. The hyperpolarising bipolar cells depolarise on surround stimulation. This contrast discrimination property is established more clearly at the level of the retinal ganglion cells. Here, 'on-ganglion cells' become active to a stimulus brighter than the background and are inhibited by a stimulus which is darker than the background. The converse occurs with 'off-ganglion cells' (i.e. the cell fires when a light is switched off). Thus, when the retina is stimulated by a chequerboard pattern, the depolarising bipolar and on-ganglion cells are excited when white squares appear at a given point in the visual field. Moreover, hyperpolarising bipolar and off-ganglion cells are excited when a black square appears. Whether the PERG reflects the summed activity of on- or off-ganglion cells remains equivocal (Holder, 2001), but there is evidence to suggest that the PERG response may be abnormal in optic nerve lesions when the conventional flash-type ERG remains normal (Holder, 2001). It has been suggested that the N95 component in the PERG response profile may be dependent on the integrity of the ganglion cell layer. The P50 component, on the other hand, appears to receive a significant contribution from bipolar cell excitation (Rudduck, 2006; Sutter and Tran, 1992). The affected or diminished peak can differentiate between macular or optic nerve problems. The P50 indicates a macular disorder, while sparing of the P50, with diminished N95, indicates a nerve problem (Lam, 2005).

9.1.6. Electrophysiology and autism

The use of electrophysiology to investigate functional integrity of sensory systems, at basic cellular levels, in autism has been fairly little used. To date only one study has been carried out looking at the ERG and autism. Ritvo (Ritvo et al., 1988) investigated 22 subjects who had been diagnosed with high functioning autism in comparison to typically developing subjects. The rationale of their study was that retinal physiology involves the same chemical pathways which may be deficient in brain chemical pathways of individuals with autism. Individuals with autism may therefore exhibit an abnormal ERG response. Subjects were chosen on the basis of an ability to co operate during the test. This skewed the selection towards patients on the milder end of the spectrum of communicative and behavioural difficulties. The study found that half of the autistic subjects showed abnormally low amplitude b-waves in the scotopic condition compared to expected values for age matched individuals. A quarter of the autistic group showed prolonged scotopic b-wave latencies. All of the photopic responses were normal but no pattern ERG testing was carried out. Ritvo suggested that the results are similar to those found in myotonic dystrophy and, thus, the two conditions might share a similar underlying congenital error in metabolism effecting retinal physiology. This suggested a possible subtype of autism. There have been many studies and theories put forward concerning metabolic abnormalities and autism disorders, but most are contentious. It has been suggested that abnormal food metabolism could lead to an altered chemical environment in the brain. This inability to metabolise specific foodstuffs, gluten or casein for example, adequately may lead to toxins entering the bloodstream via the gut wall and potentially crossing the blood brain barrier (Jordan, 1999). Anecdotal evidence has suggested that some individuals with an ASD may find improvements by using gluten free (wheat free) or casein (dairy free) free diet. There is, though, little experimental research into this and results have proved so far inconclusive (Adams and Holloway, 2004; Knivsberg et al., 2002; NAS, 2006b; Stevens et al., 1995).

9.2. Aims

To investigate whether ERG results are within normal limits in individuals with Asperger's syndrome, to determine whether the neural cellular pathway is intact in this condition. Unfortunately, time limitations meant that only one volunteer was willing to tested.

In addition, the nature of Asperger's syndrome means that patients are often reluctant to take part in experiments because of their anxiety and fears. In this case about fibre electrode contact with the eyes, or having to use mydriatic eye drops.

9.3. Method

9.3.1. Patient details

The volunteer was 30 years old and had a diagnosis of Asperger's syndrome. She did not suffer from any medical conditions. She was a -5D myope and obtained a visual acuity of 6/6 in each eye.

9.3.2. Ethical approval and consent

The Aston University Ethics Committee approved the project and the patient gave her written informed consent prior to taking part, having the opportunity to ask questions and withdraw at anytime should she have chosen to do so.

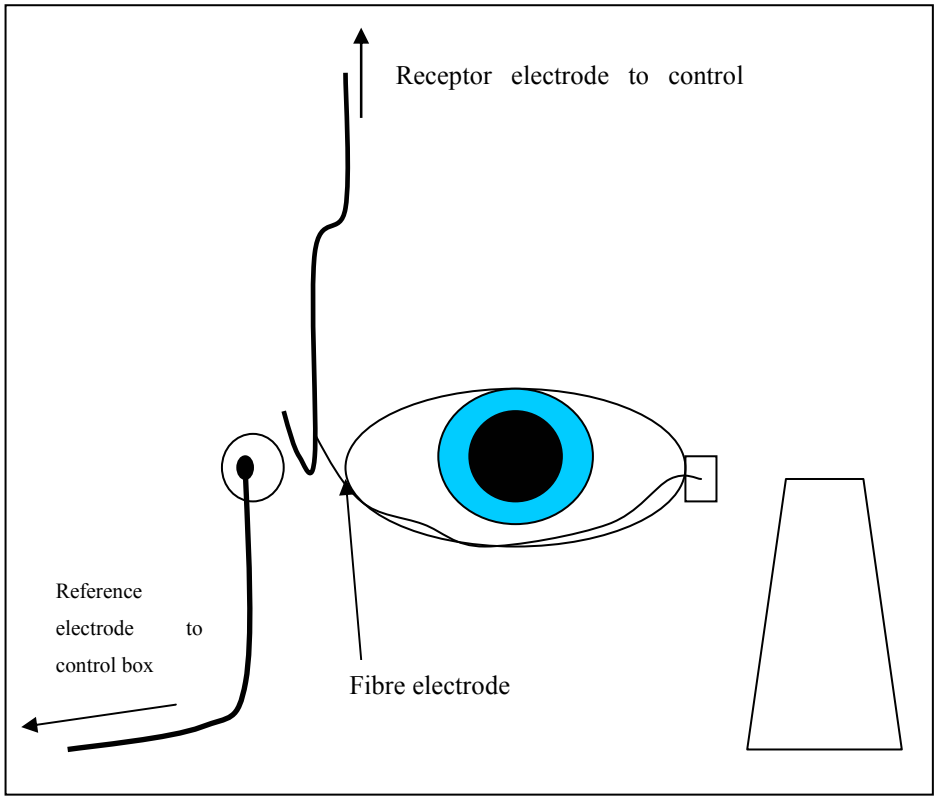
9.3.3. Electrophysiology

All procedures were carried out in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards (ISCEV, 2008) using a DTL fibre electrode was used for all recordings of ERGs.

The skin was prepared for electrode placement by cleaning and exfoliation using an abrasive gel (omni-prep) and a conductive paste or gel used to ensure a good electrical connection. This was done to ensure that reference electrodes had a 5kΩ or less impedance (measure of the total opposition that a circuit or a part of a circuit presents to electric current). Pupils were dilated using Tropicamide 0.5% and the volunteer was (1) dark adapted for 20 minutes before looking at rod responses and (2)light adapted for 10 minutes before looking at cone responses. A Dawson Trick Litzkow

(DTL) fibre electrode was used in this study. This was due to its low level of patient discomfort, it is the most likely to produce a good patient compliance whilst also being a reliable a testing method (Hennessy and Vaegan, 1995; McCulloch et al., 1997; Mohidin et al., 1997; Prager et al., 1992). The alternative, contact lens electrode was discounted due to compliance issues and its unsuitability for use in pattern ERG (Prager et al., 1992). Electrodes were placed as in figure 9.4. and 9.5.

Figure 9.4 Placement of electrodes on a sample subject (researcher, M. Conway).



9.5 Electrode set up using the DTL fibre; reference and recording electrodes visible, earth if placed on the ear lobe or forehead.

Pattern ERG (PERG)

The pattern ERG was performed first, before mydriasis, since this required optimal visual acuity and accommodation to view the chequerboard stimulus. The square size was 26 minutes and 58minutes for the small and large chequer board respectively (these values are as close to a half and 1 degree as the system would allow). The viewing distance was 70cm and the fixation point was a dot in the centre of the screen at a node of the checkerboard. Excessive blinking during recording was reduced with regular prompts and pauses. The reversal rate was 2 per second, with a total of 256 reversals recorded. Because of the nature of the stimulus, PERG examination should be performed with optimal visual acuity at the testing distance. So the volunteer was allowed to wear their refractive correction.

Photopic ERG

A Ganzfeldt stimulus bowl was used for all full fields testing, with background luminance of 17-34cdm (20cdm^{-2}) and a flash luminance level of 3cdm^{-2}. The flash stimulus had a colour temperature of near 7000°K and a dome which was visibly white. The volunteer underwent pupil dilation in both eyes, using tropicamide 0.5% prior to recording.

30Hz Flicker stimulus ERG

The flicker ERG was recorded in the light-adapted state to reduce discomfort and allow the photopic adaptation to be standardized. Flashes were presented at a rate of approximately 30 Hz and the rate that was chosen was consistent with the laboratory normal values.

Oscillatory potentials

There is considerable debate in the literature about how to measure and describe oscillatory potentials. Their appearance is highly dependent upon adaptation state and the filter characteristics of the amplifier. Most authors describe three major peaks often followed by a fourth smaller one (Asi and Perlman, 1992; La Chapelle, 2006; Speros and Price, 1981). Observing the presence of three peaks, and their normality relative to the standards of the laboratory, is considered adequate for clinical purposes (ISCEV, 2008).

Scotopic ERG

30 minutes of dark adaptation was given prior to recording. The combined rod-cone response was induced using a white 3 cdm^{-2} flash with an interval of at least 10s between stimuli.

9.4. Results

9.4.1. Normal values

Normal values have been previously established for the ERG equipment. The details of these are given below (table 9.1).

PERG 56' size checks N=40 eyes					
	N35ms	**P50ms**	**N95ms**	**N35-P50µV**	**P50-N95µV**
Mean	29.893	52.895	94.05	5.88	7.2
ST. DEV.	2.68	1.994	6.9	1.5	2.68
ULN	36.59	57.87	111.31	2.08	1.844
Intra-ocular difference N=40 eyes					
Mean	0.71	1.64	1.83	0.77	0.99
ST. DEV.	0.94	1.39	2.19	0.82	0.90
PERG 28' size checks N=40 eyes					
	N35ms	**P50ms**	**N95ms**	**N35-P50µV**	**P50-N95µV**
Mean	30.14	54.13	98.37	5.32	6.74
ST. DEV.	2.63	1.99	6.03	1.47	2.29
ULN	36.70	59.1	113.44	1.64	1.01
Intra-ocular difference N=40 eyes					
Mean	0.961	0.775	1.495	0.870	1.145
ST. DEV.	0.98	0.999	1.155	0.657	0.829

Dilated ERG normal values N=28 eyes			
Photopic	**Latency a**	**Latency b**	**a-b amplitude**
Average	14.81	34.10	136.88
1SD	0.75	1.71	44.04
2SD	1.50	3.43	88.09
Plus 2SD	16.30	37.53	224.97
Minus 2SD	13.31	30.67	48.79
30Hz Flicker	**Latency a**	**Latency b**	**a-b amplitude**
Average	14.32	27.66	94.79
1SD	1.35	1.15	27.80
2SD	2.71	2.29	55.59
Plus 2SD	17.03	29.95	150.38
Minus 2SD	11.61	25.37	39.20
Scotopic	**Latency a**	**Latency b**	**a-b amplitude**
Average	15.29	42.39	347.93
1SD	0.68	5.73	113.45
2SD	1.35	11.47	226.89
Plus 2SD	16.64	53.86	574.82
Minus 2SD	13.94	30.93	121.04

Oscillatory potentials (OP)	Latency a (ms)	Latency OP1 (ms)	Amplitude a-OP1 (µV)	Latency OP2 (ms)	Amplitude OP1-OP2 (µV)
Average	10.40	18.23	31.70	25.21	11.24
1 SD	0.88	0.54	10.58	0.66	6.39
2 SD	1.77	1.09	21.16	1.32	12.77
Plus 2SD	12.16	19.32	52.86	26.53	24.01
Minus 2SD	8.63	17.15	10.54	23.89	-1.53

Table 9.1 Normal values previously established for the ERG equipment (ULN= Upper limit normal).

9.4.2. PERG

Compliance was difficult due to excessive tearing and blinking. Despite regular rest periods, she found it hard to maintain her concentration for extended periods. This led to excessive tearing in the left eye relative to the right and resulted in a slightly reduced amplitude of responses in the left eye. Latencies and amplitudes of waveform features are shown in table 9.2. Responses were clearly present, within normal limits and comparable for both eyes.

Pattern ERG	Right eye		Left eye	
	56'	**28'**	**56'**	**28'**
N35	25.6ms	28.0ms	25.6ms	30.4ms
P50	51.2ms	52.0ms	52.8ms	50.4ms
N95	87.2ms	87.2ms	84.8ms	88ms
N35-P50	4.11µV	4.29µV	3.21µV	1.56µV
P50-N95	7.17µV	6.84µV	5.79µV	3.90µV

Table 9.2 PERG results

9.4.3. Photopic

All of the values (figure 9.3 to 9.5) were within normal limits as established for this equipment (see table above 9.1). Oscillatory potentials (OP's) were found to be present in both eyes at 18ms.

	Right eye		Left Eye	
a-wave latency	13.7ms	14.2ms	13.7ms	14.2ms
b-wave latency	30.7ms	30.7ms	30.7ms	30.7ms
a-b amplitude	282µV	273 µV	211 µV	201 µV

Table 9.3: Photopic results

	Right	Left
Latency OP	18ms	18ms
Amplitude a-OP1	33.9μV	26.2μV
Amplitude OP1-OP2	11.5μV	8.06μV

Table 9.4: Oscillatory potentials results

	Right eye		Left Eye	
a-wave latency	13.2ms	12.4ms	12.4ms	12.4ms
b-wave latency	28.6ms	28.6ms	27.9ms	28.1ms
a-b amplitude	180μV	180μV	145μV	140μV

Table 9.5 30 Hz flicker results

9.4.4. Scotopic

Scotopic values for latency and amplitudes were also within the normal range established.

	Right eye		Left Eye	
a-wave latency	15.2ms	15.2ms	15.2ms	15.2ms
b-wave latency	41.6ms	43.2ms	41.7ms	41.9ms
a-b amplitude	494μV	480μV	339μV	420μV

Table 9.6 Scotopic dark adapted results

9.5. Discussion

Despite limited compliance from the patient, all of the techniques examined were within normal limits. Although a single case study is limited, the results indicate that abnormal ERG's were not present in this case of Asperger's syndrome.

Recruitment of an increased number of people with Asperger's syndrome would be challenging, because (1) this is not a large population and (2) many individuals are reluctant to have foreign substances such as eye drops and electrodes placed against the eyes. Without a medical reason for performing this set of tests, it is difficult to get compliance even from some neurotypical volunteers.

The reasons which Ritvo (1989) suggested for suspecting an abnormality are based on theories concerning metabolic/neurochemical differences between the neurotypical population and those with autism. There have been many studies concerning autism and metabolism, brain chemistry and diet. Most of the theories are still contested and the evidence contradictory (Anderson gm, 1997; Jordan, 1999; Lam et al., 2006). At best, we might say there may be subgroups of individuals within the autism spectrum who have abnormal metabolism of specific nutrients and substances. Studies which examine the neurochemical correlates of autism are complicated by the many co-morbid conditions which can occur with the disorder. So it would need to be established whether a group exhibiting abnormal ERG responses were also grouped together by any other variable or conditions.

9.6. Conclusions

In this single case history of a person with Asperger's syndrome, the ERG was normal. This case study cannot comment on whether there are subgroups within the autism spectrum in which delayed latencies or reduced amplitudes of ERG responses might occur.

10.Conclusions and Future Work

10.1. The Eye Examination

Many parameters measured in an eye examination are the same in the autistic and the general neurotypical populations, whether diagnosis be Asperger's syndrome or autism with learning disabilities. Previous research suggests that since many individuals have an associated learning disability in the autism spectrum (75%), this may mean they are at increased risk of vision problems through refractive errors or ocular abnormalities. The distribution of refractive error and visual acuity in Asperger's syndrome was found to be no different from the typically developing population. Larger scale studies would be required to establish whether this finding transposes to the general population with autism. Individuals with an ASD did not have eye examinations at regular intervals. This is a problem common to many sections of the population, and particularly individuals with learning disabilities. Therefore, these individuals should be encouraged to attend for sight tests and raised awareness amongst care workers could impact on the frequency interval of eye examinations. This thesis suggests that a person with Asperger's syndrome or autism without any learning disability should be tested using the same methods as a member of the general population, with special consideration being given to communication. In particular, instructions should be given carefully and unambiguously. The examiner should take extra care to provide the patient with information about what is about to happen before each component of the eye examination. Each procedure should be discussed. For example, time should be taken to explain that, during ophthalmoscopy; the Optometrist will come very close and will shine a bright light into the eyes. Someone who has autism may have difficulty in communication but be highly intelligent. So, although at initial observation, they may appear to be potentially difficult to examine, in fact, most normal testing methods could be achieved with a little extra time.

10.2. Investigation of M-pathway function using perimetric methods in Asperger's syndrome

Over half of the group with Asperger's syndrome yielded a defect in visual field sensitivity using perimetric methods tuned to the magnocellular pathway. The defect manifested as a generalised reduction in sensitivity across the whole field in the FDT large stimulus perimeter and a slightly greater depression in the inferior hemifield with small stimulus FDT and flicker perimetry. This finding supports the theory of a specific M-pathway deficit being present in Asperger's syndrome. A depression of sensitivity in the visual field may help to explain some sensory issues suffered by the individual being tested, such as hyposensitivity to some stimuli or some mobility issues. If the person has decreased sensitivity, peripheral objects may be harder to distinguish, perhaps making activities like crossing roads or using stairs more difficult (Bodis-Wollner et al., 1987; Owsley et al., 1995; Turano et al., 2004).

In addition to the recommendations for eye examinations given already, individuals with Asperger's syndrome or an ASD should undertake examination with FDT. The N-30f program, using large stimuli is the most suitable test to use, owing to its short test duration compared to other techniques, and its low level of testing errors. Although flicker perimetry also detects the M-cell deficit, it requires a great deal of concentration and may not be particularly viable in the clinical situation. These findings could be confirmed in a larger population in order to estimate the population incidence of M-cell deficits in Asperger's syndrome. Included in this study could be other measures of magnocellular function such as motion coherence or form coherence detection.

10.3. Dyslexia and reading speed

The study found a higher incidence of dyslexia in high functioning ASD and Asperger's syndrome compared to the general population; 22.6% of the volunteers had previously been diagnosed as dyslexic in comparison to previous studies of the general population which found only up to 10%. This investigation showed that only a small the percentage of individuals with Asperger's syndrome might benefit from the use of a coloured overlay. Coloured overlay testing and assessment for visual dyslexia could be considered when examining an individual with high functioning autism or Asperger's syndrome as some individuals do appear to benefit significantly from this

form of intervention. The current advice from DANU (Disability and additional needs unit, Aston University) is that students with Asperger's syndrome be assessed individually in order to investigate their strengths and weaknesses. The results from this investigation would suggest that assessment of reading speed with and without coloured overlays would be a useful addition to this assessment and could easily be incorporated as part of an eye examination. Given the increased rate of dyslexia discovered in individuals with Asperger's syndrome, a larger population study is needed to investigate the prevalence of Dyslexia and or Meares-Irlen syndrome within this group.

Individuals with Asperger's syndrome use a greater number of saccades when reading. This finding may indicate a motor deficit, possibly originating in the cerebellum or neocortex, or a visual attentional deficit. People with Asperger's syndrome also make more regressive saccades when reading, possibly reflecting initial saccadic inaccuracy. These factors may cause the reduction in reading speed in individuals with Asperger's syndrome. No measure of text comprehension was made when looking at the rate of reading and eye tracking. Such an additional measure could be useful when explaining the finding of increased regressive saccades. Some other characteristics of text could be investigated with respect to changing numbers of saccades and regression rates. Font size, line/word spacing and underlining could be included. The colour of text or font used (Arial vs. Times New Roman) did not influence eye movement characteristics when reading. An extension of this study could consider the effect of using a coloured overlay on eye movements made when reading. Further research into the saccadic differences made during reading, might include electrophysiology or functional magnetic resonance imaging to investigate brain activity and identify the source of this dysfunction.

When measuring eye movements in the Asperger's population, the Digital Eye Trace (DET) system appeared to be less sensitive in detecting saccadic eye movement than the EOG but it yielded results which followed the same trend and with less variance. Clinically, the set up of this procedure is easier and less invasive. This is of particular importance when examining patients with Asperger's syndrome. Thus, DET can be considered as a viable clinical substitute for EOG when examining this patient group.

10.4. Gaze strategies in Asperger's syndrome

Individuals with Asperger's syndrome show abnormal patterns of looking. They look at human figures in preference to the surrounding background detail (neutral objects), as do we all, but with a lack of interest in the face and in particular the eyes. A typically developing individual will look at the eyes of others for a source of social information and a large amount of non-verbal communication. Thus, abnormal gaze behaviour in Asperger's syndrome may contribute to the impaired ability of these individuals to process social information and non-verbal communication. Eye tracking should be considered as a useful diagnostic tool for the assessment and quantification of the developmental processes in autism and Asperger's syndrome. Eye movements to facial details in individuals with autism may be a particularly useful means of investigating the underlying cause of social communication difficulties in this condition. An extended study of this type, conducted on a larger sample would provide further insight into the benefits of interventions directed at (1) increasing attention on the informative area of the face and (2) teaching individuals how to interpret face borne information. A future development may also be to investigate eye movements, using digital eye tracking, when this group of individuals observe video images of everyday situations.

10.5. The Electroretinogram: a case study

In this single case of Asperger's syndrome, the ERG was normal. This does not rule out, however, that there are subgroups within the autism spectrum in which delayed latencies or reduced amplitudes of ERG responses. The limited recruitment of a single patient for this study, in the time frame allowed, highlights the difficulty that is experienced in recruiting volunteers with Asperger's syndrome to take part in studies involving invasive procedures. When approached about the possibility of taking part in this study, all the other volunteers declined, giving reasons of not wanting to have drops instilled and/or the fibre electrode in contact with their eyes.

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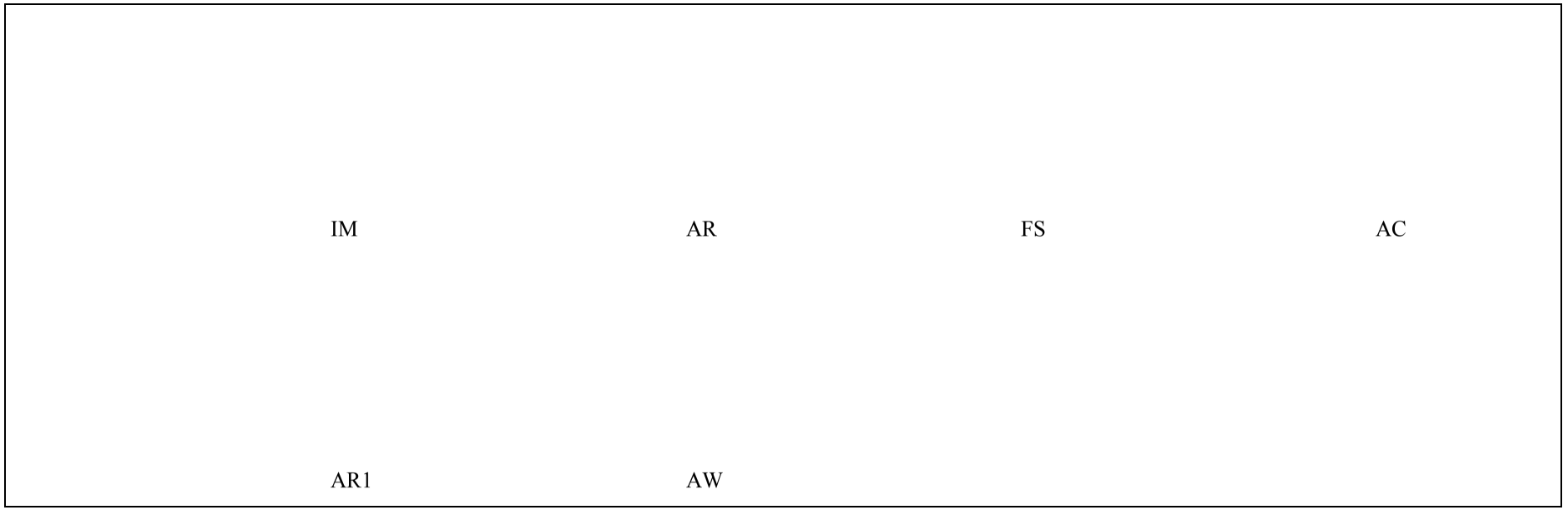
12. Appendix

Mimic Images from Digital Eye Trace.

Image 1 Painting of a coronation scene.

Controls			
RW	RC	PS	PB
PS1	MS	MC	MN
MB	LH	JB	JA


IM
AR
FS
AC
AR1
AW

Asperger's group			
AE	AW	BC	BH
LH	CF	GS	ID
JM	KS	NM	PJ

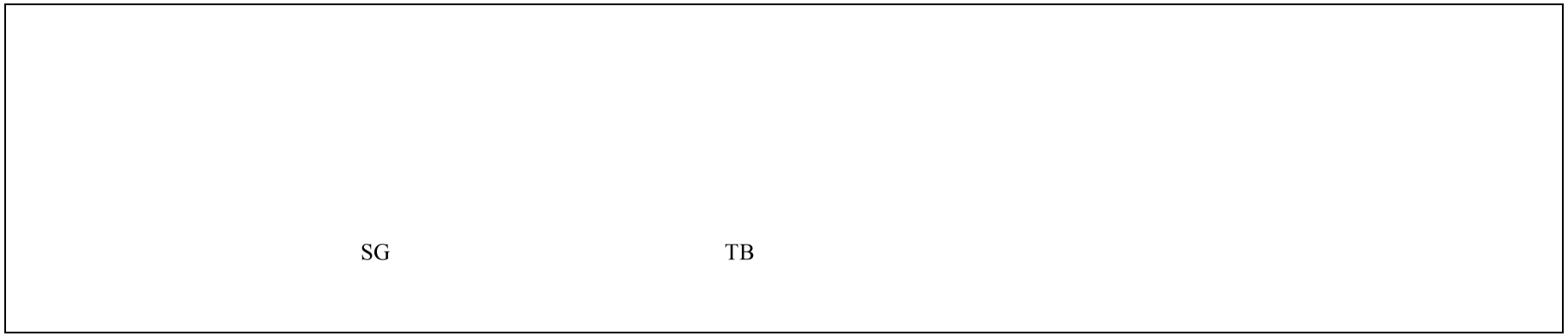
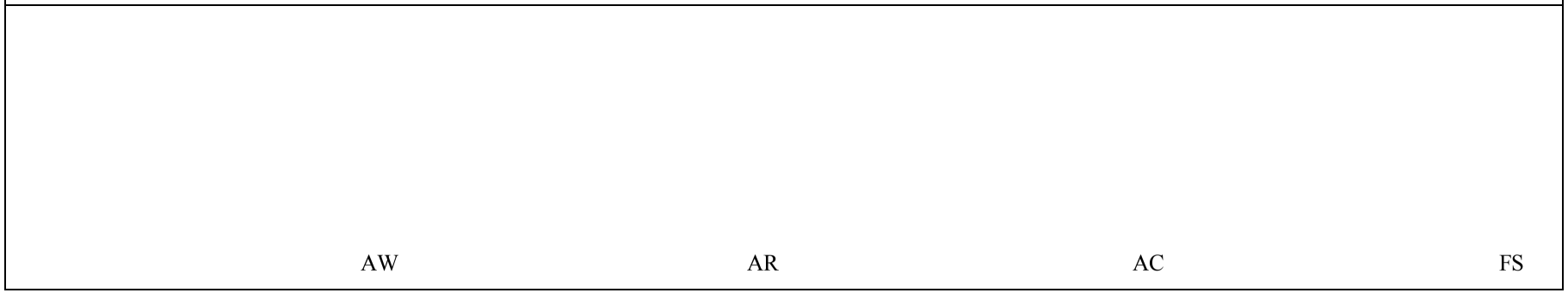
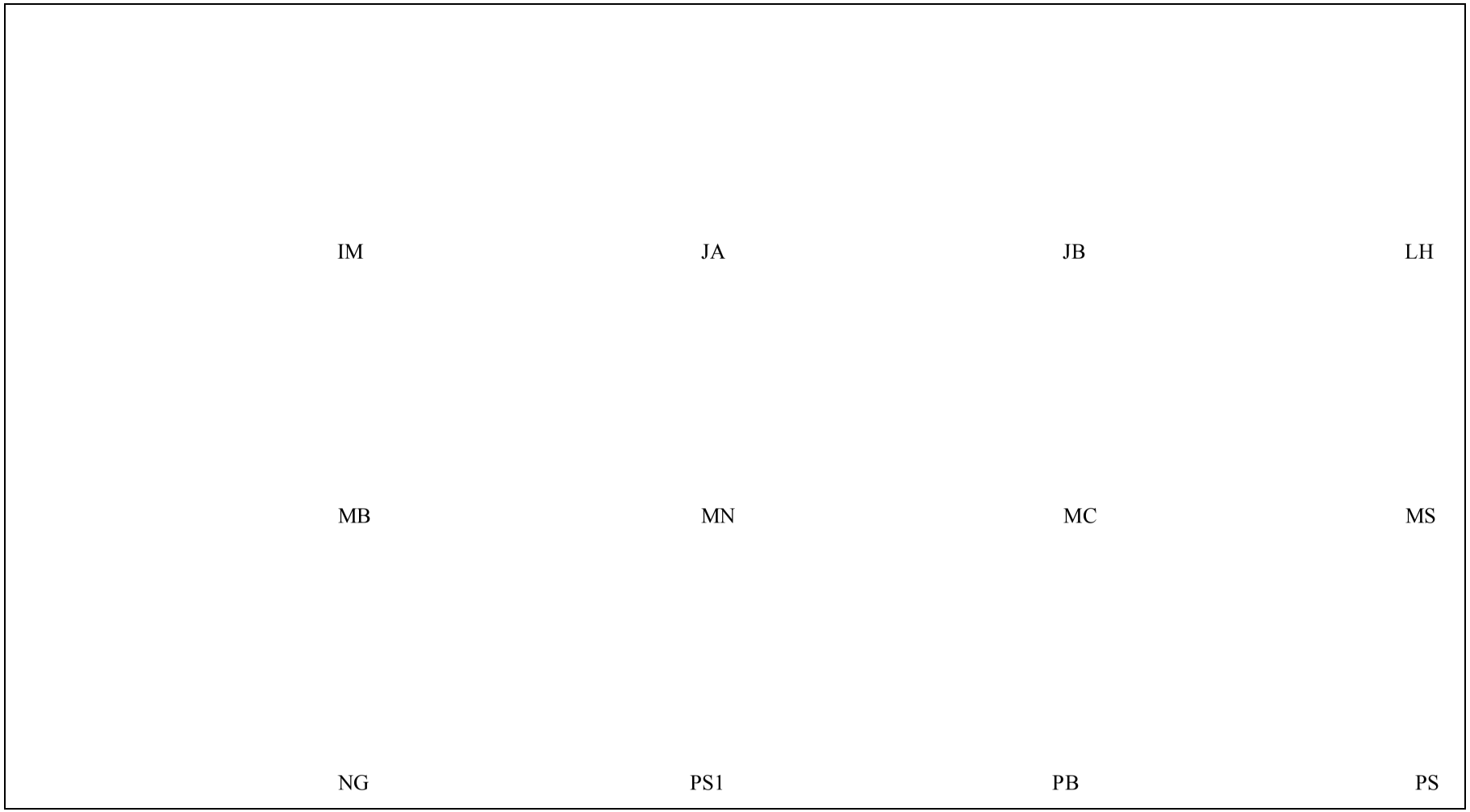


Image 2 Glasgow street scene.

Controls



IM
JA
JB
LH
MB
MN
MC
MS
NG
PS1
PB
PS

RC	RW

Asperger's group			
AE	AW	BC	BH

CF	GS	ID	JM
JS	KS	LD	LH
NM	PJ	SG	TB

Image 3 Optometry reception.

Controls			
AW	AR	FS	IM
JA	JB	LH	MB
MC	MS	PS1	PB

PS	RC	RW	AR1
MC	NG		

Asperger's group			
AE	AW	BC	BH

CF	GS	ID	JM
JS	KS	LD	LH
NM	PJ	SG	TB

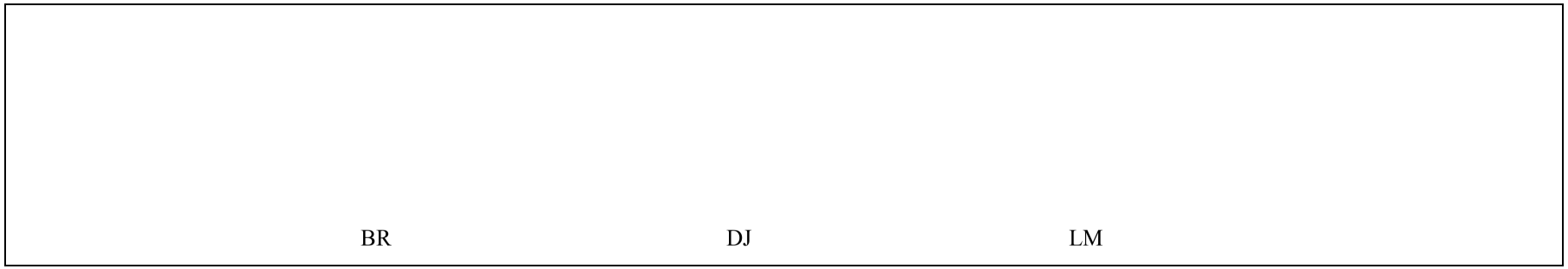
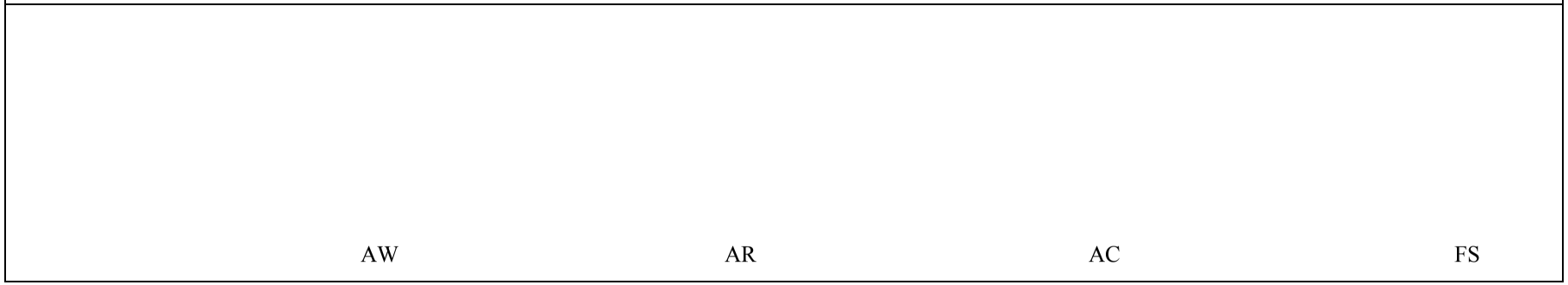


Image 4 Optometry clinic dispensing area.

Controls


IM	JA	JB	LH
MB	MN	MS	NG
PS1	PB	PS	RC

RW

Asperger's syndrome group			
AE	AW	BC	BH

CF	GS	ID	JM
JS	KS	LD	LH
NM	PJ	SG	TB

DJ	LM

Image 5 Two women looking into a camera.

Asperger's syndrome group			
AR	AC	FS	IM

JA	JB	LH	MB
MN	MC	MS	NG
PS1	PB	PS	RC

	RW			
Asperger's syndrome group				
	AE	AW	BC	BH
	CF	GS	ID	JM

JS	KS	LD	LH
NM	PJ	SG	LM
TB	BR		

Appendix II. Applications for ethical approval.

Project 06/6 and Project 07/O: Visual function in autistic spectrum disorders