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Symptoms of Autism in ADHD

A familial trait in a subset of children with ADHD which correlates with comorbid oppositional defiant disorder, conduct disorder and motor disorder

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MD Thesis

Trinity College, Dublin

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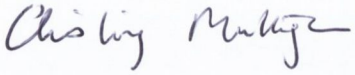
Signed: 

Aisling Mulligan

SUMMARY

Introduction: This study examines autism symptoms in a sample of children with ADHD, in their siblings, and in a control sample.

Study sample: 821 children with ADHD, combined type who were participating in the International Multicentre ADHD Genetics (IMAGE) study and their 1050 siblings were studied. A control sample of 149 children was also studied.

Measurements: Symptoms of ADHD and of comorbid disorders were assessed using parent and teacher Conners' rating scales, the Strengths and Difficulties Questionnaires and the Parental Account of Children's Symptoms semistructured interview. The Social Communication Questionnaire (SCQ) was used to measure symptoms of autism in the ADHD sample, the sibling sample and normal controls.

Statistical analysis: Symptoms of autism were compared in the ADHD sample, sibling sample and normal controls. The familiality of symptoms of autism in the sibling pairs was calculated. The percentage of the correlation of autism symptoms and ADHD symptoms which was due to shared familial effects was calculated using DeFries Fulker analysis. The relationship between symptoms of autism in probands and symptoms of oppositional defiant disorder, conduct disorder, motor disorder and reading disorder was examined. Finally a cluster analysis was performed using symptoms of autism in the proband group, and the clinical characteristics of the various clusters were examined.

Results: Children with ADHD have more symptoms of autism (mean SCQ = 8.49) than their siblings (mean SCQ = 4.42) and than normal control children (mean SCQ = 3.89). The relationship between symptoms of autism and symptoms of ADHD was non- linear, with low autism symptoms in some of those with high ADHD symptoms. Symptoms of

autism were shown to be familial, with an intraclass correlation of 0.37 for autism symptoms in unselected sibling pairs, and of 0.54 for concordant sibling pairs. DeFries Fulker calculations found that 27% to 43% of the correlation between autism symptoms and ADHD symptoms was due to shared familial effects. The analysis of autism symptoms in children with and without comorbid disorders found that children with ADHD and comorbid oppositional defiant disorder, conduct disorder and motor disorder all had increased symptoms of autism in comparison to children without these disorders. The cluster analysis demonstrated five clusters of children with ADHD. Cluster 1 had children with low symptoms of autism, (mean SCQ score = 2.24) and low risk of comorbid disorders. In contrast, children in cluster 5 had high symptoms of autism (mean SCQ = 21.4) and a high risk of oppositional defiant disorder (77%) and conduct disorder (44%). Children in clusters 2, 3 and 4 had intermediary levels of autism symptoms, and intermediary risk of comorbid disorders.

Conclusions: Symptoms of autism are increased in some children with ADHD, but not in others, and are familial in nature. Some of this familiality is shared with the familiality of ADHD. The finding that children with ADHD and comorbid oppositional defiant disorder, conduct disorder and motor disorder have increased symptoms of autism may guide future clinical studies on the early identification of children at risk of developing or at risk of having these disorders. The cluster analysis has shown that ADHD is not a homogenous disorder but one with different levels of autism symptoms and different risks of comorbid disorders. This study may have implications for molecular genetic research on ADHD as well as clinical research.

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CHAPTER 1: INTRODUCTION

1.1 Introduction

1.1.1 Introduction

The clinical disorders of autistic spectrum disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are classified separately under diagnostic classification systems, such as the Diagnostic Statistical Manual of Disorders, 4th Edition-Text Revision (DSM-IV TR) (American Psychiatric Association, 2000) or the International Classification of Diseases (ICD-10) (World Health Organization, 1992) with ADHD classified as a behaviour disorder and autistic spectrum disorders classified as pervasive developmental disorders. There have been numerous studies which have shown that children with autistic spectrum disorders can also have symptoms of ADHD. However the diagnostic classification for ADHD does not allow a child to be diagnosed with ADHD and comorbid ASD – the child's diagnosis is by definition an ASD diagnosis. This hierarchical diagnostic classification system has led to more research into symptoms of ADHD in children with ASD in comparison to the amount of research into symptoms of autism in children with ADHD.

In this thesis, literature relevant to the topic of symptoms of autism in children with ADHD is reviewed and symptoms of autism in a large group of sibling pairs concordant and discordant for ADHD are studied. Symptoms of autism are compared in the proband and sibling groups, and with children from the general population. The familial correlation of symptoms of autism is studied, and the shared familiality of autism

symptoms and ADHD symptoms is calculated, for male sibling pairs and for female sibling pairs. Finally the relationship between symptoms of autism and comorbid disorders in ADHD is explored firstly by comparison of mean symptoms of autism in those with and without each comorbid condition, and secondly, by performing a cluster analysis using autism symptoms in probands with ADHD, followed by comparison of the comorbid conditions in each of the clusters.

1.2 Introduction to the clinical features, heritability and molecular genetics studies of ADHD

1.2.1 Clinical features and diagnostic criteria for ADHD

Attention deficit hyperactivity disorder (ADHD) is characterised by symptoms of hyperactivity, impulsivity, and inattention with an onset in early childhood. Historically there have been many different descriptions and names for the group of symptoms and behaviours, but consistent key features over time include symptoms of hyperactivity, impulsivity and inattention. The DSM-IV TR definition of Attention-Deficit/Hyperactivity Disorder is frequently used by researchers and clinicians today. Six of nine symptoms of inattention and/or six of nine symptoms of hyperactivity or impulsivity must be present for six months or more, with an onset of the disorder before seven years of age. ADHD is subdivided in DSM–IV TR into three subtypes: ADHD predominantly hyperactive-impulsive type, ADHD predominantly inattentive type, and ADHD combined type (where the child has 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity/impulsivity). According to DSM-IV TR, a primary

diagnosis of ADHD can only be made if symptoms of ADHD are not accounted for by another diagnosis, such as a diagnosis of autism or learning disability.

The ICD-10 describes a similar clinical entity to ADHD in section F90, Hyperkinetic Disorders. However there are two major differences between the definition of Hyperkinetic Disorder in ICD-10 and ADHD in DSM-IV: (1) the ICD-10 diagnosis of a Hyperkinetic Disorder requires that the child is overactive and inattentive, and hence this diagnostic category cannot be used if the child presents with inattention in the absence of overactivity; (2) the ICD–10 category of Hyperkinetic Disorder is subdivided into categories including the diagnosis of Hyperkinetic Conduct Disorder (if symptoms of conduct disorder are present with symptoms of overactivity) and Disturbance of Activity and Attention (for children with overactivity without conduct disorder symptoms). When using DSM-IV TR, children with symptoms of conduct disorder and symptoms of overactivity should be diagnosed with ADHD and with comorbid conduct disorder. In keeping with DSM-IV TR, the diagnosis of Hyperkinetic Disorder using ICD-10 requires that symptoms are present from early childhood (before the child is 6 years of age), and that pervasive developmental disorders and other psychiatric illnesses are absent.

DSM-IV and ICD-10 clearly define symptoms of ADHD and Hyperkinetic Disorder, but there have been previous descriptions of the same clinical entity, using various different terms. The earliest scientific study of ADHD symptoms in medical literature dates to Still's description, in 1902, of a group of children with symptoms of overactivity and inattention. (Still, 1902). Since then different terms have been used to describe children

with symptoms of overactivity including Postencephalitic Behaviour Disorder, Minimal Brain Damage Syndrome and Minimal Brain Dysfunction. (Anastopoulos and Shelton, 2001). These terms reflect the early opinions that such symptoms of overactivity and inattention were related to organic causes such as encephalitis (Hohman, 1922) or in relation to brain injury (Strauss and Kephart, 1955). The phrase Attention Deficit Disorder with Hyperactivity was introduced in Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition - Text Revision (DSM-III) (American Psychiatric Association, 1980) and later ADHD was defined as described above in DSM-IV TR.

It should be noted that the diagnosis of ADHD using DSM-IV TR or of Hyperkinetic Disorder using ICD-10 does not infer causality for the symptoms in an individual case – the symptoms of the disorder are merely described as being present or absent. However the reliable description of the disorder using DSM-IV TR criteria and ICD-10 criteria has allowed extensive research into the aetiology of ADHD. Despite many changes in the terms used to describe ADHD or Hyperkinetic Disorder, the features of hyperactivity, impulsivity and inattention have consistently been considered essential to the diagnosis, as has the absence of a diagnosis of autism or pervasive developmental disorder. Another characteristic which has been consistently associated with the disorder is a predisposition to oppositional symptoms and to symptoms of conduct disorder. The clinical association between hyperactivity and conduct disorder led to Still's description of "defects in moral control" and to the ICD-10 description of Hyperkinetic Conduct Disorder. Taylor et al, (1991) studied the association between conduct disorder and hyperactivity in an epidemiological study of all boys aged 6 – 7 years attending mainstream schools in the

London borough of Newham. A questionnaire assessment, using Rutter's questionnaires (Rutter, 1967) and Conners' rating scales (Conners, 2001), was used to divide the sample into groups according to hyperactive symptoms and symptoms of conduct disorder. The groups with 'hyperactivity only' or 'conduct disorder only' did not differ from the total hyperactivity group ('hyperactivity only' and 'hyperactivity with conduct disorder') or from the total conduct disorder group ('conduct disorder only' and 'conduct disorder with hyperactivity') and so the presence of one or both disorders did not reflect the severity of the overall disorder (Taylor et al, 1991). However boys with both hyperactive symptoms and conduct disorder symptoms were noted to have more severe symptoms of each disorder than boys with symptoms of one disorder only. It was concluded that symptoms of conduct disorder and symptoms of hyperactivity can occur simultaneously or can occur independently of each other in the population.

Taylor et al, (1991) have shown that ADHD and conduct disorder are partially independent of each other. Genetic studies of ADHD usually use the DSM-IV TR diagnostic classification system rather than the ICD-10 to identify the phenotype, as DSM-IV TR identifies ADHD and conduct disorder as two separate disorders, which must both be diagnosed if symptoms fulfilling criteria for both disorders are present. Symptoms of ADHD and symptoms of conduct disorder may represent candidate symptoms which may be more closely related to the underlying genetic aetiology of the disorders than the ICD-10 diagnosis of Hyperkinetic Conduct disorder.

1.2.2 Prevalence rates of ADHD and comorbid disorders

Taylor et al, (1991) found that 1.7% of boys have hyperkinetic disorder (ICD-10) in an epidemiological study with screening questionnaires followed up with a semistructured interview. In the same study, 4% of boys were found to have Attention Deficit Disorder with Hyperactivity (ADDH) as described in DSM-III. Children with a predominantly inattentive subtype of ADHD are included in the diagnosis using DSM-IV, and hence the rates of ADHD using DSM-IV are generally higher than the rates of hyperkinetic disorder using ICD-10. Taylor's study (1991) clearly shows that the rate of ICD-10 hyperkinetic disorder in the population is less than the rate of DSM-IV ADHD (Taylor et al, 1991). A more recent epidemiological study of the prevalence of DSM-IV disorders in children in Great Britain by Ford et al, (2003) found that the prevalence rate for ADHD (DSM-IV, any type) was 3.62% for males and .85% for females, with a total prevalence of 2.23%. The rates for combined type ADHD were 2.34% for males, 0.48% for females, with a total prevalence of 1.41%. Both Taylor's study (1991) and Ford's study (2003) used an interview with the child's parent(s) to assess for the diagnoses, with the structured Development and Well-Being Assessment used by Ford et al, (2003) and the Parental Account of Children's Symptoms used by Taylor et al, (1991). Questionnaire information from teachers was also used in both studies, and a screening questionnaire with parents was used by Taylor et al, (1991).

Higher prevalence rates for ADHD have been reported when teacher reports alone have been used to make the diagnosis, such as in the study by Baumgaertel et al, (1995). In this study, school teachers in a defined area of Bavaria, completed questionnaires on children

in their classes. Using this assessment method it was found that 9.6% of children in the area had symptoms of DSM-III ADDH and 17.8% of children had symptoms of DSM-IV ADHD (any type). The difference between these prevalence rates and the prevalence rates reported in the UK epidemiological studies is believed to be due to the use of teacher rated questionnaires in isolation. In the USA, data from the National Health Interview Survey Sample 2001 showed that 4.19% of males and 1.77% of females have symptoms of ADHD, using a parent rated Strengths and Difficulties Questionnaire. (Cuffe et al, 2005). It is likely that questionnaire information, used in isolation, is associated with a higher prevalence rate of ADHD than questionnaire information in association with a research interview.

As can be seen from the studies quoted above, ADHD occurs more frequently in males than in females, with ratios of approximately 4:1 and 2:1 reported by Ford et al, (2003) and by Cuffe et al, (2005) respectively. These studies represent the rates of ADHD in males and females in epidemiological samples, but in samples from child psychiatry clinics the male preponderance is higher, perhaps reflecting that more males with ADHD are referred to clinics than females. A ratio of 9:1 for combined type ADHD was reported in a research sample of children attending psychiatric clinics (Brookes, Xu, Chen, Zhou, Neale, Lowe, et al., 2006).

Children with ADHD often have symptoms of other disorders, such as oppositional defiant disorder, conduct disorder, speech and language delay and specific reading or writing difficulties. In a study of children attending a mainstream school in Sweden, it

was found that 87% of children with ADHD defined according to DSM-III-TR had one or more comorbid diagnoses, while 67% had 2 or more comorbid diagnoses. It was found that 60% of children with ADHD also had oppositional defiant disorder, 33% also had tics, 7% also had Asperger's Syndrome, 47% had developmental co-ordination disorder and 40% had reading or writing disorder (Kadesjo & Gillberg, 2001). Taylor et al, (1991) also found that children with hyperkinetic disorder had significantly higher rates of motor clumsiness (43% vs 3%) and speech disorder (64% vs 32%) than controls. Ford et al, (2003) found that the rate of comorbid disorders in ADHD was lower than previously reported by Kajesjo and Gillberg, (2001), with just over half of children with ADHD having a comorbid behaviour disorder, either oppositional defiant disorder or conduct disorder.

A disorder related to ADHD and which may represent a subgroup of children with ADHD is the disorder known as DAMP or Deficits in Attention, Motor control and Perception, which was originally described by Gillberg et al, (1982). The original description was of a subgroup of children with deficits of attention, motor control and perception in a childhood population sample (Gillberg et al, 1982). DAMP was later described as "attention deficit/hyperactivity disorder and comorbid developmental co-ordination disorder in children who do not have severe learning disability or cerebral palsy" (Gillberg, 2003).

1.2.3 Treatment of ADHD and comorbid conduct disorder

ADHD is usually treated using psychosocial management, medication or a combination of both of these. In the Multimodal Treatment Study of Children with ADHD (MTA), 579 children were studied in 4 groups: those who received (1) behavioural treatment, (2) medication management, (3) combined treatment and (4) community care (MTA Cooperative Group, 1999). The children were followed up over 14 months initially, and it was found that combined medication and psychosocial management treatment was most effective at reducing symptoms of ADHD. Medication alone was almost as effective as combined treatment. However it is important to note that psychosocial management alone was an effective treatment of ADHD in the MTA study, and hence current NICE guidelines recommend that psychosocial management is the first line of management for ADHD (www.nice.org.co.uk). Children from the MTA study were then followed up three years later, and the early beneficial effect of medication was no longer evident (Jensen et al, 2007).

The psychosocial management delivered in the MTA study consisted of child focused treatment (an 8 week summer camp with a 9 hour day), parent training using recommendations from Barkley (1987) and Forehand and MacMahon (1980) and school treatment as described by Pelham, (1998). The medications which are usually used to treat ADHD include stimulants such as long or short acting methylphenidate, dexamphetamine or the noradrendergic reuptake inhibitor atomoxetine.

It has been estimated that the implementation of the most recent NICE guidelines for ADHD in England will cost £40 million per year. (www.nice.org.co.uk). Disorders comorbid to ADHD such as conduct disorder are also expensive to treat. Parenting programmes, multisystemic therapy and psychopharmacology are of proven efficacy in the treatment of antisocial behaviour disorders. Webster-Stratton's parent training programme was shown to reduce conduct problems in a multicentre study by Scott et al, (2001). However early identification and treatment is considered essential (Webster-Stratton, 2001). Romeo et al (2006) calculated a mean cost of £5960 per year per child aged 3-8 years with severe antisocial behaviour in the UK, with considerable costs borne by the family. By age 28 the cost for those with conduct disorder is 10 times higher than for those with no problems, with an average cost of £70,019 in 1998 prices (Scott et al, 2001). Families with children with antisocial behaviour disorder are frequently from disadvantaged backgrounds (Ford et al, 2003), and the UK government has introduced the Sure Start programme to target preschool children living in disadvantaged areas. The Sure Start aims to improve outcomes for children and an average expenditure of £900 per child has been reported (Birbeck: National Evaluation of Sure Start, 2004). However this strategy targets all children in a geographical area, rather than intervene intensively with those of high risk of developing an antisocial behaviour disorder. It is possible that the cost of delivering this service could be reduced or that the effectiveness could be increased if those of high risk of developing antisocial behaviour disorders could be identified at a young age, and intensive interventions provided for high risk children.

1.2.4 Familiality of ADHD

ADHD has been noted to occur more frequently in family members of children with ADHD than in others, and family based studies have confirmed that parents and siblings of children with ADHD have a greater risk of the disorder than normal controls. Biederman et al, (1990) found that first degree relatives of a sample of clinic children with ADD, as defined in DSM III TR, had a significantly higher risk of ADD than relatives of children with other psychiatric illnesses and than relatives of normal controls. (25.1% versus 5.3% versus 4.6%). Frick et al, (1991) studied the biological relatives (mothers, fathers and siblings) of a sample of 177 males with ADHD or with conduct disorder. It was found that biological relatives of children with ADHD had a greater risk of ADHD, but not of problems associated with antisocial behaviour. Schachar and Wachsmuth (1990) studied the rates of DSM III disorders in parents of boys with ADDH, conduct disorder (CD), ADDH + CD, normal controls and emotional disorders. It was found that when the groups with ADDH, CD and ADDH + CD and were studied together, significantly more boys in this group had family histories of parental childhood hyperactivity than did boys in the emotional disorder and normal control groups. In his review of ADHD, Faraone summarizes that "the parents and siblings of ADHD children have a two- to eight- fold increase in the risk for ADHD" (Faraone, 2005).

1.2.5 Familiality of disorders comorbid to ADHD

Studies have examined the shared familiality of disorders comorbid to ADHD, including learning disorders, affective disorders and anxiety disorder. ADHD and learning disorders are often comorbid conditions, and a considerable number of research studies have looked for shared familial influences (Gilger et al, 1992; Doyle et al, 2001; Willcutt et al, 2007; Del'Homme et al, 2007). Gilger et al, (1992) studied symptoms of ADHD in twin pairs with reading disorder, and reported that reading disorder and ADHD may be genetically independent. There was however a trend which suggested that in some cases ADHD and reading disorder occurred together, and that in these cases there may be a genetically mediated comorbid subtype (Gilger et al, 1992).

Doyle et al, (2001) compared the risks of ADHD and learning disorders in first degree relatives of three groups of girls: a group with ADHD and no learning disorder, a group with ADHD and learning disorder and a group without ADHD. It was shown that first degree relatives of the girls with ADHD and learning disability were more likely to have learning disability than first degree relatives in the other groups of girls. Willcutt et al, (2007) showed that reading disorder and inattention have shared familial influences whereas reading disorder and hyperactivity-impulsivity did not have shared familial influences. Del'Homme et al, (2007) studied the rates of learning disability in sibling pairs with ADHD, and in their parents. It was found that reading disorder sibling concordance rates and parent child concordance rates were higher than writing disorder concordance rates. However the presence of ADHD in a parent did not predict learning

disorder in a child, giving some evidence for independent familial influences (Del'Homme et al, 2007).

Biederman et al, (1991) found that the risk of DSM III Attention Deficit Disorder and the risk of affective disorders was increased in first degree relatives of those with ADD, in comparison with normal controls. However ADD and affective disorders did not co-segregate within families (Biederman et al, 1991). In a further study of the risks of anxiety disorder in the first degree relatives of probands with ADHD, Biederman et al, (1991) found that the risk for anxiety disorder in relatives was higher if the proband had ADD and anxiety disorder than if the proband had ADD without anxiety disorder. (Biederman et al, 1991). It was also found that the risk of anxiety disorder in a relative was higher if that relative also had ADD, suggesting some cosegregation of ADD and anxiety disorder (Biederman et al, 1991).

1.2.6 Adoption and twin studies in ADHD

Adoption and twin studies both suggest that there are heritable factors in ADHD. A comparison of the rates of ADHD in parents of three groups of children, (a) adopted probands with ADHD, (b) non-adopted ADHD children and (c) non-adopted non-ADHD control children, found that the rates of ADHD was greater in the biological parents of children with ADHD (18%) than in the adoptive parents of those with ADHD (6%) and than in parents of control children (3%) (Sprich et al, 2000). Numerous twin studies have been performed, and have shown that monozygotic twins have a greater concordance rate for ADHD symptoms than dizygotic twins such as the Australian twin study (Levy et al, 1997). The higher concordance of DSM-III-R ADHD symptoms in identical twins than in non-identical twins can be clearly seen in Levy and Hay's graphs, copies of which are shown below in Figure 1 (Hay et al, 2001). Faraone et al, (2005) pooled twin study data from 20 worldwide twin studies of ADHD and estimated that the heritability of ADHD is 0.76.

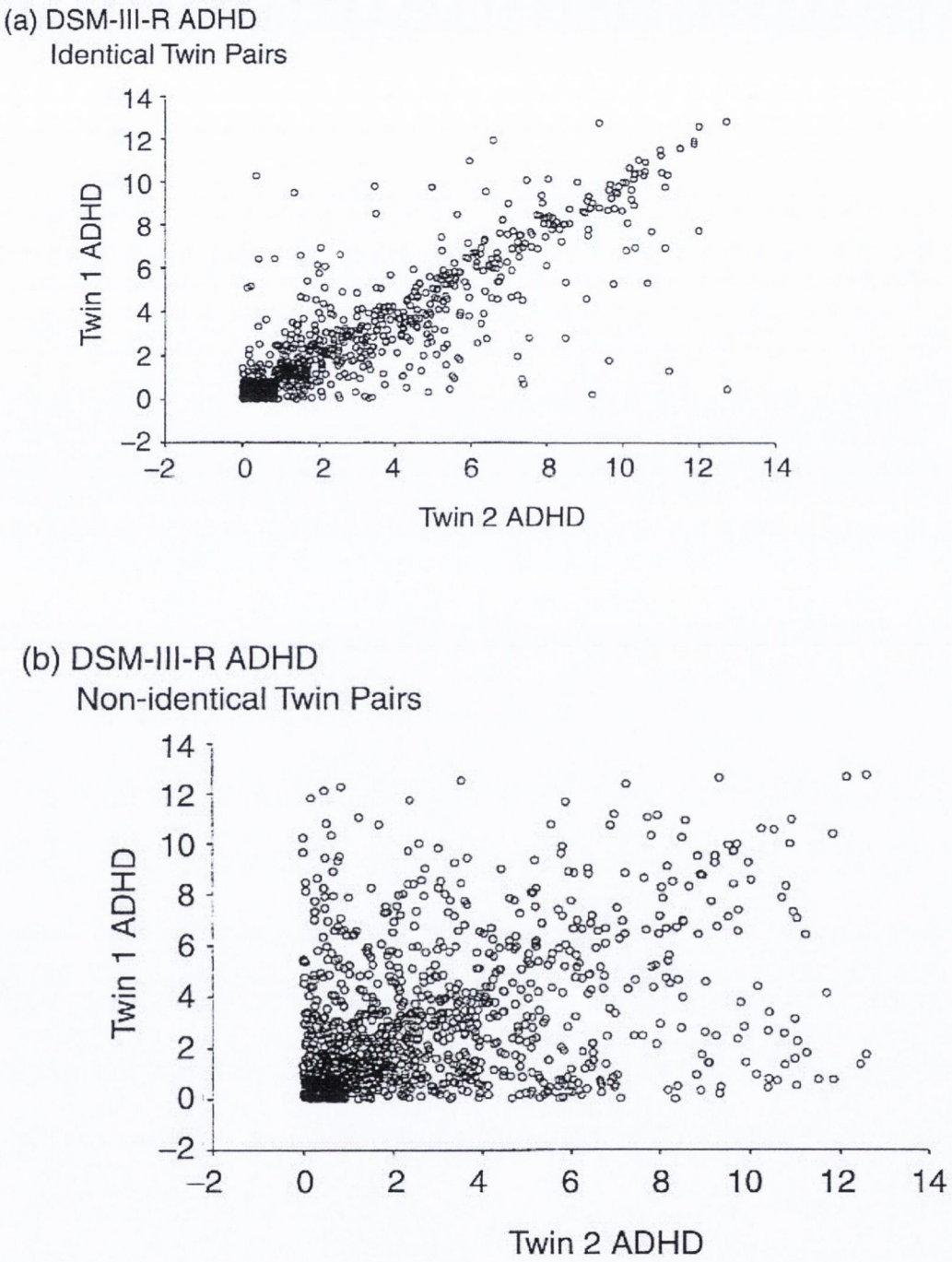

Figure 1: Familiality of ADHD symptoms in a twin population study
Modified from "Attention Genes and ADHD," edited by Florence Levy and David Hay, with permission from Florence Levy.

1.2.7 Molecular genetic studies in ADHD

Family, twin and adoption studies all suggest that there are strong heritable influences in ADHD, although the mode of inheritance remains unknown. Given the frequency of the condition in the population, and the pattern of concordance in families and twins, it is likely to be due to the combined effects of many genes, each of minor effect. Molecular genetics studies of ADHD have generally focused on the association design applied to candidate genes (Cook EH Jr, 1995; Mill et al, 2001; Hawi et al, 2002; Roman et al, 2003; Lowe et al, 2004; Li et al, 2006; Brookes et al, 2006), although several linkage studies have also been reported (Barr et al, 2000; McCracken et al, 2000; Brophy et al, 2002).

Genes from the dopaminergic system (Cook EH Jr, 1995; Mill et al, 2001; Lowe et al, 2004), serotonergic system (Hawi et al, 2002; Li et al, 2006) and noradrenergic system (Roman et al, 2003) have been studied in ADHD, with a surprising number of well replicated findings. Early studies focused on the dopaminergic system in ADHD, (Kirley et al, 2002) due to the known mode of action of methylphenidate, used to treat ADHD. Methylphenidate blocks the reuptake of dopamine by the dopamine transporter, thus increasing the concentration of dopamine in the synapse. Currently there is strong evidence that the dopamine transporter (DAT-1), the dopamine D4 receptor (DRD4) and the dopamine D5 receptor (DRD5) are involved in the aetiopathology of ADHD (Faraone et al, 2005). In view of the variation of results between studies from different centres, larger multi-centre candidate gene studies have been performed, such as the International Multi-center ADHD Genetics study (IMAGE). The IMAGE study confirmed some of the

previous candidate gene findings (DRD4 and DAT-1) and identified new genes including ARRB2, PNMT and SLC9A9, which may be associated with ADHD (Brookes et al, 2006).

1.2.8 The role of the phenotype in ADHD genetics studies

All of the genes (strictly speaking, DNA variants) thought to be associated with ADHD are of small effect size, with odds ratios less than 2. There are several possible reasons why effect sizes are small. The first is that it is a true polygenic trait with very many genes involved, each of small effect. A second is that the relationship between individual genes and the clinical phenotype might be weak, whereas the relationship between the genes and underlying biological systems might be stronger. Leboyer et al, (1998) discussed the challenges of the current nosological system and limitations in the current description of the phenotype and suggested that psychiatric genetics should use either a candidate symptom approach or study endophenotypes. The candidate symptom approach uses the core symptoms of the illness – those symptoms which allow the disorder to be described, ie hyperactivity, impulsivity and inattention rather than the diagnosis of ADHD.

It is also possible that there may be clinical subtypes of ADHD, either a sub-phenotype with ADHD and comorbid reading disorder as described in Section 1.2.4 or a clinical subtype related to the presence of symptoms of autism. A clinical subtype of ADHD may

have different heritability characteristics and genetic determinants than the overall disorder of ADHD.

The phenotypic analysis of children for inclusion in previous molecular genetic studies varied from site to site, and it may be that previous studies of ADHD had varied results due to differences in the inclusion criteria for the study. In most studies children with conduct disorder are included, but children with specific learning disorder are included in some studies (ie IMAGE) but not in others. Hence the genes identified may be in common with genes for reading disorder.

1.2.9 Summary and future directions in ADHD research

In summary, ADHD is present in approximately 2% of school aged children and is associated with many comorbid disorders, such as oppositional defiant disorder, conduct disorder, motor and speech disorder. There is strong evidence from family, twin and adoption studies that ADHD is a heritable disorder. There is also evidence of environmental influences on ADHD, such as low birth weight/prematurity, exposure to nicotine in utero and environmental adversity. Candidate gene studies have identified genes associated with ADHD, especially genes from the dopaminergic system. However the odds ratios for many of these genes are in the region of 1- 2, and hence the risk of developing ADHD for somebody with one of these genes is at most twice the risk of developing ADHD for somebody without the associated gene. The accuracy of genetic findings is related to the accurate description of the phenotype. It is possible that previous

molecular genetic studies of ADHD had varied results due to the heterogeneity of the phenotype in these studies – some studies included those with comorbid conditions and while others did not. This thesis examines subthreshold autism symptoms in ADHD, which may help to better define the phenotype of ADHD. The study also tests the hypothesis that autism symptoms in children with ADHD represent a familial sub-phenotype of ADHD with specific clinical characteristics.

1.3 Introduction to Autism and comorbid symptoms

1.3.1 Symptoms of autism

As this is a study of subthreshold symptoms of autism in ADHD, it is necessary to devote some time to the topic of autism. Autism was originally described in 1943 by Leo Kanner (Kanner, 1943) and is characterized by symptoms of impaired social interaction, impaired communication, and the presence of repetitive or stereotyped behaviours. The current description of Autistic Disorder in DSM-IV requires that 6 of 12 listed symptoms are present, including 2 of 4 listed symptoms of impaired social interaction, at least 1 of 4 symptoms of impaired communication and at least 1 of 4 symptoms of repetitive and stereotyped patterns of behaviour, interests and activities. The onset of the disorder must be before the child is 3 years of age. DSM-IV describes a group of disorders, known as Pervasive Developmental Disorders (PDD) which includes Autistic Disorder, Rett's disorder, Childhood Integrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified, (PDD-NOS) including atypical autism. The diagnosis of PDD-NOS can be used if the child has some but not all symptoms of Autistic Disorder, or if the age of onset is after 3 years of age. Typically a child with autistic disorder or Asperger's disorder may have poor eye contact and poor peer social interaction. Children with autistic disorder typically have more severe communication deficits and may be non-verbal.

1.3.2 Prevalence rates and distribution of autistic traits in the population

The prevalence rate of autistic spectrum disorder in the USA was recently reported as 6.6 per 1000 children or 1 in 152 children (MMWR Surveillance Study, 2007). Previously lower prevalence rates for autistic spectrum disorders have been reported, such as 3.4 per 1000 reported in an epidemiological study in Atlanta funded by the National Disease Surveillance Centre (Yeargin-Allsopp et al, 2003). Yeargin-Allsopp, (2003) described a male predisposition for autism, which was most evident in those with higher cognitive abilities. The male to female ratio was 6.7 in those with no cognitive impairment and was 1.3 in those with profound mental retardation. Yeargin-Allsopp, (2003) found that 68% of children with autism had a cognitive impairment, 8% had comorbid epilepsy and cerebral palsy was found in 5% of children with autism.

The DSM-IV TR (APA, 2000) and ICD -10 (WHO, 1992) describe autistic disorder as a categorical disorder, and research on autism generally uses the Autism Diagnostic Interview-Revised (Lord et al, 1994) and/or the Autism Diagnostic Observation Schedule (Lord et al, 2000) to categorize patients into those with autistic spectrum disorder and those without. However a twin study of autism symptoms in an epidemiological sample found that autism traits are part of a continuum in the population (Constantino and Todd, 2003). There have been many recent suggestions that autism symptoms occur as dimensional traits in the population, and a new dimensional interview has been developed to assess for autism symptoms in the normal population as well as the clinical population (Skuse et al, 2004).

1.3.3 Molecular genetic studies of autism spectrum disorder

It has been shown that autism is associated with physical disorders, such as cerebral palsy and with epilepsy (Yeargin-Allsopp et al, 2003) and that it is also associated with inherited physical disorders such as the autosomal dominant disorders tuberous sclerosis and neurofibromatosis and the X-linked Fragile X syndrome (Muhle et al, 2004). Single gene abnormalities including the Prader Willi syndrome, which arises from loss of paternally derived 15q11-13 and Angelman syndrome, which arises from loss of maternally derived 15q11-13 are both associated with autism (Muhle et al, 2004). Wassink et al, (2001) found that 9% of children with autism referred for karyotype analysis had chromosomal abnormalities, the most common of which were Fragile X, other sex chromosome abnormalities and abnormalities of chromosome 15 (Wassink et al, 2001). Cytogenetic abnormalities have been found in persons with autism on almost every chromosome (Gillberg, 1998).

Autism has been shown to be associated with single gene defects and cytogenetic abnormalities as listed above, and it has also been shown that siblings of those with autism have a 5% risk of having a pervasive developmental disorder (Szatmari et al, 1998). Twin studies have calculated that the heritability of autism is over 90% (Folstein and Rutter, 1977; Bailey et al, 1995). Molecular genetic studies including candidate gene studies and genome wide linkage studies have been performed, looking for genes contributing to the risk of developing autism.

The results of initial genome wide linkage studies on autism were reviewed by Lamb et al, (2000) and the most significant and overlapping areas of the genome implicated are 1p, 2q, 6q, 7q, 13q, 16p, 18q, and 19p (Lamb et al, 2000; IMGSAC, 1998; Philippe et al 1999; Risch et al, 1999; Barrett et al, 1999). The most replicated areas of linkage are on 15q, 7q and 2q regions of the genome, and candidate gene studies have focused on these regions (Muhle et al, 2004).

Candidate gene studies have been performed on genes associated with the serotoninergic system, dopaminergic system, the GABAergic system and on genes in the 15q region of the genome, among others, with varied results (Muhle et al, 2004, Lamb et al, 2000). Candidate gene studies have also been performed on areas of the genome or possible deletion sites associated with autism identified through cytogenetic studies. The 15q11-15q13 region has been studied in view of the association of chromosome 15 cytogenetic abnormalities with autism. Genes for GABA, which is associated with epilepsy, are coded on chromosome 15. In view of the association of epilepsy with autism, candidate gene studies have focused on markers for GABA on chromosome 15, with varied success.

There is considerable evidence linking the 7q31-7q33 region, known as the AUTS1 region to autism (Muhle, 2004). Candidate gene studies have focused on this area, and also on the 7q22 region which codes for RELN, a glycoprotein potentially involved in neural migration in neurodevelopment (Muhle et al, 2004). HOX genes which regulate hindbrain development have been studied in association with autism, and some genes in

the HOX system are coded on the 2q region which has been implicated in autism in whole genome studies (Muhle et al, 2004).

1.3.4 Evidence of overlap of symptoms of ADHD and autism

There has been recent interest in the similarities between ADHD and pervasive developmental disorders. Some studies have shown an increase in symptoms of autism in ADHD (Clarke et al, 1999), while others have shown that there are increased symptoms of ADHD in children with autism (Goldstein et al, 2004).

Clarke et al, (1999) studied symptoms of autism using the Autism Criteria Checklist (developed by Howlin, P and referenced as personal communication by Clarke et al, 1999) in 49 children with a clinical diagnosis of ADHD. In this study, 65 – 80% of parents reported that their child had significant difficulties in social interaction and communication. However one potential limitation of the Clarke et al, (1999) study is that case notes and clinical diagnoses rather than a research interview were used to identify the relatively small number of children with ADHD in four different clinics who were included in the study. Clarke et al, (1999) also used an autism questionnaire which had not been fully standardized at the time the study was performed. Lutijn et al, (2000) used the Children's Social Behaviour Questionnaire (Lutijn et al, 2000) to compare children with autism, PDD-NOS, ADHD, clinical controls and normal children. It was found that there was no significant difference between those with PDD-NOS and those with ADHD

on the Social Insights Scale of the Children's Social Behaviour Questionnaire, but the two groups differed on the other scales of the questionnaire (Acting Out, Social Contact, Anxious/Rigid and Stereotypical Scales). Children with ADHD were shown to have social communication deficits, which were not so severe as the social communication deficits of children with PDD-NOS (Lutijn et al, 2000). Hence the group with ADHD and the group with ASD were discernable from each other, using a questionnaire for autism spectrum disorder. Geurts et al, (2004) found that children with ADHD and children with high functioning autism showed deficits in communication, although the two disorders differed from each other on assessment using the Children's Communication Checklist (Bishop, 1998). The possibility of a shared pathophysiology as well as shared symptomatology is suggested by the presence of executive dysfunction deficits in children with ADHD and in children with high functioning autism, although the pattern of deficits differs in each group (Geurts et al, 2004).

Santosh and Mijovic (2004) examined clinical and psychosocial data on 3644 children attending child psychiatry clinics, by analyzing data generated from a clinical database. Children with hyperkinetic disorder were identified in the sample, and compared with those with other disorders. Two types of social impairment were described in the study sample – relationship difficulty and social communication deficits. It was found that in children with hyperkinetic disorder, relationship difficulty was associated with conduct disorder symptoms, affective symptoms and environmental stressors. Social communication deficits were associated with language difficulties, repetitive behaviour difficulties and developmental difficulties, which the authors described as pervasive

developmental disorder symptoms. It should be noted that data analysed in this study was generated from a clinical database used by practicing or in-training psychiatrists, rather than from research tools used as part of a research study. The authors suggested that there may a subgroup of children with ADHD who have some symptoms of pervasive developmental disorder. Buitelaar et al, (1999) compared tests of theory of mind and of emotion recognition in four groups of children classified as follows: a group with autism, PDD-NOS, psychiatric controls and normal children. In this study, it was noted that children with autism and PDD-NOS could not be significantly differentiated from each other using these measures, nor could they be differentiated from a subgroup of psychiatric control children with ADHD. This study suggests that children with ADHD and children with autism spectrum disorders share some clinical features, although it does not indicate that children with ADHD have symptoms of autism spectrum disorder.

Hattori et al, (2006) compared symptoms of ADHD and symptoms of PDD in 35 children referred to a child neurology clinic. 15 of these children were subsequently diagnosed with PDD (9 male and 6 female, mean age 8 years and 8 months) and 20 were subsequently diagnosed with ADHD (19 male and 1 female, mean age 9 years and 4 months). 40 normal children participated as controls. It was found that children with PDD had the highest autism symptom scores, children with ADHD had intermediary scores and that normal children had the lowest autism symptoms scores. Similarly children with ADHD had highest ADHD symptom scores, children with PDD had intermediary scores and normal children had the lowest scores. A significant difference between autism symptom scores of the ADHD group and the PDD group was noted, but no significant

difference between the ADHD scores of the ADHD group and the PDD group was noted (Hattori et al, 2006). Hence ADHD symptoms were common to children with PDD and children with ADHD, and autism symptoms were present in both groups at a greater rate than in control children. This study had a small sample size, but suggested that children with ADHD and children with autism shared symptoms which were not present at a clinical level in control children, although the severity of symptoms differed in the two clinical groups. Thus some overlap between ADHD and autism is suggested by this study.

It is also recognised that children with autism may have symptoms of hyperactivity or inattention, and may be diagnosed with comorbid ADHD. Goldstein et al, (2004) found that 7 of 27 (26%) subjects with PDD also met criteria for ADHD. Yoshida et al, (2004) found that 36 of 53 children (68%) with high functioning PDD also met criteria for ADHD. Further evidence of the prevalence of hyperactive symptoms in autism is that parents of children with autism rated tantrums, aggression and hyperactivity as the symptoms of most concern, in the Autism Research Units on Pediatric Psychopharmacology (RUPP Autism Network) study on risperidone use in autism (Arnold et al, 2003).

It has been shown that symptoms of autism occur as a continuum in the population (Constantino and Todd, 2003). It has also been shown that symptoms from the three domains of autism in the general population studied in the Twins Early Development Study (TEDS) showed low covariation, and were heterogeneously heritable (Ronald et al,

2006). Symptoms of ADHD also occur as continuous traits in the population (Levy et al, 1997). Hence it is possible that some children in the general population could have symptoms of inattention or hyperactivity/impulsivity and symptoms from one or more of the domains of autism.

The current diagnostic classification system means that children presenting with symptoms which meet the diagnostic criteria for both an ASD and for ADHD are diagnosed with ASD. However the recent studies by Hattori et al, (2006) and by Santosh and Mijovic, (2004) and others listed above have shown that children can have similar symptoms in each disorder and hence the classification of children as PDD-NOS or as ADHD is not always simple.

While studies to date clearly indicate that symptoms of ADHD occur in children with autism spectrum disorder, the topic of symptoms of autism in children with ADHD has not been studied in the same detail. This is partly due to the hierarchical rule in DSM-IV and in ICD-10, which means that a child with symptoms of both ADHD and an ASD is diagnosed with ASD, with comorbid ADHD. In order to study symptoms of autism in children with ADHD, it is necessary either to formally exclude children with ASD from the study sample of children with ADHD or to study an epidemiological sample. There was no assessment in Clarke's study (1999) to exclude children with pervasive developmental disorder from the study sample, and it is possible that children with PDD-NOS could have been in the study sample.

In some studies, children with ADHD and children with an autism spectrum disorder were studied using the same measures, and compared with each other and with psychiatric or normal controls. Similar findings on questionnaires used may be due to poor specificity of the questionnaires rather than to autism symptoms in children with ADHD. Studies to date have also been relatively small (Clarke et al, 1999; Buitelaar et al, 1999; Hattori et al, 2006) with few studies using a research interview to diagnose ADHD.

The similarities of children with ADHD and children with ASD noted by Buitelaar et al, (1999) and Hattori et al, (2006) and studies outlined above may suggest that children with ASD and children with ADHD are part of the same spectrum of disorders. Alternatively the findings of previous studies could be due to clinical features found in common in two disorders rather than due two overlapping disorders – ie ASD and ADHD could be two separate disorders which have some clinical features in common. The topic of comorbid symptoms in psychiatric disorders is explored in more detail (see *Section 1.3.5*).

1.3.5 Comorbid symptoms in psychiatric disorders

The issue of comorbid child psychiatric disorders was studied by Caron and Rutter, (1991), who noted that the rates of comorbid child psychiatric disorders exceeded the rates expected by chance. Possible explanations for this were proposed, including detection artefacts (overlapping diagnostic criteria, artificial subdivision of a syndrome), or true comorbidity (with either shared risk factors, overlap of risk factors or one disorder creating increased risk for the other). Neale and Kendler (1995) also proposed models of comorbidity, including (1) alternate forms of the same disorder, (2) multiformity, where the presence of one disorder increases the risk of another disorder, (3) three independent disorders, where the presence of each disorder is due to a third disorder, (4) correlated liabilities where the risk factors of the two disorders correlate, and (5) direct causal models. Angold et al, (1999) considered the issue of comorbidity in child psychiatric conditions, and noted that familial comorbidity is common, with increased rates of other psychiatric conditions seen in relatives of children with ADHD.

There are several possible explanations for the presence of autism symptoms in ADHD. The first is that a questionnaire which measures symptoms of autism may actually also inadvertently measure symptoms of ADHD, if the rating scale is not sufficiently specific. For example, a negative response to the question "has his facial expression usually seemed appropriate to the particular situation, as far as you could tell?" might in an ADHD child reflect the child's distractibility from the situation but in an autistic child reflect a social communication deficit. Another possible explanation for the presence of autism symptoms in ADHD is that ADHD and autistic spectrum disorder are overlapping

disorders, or that both disorders are caused by a single joint phenotype, as described by Neale and Kendler (1995). It is also possible that children with autism symptoms and ADHD are a subgroup of children with ADHD, and that this subgroup may have its own clinical characteristics and aetiology. The presence of autism symptoms in children with ADHD may thus represent phenotypic heterogeneity of ADHD. Further study of the phenotype of ADHD may guide future genetics research on ADHD.

1.4 The IMAGE sample and the Aims and Hypotheses of the Study

1.4.1 The IMAGE study and sample

This study was performed using a subset of the International Multicentre ADHD Genetics Study (IMAGE) sample. The IMAGE study is funded by the National Institute of Mental Health, US and approximately 1200 families with a child with ADHD, combined type (ADHD-CT) and a concordant or discordant sibling were recruited to the IMAGE study, as described by Brookes et al, (2006). Twelve European centres in eight countries participated in the study: Belgium, Germany, the Netherlands, Ireland, Israel, Spain, Switzerland and the United Kingdom. The aims of the IMAGE study are (1) to perform genotyping and linkage scans (in a very large sample) for candidate genes of known relevance in ADHD and for genes suspected to be of importance in ADHD, and (2) to perform a genome scan to identify novel genes associated with ADHD. Children recruited to the IMAGE study had a detailed clinical assessment, to confirm the diagnosis of ADHD-CT in the proband, assess the symptoms of ADHD in the sibling and outrule autistic spectrum disorder or learning disability. Children and parents participating in the IMAGE study also donated a blood or saliva sample for genetic analysis. A total of 5758 individuals (all either probands, parents or siblings) were included in the IMAGE study.

In each site, families who had two or more children aged 5-17 years inclusive, one of whom had a clinical diagnosis of ADHD-CT were invited to participate in the study. Each participating family had one or more parents and two children willing to donate a blood or saliva sample.

1.4.2 Aims and Hypotheses

The aim of the study was to test the following hypotheses: (1) *That autism symptoms are part of the ADHD phenotype.* If this is the case, a high correlation between ADHD symptom scores and autism symptom scores can be expected in both probands and siblings. We would also expect high shared familiality between ADHD symptoms and autism symptoms. (2) *That autism symptoms are familial in ADHD.* If this is the case, children with ADHD and autism symptoms should have siblings who also have autism symptoms. (3) *That autism symptoms in children with ADHD have the same three dimensional pattern as autism symptoms in children with ASD.* If this is the case, it could be expected that children with ADHD have autism symptoms from each of the three domains of autism, and each of the domains of autism would be expected to be heritable, as in the normal population. (4) *That the presence of autism symptoms represents a specific subtype of ADHD with particular phenotypic characteristics.* If this is the case, it would be expected that a distinct cluster of children with autism symptoms could be identified. It would also be expected that there would be certain clinical attributes associated with this subgroup of children with ADHD-CT and autism symptoms. Under this hypothesis, the familiality of autism symptoms might be partially shared with the familiality of ADHD symptoms.

Using the IMAGE sample we have investigated the relationship between autism symptoms and ADHD-CT by (1) comparing autism symptoms in children with ADHD-CT with autism symptoms in their siblings and with autism symptoms of the normal population; (2) calculating the familial correlation of autism symptoms in ADHD-CT,

using proband and sibling data; (3) calculating the familial correlation of each of the domains of autism symptoms in ADHD-CT, using proband and sibling data (4) correlating autism symptoms in children with ADHD-CT with measures of ADHD and co-morbid oppositional defiant disorder, conduct disorder, motor disorder and reading disorder (5) conducting a cluster analysis of autism symptoms in probands with ADHD-CT and examining the rates of comorbid disorders in each cluster.

CHAPTER 2: METHODS

2.1 Introduction

2.1.1 Introduction

This chapter outlines the recruitment and assessment of the study sample, which is a subset of the IMAGE study sample, and the recruitment and assessment of a control sample. The inclusion criteria, exclusion criteria and data management of the IMAGE study sample is described. This is followed by a description of the measures used in the study and the statistical methods. This includes a comparison of mean autism symptoms between probands, siblings and controls and a calculation of the familiality of autism symptoms in ADHD using the DeFries Fulker method. This is followed by a comparison of autism symptoms in children with and without comorbid disorders including oppositional defiant disorder, conduct disorder, motor disorder and reading disorder. Finally a cluster analysis is described, using a latent class analysis of autism symptoms in probands with ADHD-CT.

2.2 IMAGE Study sample

2.2.1 Inclusion criteria and recruitment to the IMAGE study

The study sample for this thesis is a subset of the International Multicentre ADHD Genetics Study (IMAGE) sample (see *Section 1.4.1*). Families with a child with a diagnosis of ADHD-CT who had a proband, sibling and one or both parents available to donate a DNA sample were recruited to the IMAGE study in 12 European centres. Recruitment was predominantly via child psychiatry clinics at each centre, and all children invited to participate in the study were patients of child psychiatric clinics. Clinical assessments were performed at each site to confirm the research diagnosis of ADHD, as outlined in *Section 2.2.5*. In total 2067 families who expressed an interest in the IMAGE study were invited to participate. 1339 families completed the Parental Account of Children's Symptoms (PACS) interview and questionnaires. 1084 of these families had a child who met the research criteria of ADHD-CT with symptoms confirmed in the home and school setting, with clinical impairment. Children with comorbid disorders such as oppositional defiant disorder, conduct disorder, mood disorders, tic disorders and obsessive compulsive disorder were included in the study, and the presence of these disorders was assessed using the PACS semi structured interview. Children with reading disorder were also included in the study. Therefore, each family included in the IMAGE study consisted of a child with a research diagnosis of DSM-IV ADHD-CT), one or more full siblings aged 5 to 17 years and one or both parents, with each family member available to donate a blood or saliva sample for DNA collection.

In Ireland, families with sibling pairs concordant and discordant for ADHD-CT were recruited to the IMAGE study over a period of 30 months by the author, in accordance with the IMAGE study recruitment criteria. Recruitment was via child and adolescent mental health services in the areas previously known as the South Western Area Health Board, the Midlands Health Board, the North Eastern Health Board, Mid Western Health Board and the South Eastern Health Board, with ethics approval for the study received from the relevant ethics boards in each area. Families were also recruited from a private psychiatric ADHD service, a paediatric ADHD service and ADHD family support groups via mailshot and public announcements at ADHD family support meetings. In Ireland, the national media expressed an interest in the IMAGE study, and two articles in national newspapers about the study were followed up by interviews on national radio. Numerous families volunteered to participate in the IMAGE study following these interviews, although only a limited number of these families were eligible to participate in the study. One family volunteered directly to participate in the study, having found details about the study on the website of the Department of Psychiatry, Trinity College Dublin.

387 families with a child with ADHD in Ireland were contacted by telephone by the author, with regard to the IMAGE study. 247 families were identified who were considered to be potentially eligible for the study following the initial telephone conversation. These families were sent information about the IMAGE study and consent forms. Following a second telephone discussion at least two weeks later, 156 (63%) of these families agreed to participate and agreed to allow IMAGE researchers to visit the family home. Each member of the family was given an IMAGE identification number

and clinical assessments were performed, as described in *Section 2.2.5*. It was found that 8 (5%) children did not meet the research criteria for ADHD-CT; 5 (3%) children had a diagnosis of autistic spectrum disorder as well as ADHD; 8 (5%) families did not complete the study or withdrew consent, and 9 (6%) families were excluded due to an IQ<70 in either the child with ADHD or the sibling. One family was excluded as the sibling of the child with ADHD developed epilepsy after initial recruitment to the study. Thus the final sample for the IMAGE study in Ireland was 133 families.

2.2.2 Exclusion criteria for the IMAGE study

Families were excluded from the IMAGE study if the proband or sibling had a diagnosis of autism, atypical autism, or Asperger's Disorder, epilepsy, IQ<70, brain injury, genetic disorder or metabolic disorder associated with hyperactivity or inattention. All families participating in the study were of Caucasian/European origin. Families were excluded if a child had one or more grandparents who were not of Caucasian/European origin. Half siblings, adopted and fostered children were excluded. Families with a proband or only sibling with autism or atypical autism were excluded as described in *Section 2.3.2* and *Section 2.3.3.*

2.2.3 Ethical considerations

The IMAGE study sample collection was performed in keeping with the UK Medical Research Council guidelines for the collection and storage of biological material. In each country, ethical approval for the study was sought from a National Institute of Health registered ethical review board and from relevant local ethics committees. In Ireland the study was approved by the Ethics Committee of the South Western Area Health Board (a National Institute of Health registered ethical review board), the Ethics Research Committee of the Mid Western Area, the Ethics Committee of Midlands Health Board, Ethics Committee of the Health Services Executive North Eastern Area, and the Waterford Regional Ethics Committee.

Detailed information pamphlets were prepared for parents, children with ADHD, siblings and teachers invited to participate in the study at each centre. Information was prepared in a format which was accessible to parents, children and teachers and was provided on the following topics: (1) storage of blood samples in a repository in the USA, under the direction of the National Institute of Mental Health, and the formation of cell lines with blood samples so as to create a permanent resource for the study of ADHD; (2) storage of anonymous clinical data on a central database in the UK; (3) that all data and genetic samples were given an anonymous identification number which was used in all data storage and analysis; (4) the possibility of the clinical data and genetic information being shared with other qualified scientists who may apply to use the data for further analysis on ADHD; (5) that there was no short term benefit from participation in the study, but that it was hoped that the study would increase medical knowledge about ADHD; (6) potential harm to the participants included the risks of phlebotomy, which includes discomfort but is generally not harmful. Families were informed that researchers were trained in paediatric phlebotomy and that local anaesthetic would be used to minimise discomfort.

Parents were invited to provide signed consent to their own participation and that of their children. Children were also invited to provide signed consent or assent for their own participation in the study, if they were sufficiently mature to understand the information provided to them. Teachers were asked to sign that they consented to participation in the study. In the Irish sample, both parents were contacted and invited to provide signed consent to the study. In the event that one parent was not contactable and was thus unable

to give consent, but both parents were legal guardians of the child, the family was not recruited into the study.

2.2.4 Data management for IMAGE

Clinical data from each site was sent to a central database at the London IMAGE site. Each individual participating in the study was given a unique identifying number, which consisted of a code unique to each centre (cc), a code unique to the person's family (fff) and a code unique to the individual (iiiii), such that each person had a final code which was composed of all three of these numbers. All data and genetic samples were labeled with this anonymous code before any data was sent from a local site to an international centre. In Ireland an Access database was used to track the course of families who agreed to become involved in the study, in keeping with the Data Protection Acts, 1988 and 2003.

2.2.5 Clinical assessments for IMAGE

For each child participating in the IMAGE study (proband and sibling), symptoms of ADHD and symptoms of autism were measured as outlined in *Section 2.3.1* and *Section 2.3.2*. The following questionnaire assessments were completed on each child: Conners' Parent Rating Scale, parent rated Strengths and Difficulties Questionnaire (SDQ), parent rated Social Communication Questionnaire (SCQ), Conners' Teacher Rating Scale and teacher rated Strengths and Difficulties Questionnaire. For children (proband or sibling) who scored above a screening cut-off on the parent or teacher Conners' rating scale, the

Parental Account of Children's Symptoms semi structured interview was performed with one or both parents (see *Section 2.3.1*).

Researchers from all sites were trained together in the recruitment criteria for the IMAGE study and in the assessment of symptoms of ADHD using the Parental Account of Children's Symptoms (PACS) semistructured interview (Taylor et al, 1986). The initial training was followed by inter-rater reliability assessments at the commencement of the study and one year later (Brookes et al, 2006). Families were excluded if the proband or sibling fulfilled one of the exclusion criteria listed above (see *Section 2.2.2*).

Assessment of families in the IMAGE study in Ireland followed the guidelines for the overall IMAGE study, as outlined above. Following referral to the study, parents were contacted by telephone, and an assessment appointment was organised. Information about the study, consent forms and parent questionnaires (Conners' parent rating scale, SDQ and SCQ) were sent to the family prior to the initial assessment. (see *Section 2.3.1).* The author (the research psychiatrist in IMAGE) and research psychologist Louise Butler visited the family at their home to perform the PACS semi-structured interview and psychological assessments with children participating in the study. At the initial assessment meeting, the author also explained the study again, gave the family an opportunity to ask questions about the study and obtained signed consent and assent from the parent(s) and children. Families were given teacher packs for each child, consisting of information about the study, a teacher Conners' rating scale, teacher Strengths and Difficulties Questionnaire and a prepaid addressed envelope for the return of

questionnaires. In the event that questionnaires were not readily returned, families or teachers were reminded by telephone after the family visit to return the questionnaires.

Where there were more than two children in the family, all children aged 6-17 years inclusive who did not fulfil exclusion criteria for IMAGE (see *Section 2.2.2)* were invited to participate. Psychological assessments performed by Louise Butler included 4 subtests of the WISC with each participating child aged 6–17 years or the WAIS with each participating child aged 17 years and over, with a prorated estimation of full scale IQ using Sattler's procedure, (Sattler, 1992) as in other IMAGE centres. Blood samples or mouth swabs were take by the author from each participating person, with the vast majority donating a blood sample. When all the data could not be gathered at one visit, a second or third visit was organised.

2.3 Measures used

2.3.1 Assessment of ADHD and co-morbid disorders for IMAGE

Parents of each child participating in the study (probands and siblings) completed the long version of the Conners' Parent Rating scale (Conners' et al, 2001) and the parent rated Strengths and Difficulties Questionnaire (Goodman 1997; Goodman et al, 2004) about their child. Teachers completed the Conners' Teacher Rating scale and the teacher rated Strengths and Difficulties Questionnaire (SDQ) about each child participating in the study. The parent and teacher Conners' rating scales were used to screen for the presence of ADHD in all children (probands or siblings). Those who scored above a cut-off point of a T-score of 63 on column N of the Conners' rating scale (DSM IV Symptoms: Total column) were further assessed for the presence of ADHD by the performance of the (PACS) semi-structured interview with one or both parents. The T-score is a percentile score with each T-score scale having a mean of 50 and standard deviation of 10, and allows comparison of the child's score with that of the general population. Children who have a T-score of 65 or above are generally considered to have a clinically significant problem (Conners' et al, 2001). The IMAGE study and this study used a T-score of 63 as a screening measure to identify those with borderline or clinically significant ADHD symptoms on Conners' assessment.

The PACS was developed specifically for the assessment of symptoms of ADHD and comorbid disorders (Taylor et al, 1986). The PACS contains detailed questions about the presence of symptoms of inattention, hyperactivity and impulsivity in various situations

as well as detailed questions about the presence of symptoms of oppositional defiant disorder and symptoms of conduct disorder. The Hypescheme data capture system (Curran et al, 2000) was used to apply a standardised algorithm to symptoms listed from the PACS interviews, SDQ parent and teacher data and Conners' parent and teacher data, thus generating DSM-IV diagnoses of ADHD (inattentive type, hyperactive-impulsive type, and combined type), conduct disorder, and oppositional defiant disorder. The teacher rated Conners' questionnaire and teacher rated SDQ were used to identify the presence of pervasive symptoms of ADHD, a diagnostic criterion for the diagnosis of ADHD using DSM-IV. The parent and teacher rated Strengths and Difficulties Questionnaires were also used to identify the duration of symptoms and the level of impact the symptoms had on the child's function, as a measure of clinical impairment. For a diagnosis of ADHD using the DSM-IV criteria, symptoms must be present for at least 6 months and there must be impairment due to these symptoms. The assessment of symptoms by questionnaire and interview took place at each local IMAGE centre. The responses to the questionnaires and the PACS interviews were sent electronically to the central database in London, where the algorithm was applied to the anonymous data, and using this information, the diagnostic category of the child was generated. Children were categorized as those with No ADHD, ADHD inattentive type, ADHD hyperactive type and ADHD, combined type. Using the responses to the PACS interview, they were also categorized into those with and without a diagnosis of ODD and/or of conduct disorder.

The PACS also contains questions about the presence of mood disorders and developmental disorders such as pervasive developmental disorders, language disorder,

motor disorder and reading disorder. Detailed information was also collected on the presence of tics, attachment disorder, pregnancy risk factors for ADHD and perinatal risk factors for ADHD, as well as the child's response to medication. As part of the training for the PACS, interviewers were trained to assess for the presence of language disorder, reading disorder, motor disorder, pregnancy risk factors and perinatal risk factors and code these disorders as "no disorder", "possible disorder" or "definite disorder."

Perinatal risk factors and were classified as 'Definite Disorder' if any of the risk factors listed in the Hypescheme Glossary were definitely present (birth weight less than 1.5kg, gestational age less than 29 weeks, apgar score less than 2 at 5 minutes, special care baby unit for more than 24 hours, severe infection, severe metabolic disturbance (hypoglycaemia, acidosis, hypocalcaemia), seizures/convulsions in the first month of life). Pregnancy risk factors were classified as 'Definite Disorder' if any of the risk factors listed in the Hypescheme Glossary were definitely present (antepartum hemorrhage, pre-eclamptic toxaemia, hypertension, diabetes, severe infection, smoking more than 20 cigarettes per day for at least 3 months of the pregnancy, use of benzodiazepines, anticonvulsants or any other drugs thought to be associated with ADHD in the offspring). A child was classified as having a definite diagnosis of reading disorder, language disorder or motor disorder if there was documentary evidence of this disorder from the child's clinic. A child was classified as having a possible disorder if there were symptoms of the disorder described by the parent but no current documentary evidence of the disorder.

2.3.2 Assessment of symptoms of autism in ADHD probands and siblings

Autism symptoms were measured in probands, siblings and controls using the 40 item SCQ questionnaire (Rutter et al, 2003). The SCQ was developed by Rutter, Bailey and Lord (2003) as a companion questionnaire to the Autism Diagnostic Interview – Revised (ADI-R) (Lord et al, 1994), and was developed with 40 yes/no questions which match discriminative questions from the ADI-R. There are two versions of the SCQ – the Current version, which focuses on current symptoms or symptoms in the past three months and the Lifetime version, which has 20 questions about the child's symptoms at age 4 – 5 years of age. Both are designed to be completed by the parent or caregiver, and the Lifetime version was used in this study. A validation study by Berument et al, (1999) found that there is a correlation of 0.71 between the SCQ and the ADI-R. In the validation study, the SCQ scores of children with autism were compared with the SCQ scores of children with other psychiatric diagnoses. Berument et al, (1999) recommended that a cut-off of 15 or more could be used to identify children who are likely to have autistic spectrum disorder, and a cut-off of 22 or more could be used to identify children who are likely to have typical autism. Berument et al, (1999) performed a factor analysis of the SCQ and found that a 4 factor model fitted the data, although a three factor model would have been expected, considering that the questionnaire was designed around the three domains of autism in the ADI-R (communcication domain, reciprocal social interaction domain and restricted, repetitive, stereotyped patterns of behaviour domain).

2.3.3 Exclusion of children with ASD from the IMAGE sample

The SCQ and the prosocial scale of the SDQ were used to screen for symptoms of autism in probands and siblings. Children with a score of 15 or higher on the parent completed SCQ, or a score of 4 or less on the parent or teacher prosocial scale of the SDQ or for whom the researcher had a clinical suspicion that the child may have an autism spectrum disorder were further assessed by a clinical researcher in each centre for symptoms of autism using the autism part of the PACS semistructured interview (see *Section 2.6.2*). This contains 12 questions which assess for symptoms in the three domains of autism (communication domain, reciprocal social interaction domain and restricted, repetitive, stereotyped patterns of behaviour domain). An algorithm applied to the autism part of the PACS at the London central database was used to classify children into those with No Autism, Atypical Autism and Typical Autism. Children identified as having atypical autism or typical autism were then excluded from the IMAGE study.

2.4 Final sample used in the present study

2.4.1 Final dataset preparation of study sample

The final dataset for the study of autism symptoms in ADHD consisted of families with sibling pairs, both of whom fulfilled all inclusion criteria for the IMAGE study. In addition to the exclusion criteria listed in S*ection 2.2.2*, all children with an incomplete SCQ questionnaire were excluded from the study. All children who had a high SCQ score (>=15) or an SDQ prosocial score of 4 or less, or strong clinical suspicion of autism but who did not have a complete autism assessment as part of the PACS interview were excluded from this study. In total, 821 families who participated in the IMAGE study were included in the present study.

2.5 Control sample of normal children

2.5.1 Recruitment of the sample of normal children

Parents of children aged 4 – 13 years attending a mainstream state funded primary school of 240 children of mixed gender were invited to complete the SCQ questionnaire about their child. The school is situated in a rural area close to a new suburb of a large town, and serves both the rural and urban community, with all socio-economic groupings represented. The questionnaire was distributed to the pupils by their teachers, accompanied by a letter explaining the study, the possibility of publication of the results of the study and the option of returning the questionnaire blank if parents did not consent to the study.

2.6 Statistical Analysis

2.6.1 Comparison of mean symptoms of autism in probands, siblings and normal children

The mean SCQ score for probands with ADHD-CT and the mean SCQ score for all siblings, unselected for ADHD status was calculated. The sibling group was then divided into those without ADHD, those with ADHD any type and those with ADHD-CT and the mean SCQ score and standard deviation for each subgroup of siblings was calculated. The mean age and the mean parent rated Conners' score of each group was calculated. The mean SCQ score and mean age of the sample of normal control children was also calculated. For each of these groups, the mean SCQ score was calculated for males, females and for the group as a whole. A random effects model controlling for status (sibling or proband) and for gender was constructed to compare SCQ scores within families. The proband SCQ scores were then compared with the SCQ scores of the (1) unselected siblings (2) siblings with ADHD (any type) and (3) siblings without ADHD, using the within family random effects model. The Stata statistical package was used to analyse the data. In keeping with statistical advice received, parametric tests were used in this study as the data sample is large and the parametric tests used are sufficiently robust to analyse data distributed as it is distributed in this study.

2.6.2 Familiality: Calculation of sibling correlation of autism symptoms

The correlation of autism symptoms within families was assessed, by calculation of the intraclass correlation co-efficient. Autism symptoms within families were compared by calculation of this coefficient for (1) probands and siblings unselected for ADHD status, (2) probands and siblings with ADHD, any type and (3) probands and siblings without ADHD. This was performed for the group as a whole, for families with male-male sibling pairs and for families with female-female sibling pairs. The intraclass correlations of each of the sub-scores of the SCQ representing the three domains of autism from the ADI were also calculated for the group as a whole, for families with male-male sibling pairs and for families with female-female sibling pairs.

2.6.3 Familiality: Calculation of familial influences on autism symptoms in ADHD

A modified method of DeFries-Fulker analysis was used to analyse the effect of shared familial influences on symptoms of autism and symptoms of ADHD in our data (DeFries and Fulker, 1985; Purcell and Sham 2003; Andreou et al, 2007). Initially the correlation of symptoms of autism and symptoms of ADHD was calculated (phenotypic correlation), and then the proportion of phenotypic correlation which was due to shared familial influences was calculated. This method of analysis of shared familial influences of a bivariate phenotype was described by Andreou et al, (2007) in a study of the shared familial influences on ADHD symptoms and reaction time in ADHD.

DeFries-Fulker analysis allows the calculation of the heritability of a trait by comparing the correlation of the trait among sibling pairs (or proband and sibling pairs) with the rate of the trait in the normal population. If the sibling rate of the trait is similar to the affected proband rate, it is hypothesized that the effect of familial influences on the trait are high. However if the sibling rate of the trait is similar to the rate of the normal population, then the influence of familial effects is small.

To be more precise, the correlation of a trait among sibling pairs can be described as representing the effect of additive genetic effects (A) and the common or shared environment effects (C). Sibling pairs share on average half of their genetic make-up, and thus if the effect of the common environment on a trait is small or negligible, then the correlation between siblings represents half of the additive genetic effects acting on a trait. The heritability can thus be calculated as twice the sibling correlation of a trait, if it is assumed that the effect of shared environment is negligible.

There are three steps in the calculation of the proportion of the correlation of autism symptoms and ADHD symptoms which are due to shared familial influences. These calculations are valid and reflect the shared familial effects of autism symptoms and ADHD symptoms if the effect of the common environment on autism symptoms and on ADHD symptoms is small. It has been shown that the effect of the shared or common environment on the variance of ADHD symptoms is negligible (Faraone and Doyle, 2000) and that the heritability of ADHD is the region of 60 – 90% (Faraone et al, 2005).

The heritability and the effect of the common environment on autistic-like traits in the normal population has also been calculated, using a sample of twins from the normal population (Ronald et al, 2006). It was found that extreme autistic-like traits have a heritability of 0.64–0.92 and autistic-like traits have a heritability of 0.78-0.81. No significant effect of shared environment on the variance of autistic-like traits in the population was found.

The first step in the calculation of the shared familiality is to calculate the correlation between symptoms of autism in probands and symptoms of ADHD in probands. The difference between the mean score of each trait in probands and the population mean for that trait was used in the calculation of the correlation. This is termed the phenotypic correlation and is calculated as follows: (mean SCQ score in probands – mean SCQ score in normal population)/(mean ADHD Conners' score in probands – mean ADHD Conners' score in normal population), with each difference expressed in units of the standard deviation of that trait in the normal population (Equation 1). The mean SCQ score of the sample of normal schoolchildren recruited in this study was used to represent the normal population, and the mean Conners' T score of the normal population is known to be 50 (Conners, 2001). The second step is to calculate the correlation between mean symptoms of autism in siblings and mean symptoms of ADHD in the proband group. This is known as the bivariate sibling correlation and is calculated as follows: (mean SCQ score of siblings – mean SCQ score of normal population)/(mean ADHD Conners' score of probands – mean ADHD Conners' score of normal population), with each difference

expressed in units of the standard deviation of that trait in the normal population (Equation 2). The third step is to calculate the percentage of the phenotypic correlation which is due to shared familial influences and is calculated using the equation 2*(bivariate sibling correlation)/phenotypic correlation, which can also be expressed as 2*(mean autism symptoms in siblings – mean autism symptoms in the normal population)/(mean autism symptoms in probands – mean autism symptoms in the normal population) (Equation 3). This figure represents the percentage of the phenotypic correlation of autism symptoms with ADHD symptoms which is due to shared familial influences if the effect of the shared environment is small or negligible for each trait, which has already been shown to be the case.

The shared familiality of autism symptoms and ADHD symptoms was calculated for the group as a whole, for male-male sibling pairs and for female-female sibling pairs. The shared familiality of each of the subscales of the SCQ (which correspond to the domains of autism measured using the ADI) and symptoms of ADHD was also calculated for the group as a whole, for male-male sibling pairs and for female-female sibling pairs.

2.6.4 Autism symptoms and comorbid oppositional defiant disorder and conduct disorder

The proband group was divided into those with and without oppositional defiant disorder, and the mean SCQ score of each group compared using the independent t test. The proband group was then divided into those with and those without conduct disorder and the mean SCQ score of each group compared using the independent t test.

2.6.5 Autism symptoms and neurodevelopmental difficulties

The proband group was subdivided into those with a reading disorder, a possible reading disorder and no reading disorder, and the mean SCQ of each group compared using one way analysis of variance. The proband group was then subdivided into those with no motor disorder, a possible motor disorder and those with a definite motor disorder, and the mean SCQ compared using one way analysis of variance. All analysis described in this section and in 2.6.4 were performed using SPSS 15.0 (SPSS Inc, IL, USA).

2.6.6 Cluster analysis

We wished to ascertain whether or not the sample of children with ADHD-CT formed different groups or clusters, according to their symptoms of autism, as measured using the SCQ score. The response pattern of the 39 informative questions of the 40 item SCQ questionnaire was analysed for the proband group (who have ADHD-CT), using a latent class analysis. The Latent Gold statistical package was used for this purpose (Vermunt and Magidson, 2000).

The latent class analysis approach is a model based approach for the generation of clusters, and can be described as follows: It is assumed that there is an underlying latent class variable x, which has a number of different categories, each of which corresponds to a particular latent class or cluster. The probabilities of belonging to each cluster or each latent class can be used to express the model. We could assume that there are two variables A and B, and that there are three clusters or latent classes. The probability of getting a response i from item A and response j from item B and belonging to class t can be written as follows:

$\pi_{ijt} = \pi_t^x \pi_{it}^{A|x} \pi_{jt}^{B|x}$ where $t = 1, 2, 3$

π_t^x = probability of being in cluster / latent class t
$\pi_{it}^{A|x}$ = conditional probability of obtaining i^{th} response to item A for members of class t
$\pi_{jt}^{B|x}$ = conditional probability of obtaining j^{th} response to item B for members of class t

Each case can be a member of only one latent class or cluster, and it is assumed that variables A and B are independent, referred to as local independence.

The clinical characteristics of each of the clusters formed using the latent class analysis was studied, and the clinical characteristics of clusters were compared. The mean SCQ score of each cluster was compared as well as the mean age of each cluster. The rates of comorbid oppositional defiant disorder (ODD), conduct disorder (CD), reading disorder (RD), motor disorder (MD), perinatal difficulties and pregnancy difficulties were calculated, with the rates of possible disorders and definite disorders calculated for the presence of reading disorder (RD), motor disorder (MD), perinatal difficulties and pregnancy difficulties. Chi squared analysis was used to compare the rates of comorbid disorders in the various clusters or latent classes formed.

CHAPTER 3: RESULTS

3.1 Introduction

3.1.1 Introduction

The results of the study are presented in five parts in this chapter. In the first part, there is a description of the rates of comorbid disorders in the proband and sibling groups *(Section 3.2.1)* and a description of the distribution of SCQ scores in the normal population sample *(Section 3.2.2)*. The second part of the chapter contains a comparison of mean autism symptoms of the proband, sibling and control samples and explores the relationship between ADHD symptoms and autism symptoms. *(Section 3.3)*. The third part of the chapter contains both a graphical presentation and numerical calculation of the familiality of autism symptoms in ADHD. The intraclass correlation of autism symptoms in the family is expressed to measure the familiality. This part of the chapter also contains the calculation of the shared familiality of ADHD and autism symptoms, using DeFries Fulker analysis *(Section 3.4)*. This is followed by a comparison of mean autism symptoms in those with ADHD with and without comorbid oppositional defiant disorder, conduct disorder, reading disorder and motor disorder *(Section 3.5)*. The final part of the chapter contains the results of the cluster analysis of children with ADHD according to symptoms of autism, and a comparison of the clinical characteristics of the various clusters which were found. This was performed in order to test the fourth hypothesis - that the presence of autism symptoms represents a specific subtype of ADHD-CT with particular phenotypic characteristics (see *Section 1.4.2)*.

3.2 Proband, sibling and control groups

3.2.1 Description of the proband and sibling groups

The study sample contained 821 probands with ADHD-CT, 88% of whom were male. Because many probands had more than one sibling participating in the study, the sample contained a total of 1050 sibling pairs, with 458 male-male sibling pairs, 59 female-female sibling pairs, and the remainder mixed gender sibling pairs. There were 67 male-male sibling pairs concordant for ADHD-CT and 9 female-female sibling pairs concordant for ADHD-CT. 66% of probands (N = 536) had oppositional defiant disorder and 25% (N=202) had conduct disorder. 12% had a possible language disorder and 13% had a definite language disorder. 20% had a possible reading disorder and 28% had a definite reading disorder. 27% had a possible motor disorder and 21% had a definite motor disorder (Table 1).

The sibling group contained 1050 children, with a 1:1 male to female ratio in sharp contrast to the male bias in probands. The sibling group contained 868 children who did not have ADHD and 182 who had ADHD, either inattentive, hyperactive or combined type according to DSM IV. 10.6% (N=111) of siblings had ADHD -CT. 43% of siblings with ADHD-CT had oppositional defiant disorder and 22.5% of siblings with ADHD-CT had conduct disorder. 9% of siblings with ADHD-CT had a definite language disorder, 21% had a definite reading disorder and 13% had a definite motor disorder (Table 2).

Table 1: Rate of comorbid disorders in probands with ADHD, combined type

	Possible Disorder	Definite Disorder
Oppositional Defiant Disorder		66%
Conduct Disorder		25%
Language Disorder	12%	13%
Reading Disorder	20%	28%
Motor Disorder	27%	21%

Table 2: Rate of comorbid disorders in siblings with ADHD, combined type

	Possible Disorder	Definite Disorder
Oppositional Defiant Disorder		43%
Conduct Disorder		22.5%
Language Disorder	9%	9%
Reading Disorder	15%	21%
Motor Disorder	13%	13%

3.2.2 Distribution of SCQ scores in normal control sample

A total of 182 SCQ questionnaires were returned from the 240 normal school children sample (a response rate of 75.8%). 14 questionnaires were returned blank; 11 questionnaires were returned incomplete and 4 were returned for whom the gender was not known. 153 completed questionnaires from normal children were studied, with a male to female ratio of 1:1. They ranged in age from age 4 to 12 years and had a mean age of 8.14. The group of normal control children had a mean SCQ score of 3.89, SD = 2.77, calculated with outlier values greater than 2 SD above the mean excluded. The mean SCQ score of males was 4.00, SD = 2.65 and in females was 3.78, SD = 2.90. The distribution of SCQ score for normal control children can be seen in Figures 2, 3 and 4 below.

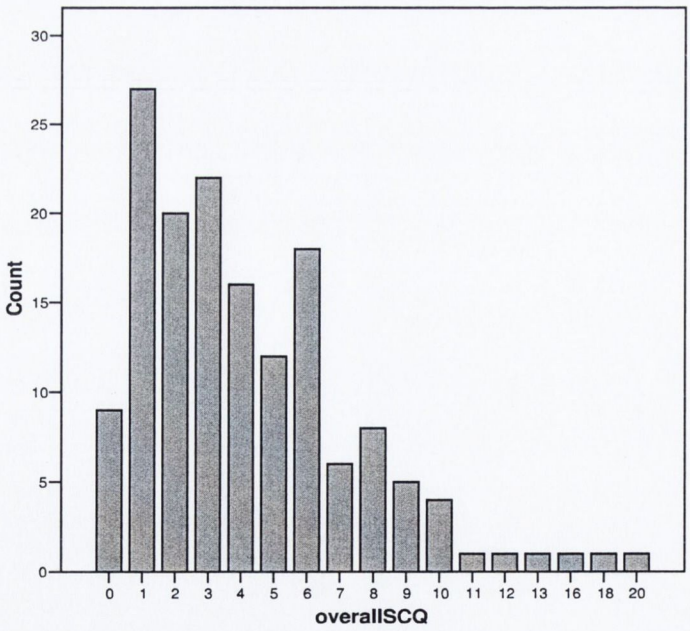

Figure 2: Distribution of SCQ in normal control sample

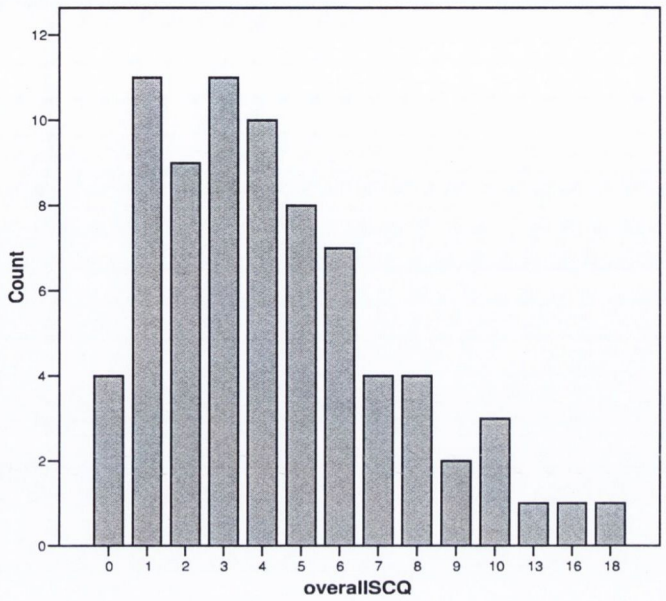

Figure 3: Distribution of SCQ in normal control males

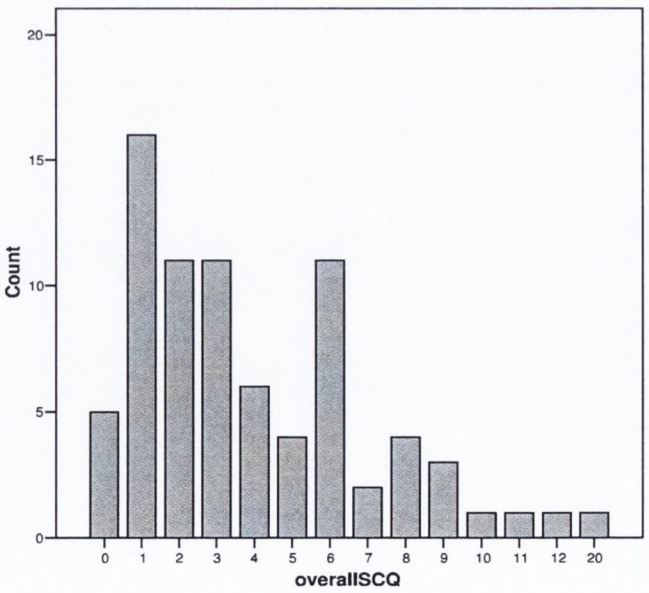

Figure 4: Distribution of SCQ in normal control females

The mean score for the subscales of the SCQ in normal control children which correspond to the three domains of autism are listed in Table 3.

Table 3: Normal control sample - means of subscales of the SCQ

	Minimum	Maximum	Mean	Std. Deviation
Total SCQ	0	12	3.89	2.769
Communication total	0	6	2.04	1.660
Repetitive Behaviour total	0	7	0.84	1.186
Social Reciprocal Interaction total	0	6	0.93	1.149

3.3 Symptoms of autism in ADHD

3.3.1 Symptoms of autism in probands with ADHD, siblings and normal children

The proband group were found to have a mean SCQ score of 8.49, SD = 6.23, with a score of 8.48, SD = 6.22 in males and 8.54, SD = 6.40 in females. The total sibling group had a lower mean SCQ score of 4.42, SD = 4.18, with a mean SCQ score of 5.23, SD = 4.65 in males and of 3.61, SD = 3.49 in females. The mean SCQ score of siblings without ADHD was 4.01, SD= 3.79, while the mean SCQ of siblings with ADHD (any type) was 6.36, SD = 5.28. Siblings with ADHD-CT had a mean SCQ score of 6.78, SD = 5.27 (Table 4). A significant difference between the male and female mean SCQ scores was noted for the unselected sibling group ($t = 6.355$, $df = 966.5$, $p < .001$, 95% CI = 1.11 – 2.11), siblings without ADHD ($t = 5.10$, $df = 763.5$, $p < .001$, 95% CI = 0.81 – 1.82), and siblings with ADHD, any type ($t = 2.49$, $df = 162.1$, $p = .014$, 95% CI = 0.39-3.36). As the SCQ can be related to age (see *Section 4.3.2*) the mean age of each group was calculated. The mean SCQ score for probands, siblings and normal control children in each of the age groups <5years, 5-7 years, 8-10 years and >10 years can be seen in Table 5. It can be seen that the greater mean SCQ score seen in probands and siblings in comparison to normal control children is generally present in all age groups, though not at a significant level.

Table 4: Comparison of SCQ scores in probands, siblings and normal controls

Group	Number	Mean SCQ +/- SD	Mean Age +/- SD	Mean Conners'+/-
All Probands	821	8.49 +/- 6.23	10.9 +/- 2.8	77.84 +/- 8.87
Probands Male	723	8.48+/- 6.22	19.9 +/- 2.7	77.0 +/- 8.70
Probands Female	98	8.54 +/- 6.40	10.5 +/- 3.0	83.74 +/- 7.90
All Unselected Siblings	1050	4.42 +/- 4.18	10.7 +/- 3.3	55.7 +/- 13.87
Unselected Siblings Male	522	5.23* +/- 4.65	10.5 +/- 3.2	56.52 +/- 13.70
Unselected Siblings Female	527	3.61+/- 3.49	10.8+/- 3.3	54.91 +/- 14.03
All non-ADHD siblings	868	4.01 +/- 3.79	10.7-+/- 3.3	52.14 +/- 11.49
non-ADHD siblings Male	406	4.71*+/- 4.20	10.6-+/- 3.3	52.42 +/- 11.27
non-ADHD siblings Female	461	3.39 +/- 3.28	10.9 +/- 3.3	51.91 +/- 11.69
All Siblings ADHD any type	182	6.36 +/- 5.28	10.4 +/- 3.1	72.65 +/- 11.64
Siblings ADHD any type Male	116	7.04* +/- 5.62	10.4 +/- 3.0	70.91 +/- 11.64
Siblings ADHD any type female	66	5.17 +/- 4.42	10.3 +/- 3.4	75.67 +/- 11.07
All Siblings Combined Type ADHD	111	6.78 +/- 5.27	10.4 +/- 3.3	75.01 +/- 11.98
Siblings Combined Type ADHD Male	79	6.92 +/- 5.47	10.4 +/- 3.1	72.53 +/- 11.89
Siblings Combined Type ADHD Female	32	6.44 +/- 4.83	10.3 +/- 3.9	81.06 +/- 10.05
All Normal Controls	149	3.89 +/- 2.77	8.07 +/- 2.33	n/a
Normal Controls Male	73	4.00 +/- 2.65	8.18 +/- 2.46	n/a
Normal Controls Female	76	3.78 +/- 2.90	7.96 +/- 2.21	n/a

*A significant difference between male and female SCQ score was noted for the unselected sibling group ($t = 6.355$, $df = 966.5$, $p < .001$, 95% CI = 1.11 – 2.11), the siblings with ADHD any type ($t = 2.49$, $df = 162.1$, $p = .014$, 95% CI = 0.39-3.36) and siblings without ADHD ($t = 5.10$, $df = 763.5$, $p < .001$, 95% CI = 0.81 – 1.82).

Table 5: Description of SCQ scores in probands, siblings and normal controls in each age group

Agegroup	Status	Mean SCQ	N	Std. Deviation
<5yrs	Siblings	6.00	7	7.024
	Normal population	5.14	7	2.91
5-7 yrs	Probands	7.78	88	6.069
	Siblings	4.95	207	4.109
	Normal population	4.24	55	2.89
8-10 yrs	Probands	8.06	297	6.225
	Siblings	4.39	284	4.162
	Normal population	3.97	59	3.43
>10 yrs	Probands	8.93	435	6.258
	Siblings	4.19	528	4.186
	Normal population	4.57	30	4.55
Total	Probands	8.49	821	6.233
	Siblings	4.42	1050	4.182
	Normal population	3.89	149	2.77

A random effects model was used to compare autism symptoms or total SCQ score within families, controlling for gender and for the status of the child (proband or sibling). Using this method, the proband SCQ score was compared with the SCQ score of each sibling in the family. This was initially performed for all families together, regardless of whether sibling pairs were concordant or discordant for ADHD. It was found that there was a significant effect of diagnostic status (whether proband or sibling) on the SCQ score, with the proband SCQ score 3.67 to 5.68 SCQ points greater than the sibling SCQ score, $p<.001$. A statistically significant effect of gender on SCQ score was also found, with the male SCQ score 1.22 to 2.36 SCQ points higher than the female SCQ score, $p<.001$. There was a statistically significant interaction between the effects of status and the effect of gender, with an effect of 0.29 to 2.60, $p =0.014$. This means that part of the increase in SCQ score in male probands was due to the effect of gender, part was due to the effect of status and part was due to an interaction between these two factors (Table 6).

The large group of families was then divided into two groups – one with sibling pairs which were concordant for ADHD, and one with sibling pairs which were discordant for ADHD. It should be recalled that all probands had ADHD-CT while the concordant siblings had ADHD, any type. For each of these two family groups, the within family random effects model was used again to compare the effect of status (whether proband or sibling) and the effect of gender on SCQ score. For the group with probands and siblings with ADHD, any type, the effect of status on SCQ score was 0.9 to 2.54 SCQ points, which is considerably smaller than the effect of status on SCQ score for the group of probands and unselected siblings described above. The effect of status on SCQ score was

greatest in the group of families with probands and siblings without ADHD, where the SCQ score of probands was 3.98 to 6.23 SCQ points greater than the SCQ score of siblings (Table 6).

The effect of gender on SCQ score noted in the total family group (probands and unselected siblings) was also seen in the family group with probands and siblings with ADHD, any type and in the group of families with probands and siblings without ADHD (Table 6). There was a significant interaction between the effect of status and the effect of gender for the family group with discordant siblings, but not for the family group with concordant siblings. This means that there was a greater than expected increase in the SCQ score for male probands than for female probands in the group of families with probands and siblings without ADHD, but that this was not noted for the family group with concordant siblings.

Table 6: Comparison of autism symptoms within family groups

Comparison group	Effect	Significance	Size of effect
Probands and unselected siblings	Status*	P<0 .001	3.67 to 5.68
	Gender	P<0 .001	1.22 to 2.36
	Status x gender	P=0.014	0.29 to 2.60
Probands and siblings with ADHD, any type	Status	P< .001	0.90 to 2.54
	Gender	P< .001	1.07 to 3.40
Probands and siblings without ADHD	Status	P< .001	3.98 to 6.23
	Gender	P< .001	0.79 to 2.05
	Status x gender	P=.029	0.14 to 2.73

*A random effects model controlling for status (sibling or proband) and for gender was constructed to compare SCQ scores within families. Proband SCQ scores were compared with (1) unselected sibling SCQ scores, (2) SCQ scores of siblings with ADHD and (3) SCQ scores of siblings without ADHD, using the within family random effects model. The size of the effect of status (proband or sibling) on SCQ score is shown, with 95% confidence intervals; the size of the effect of gender on SCQ score and the size of the effect of status x gender are also shown.

3.3.2 Correlation of autism symptoms with ADHD symptoms

Symptoms of autism measured using the SCQ questionnaire were correlated with symptoms of ADHD and displayed graphically using a dot plot. For each child in the study sample (probands and siblings), symptoms of ADHD measured using the parent rated Conners' DSM-IV:Total T score were plotted on the X-axis and symptoms of autism (SCQ score) were plotted on the Y-axis (Figure 5). It can be seen that children with high symptoms of ADHD are more likely to have high symptoms of autism than children with low symptoms of ADHD. However there are many children who have very high symptoms of ADHD but do not have raised symptoms of autism. There is less variation of autism symptoms among children with low ADHD symptoms than in children with high ADHD symptoms. Thus it can be summarized that the relationship between symptoms of autism and symptoms of ADHD is non-linear. From these analyses it can be seen that autism symptoms are not merely a measure of severity of ADHD, as postulated in the first hypothesis, and the possibility that autism symptoms in ADHD are familial, as outlined in the second hypothesis, was explored (see *Section 1.4.2*).

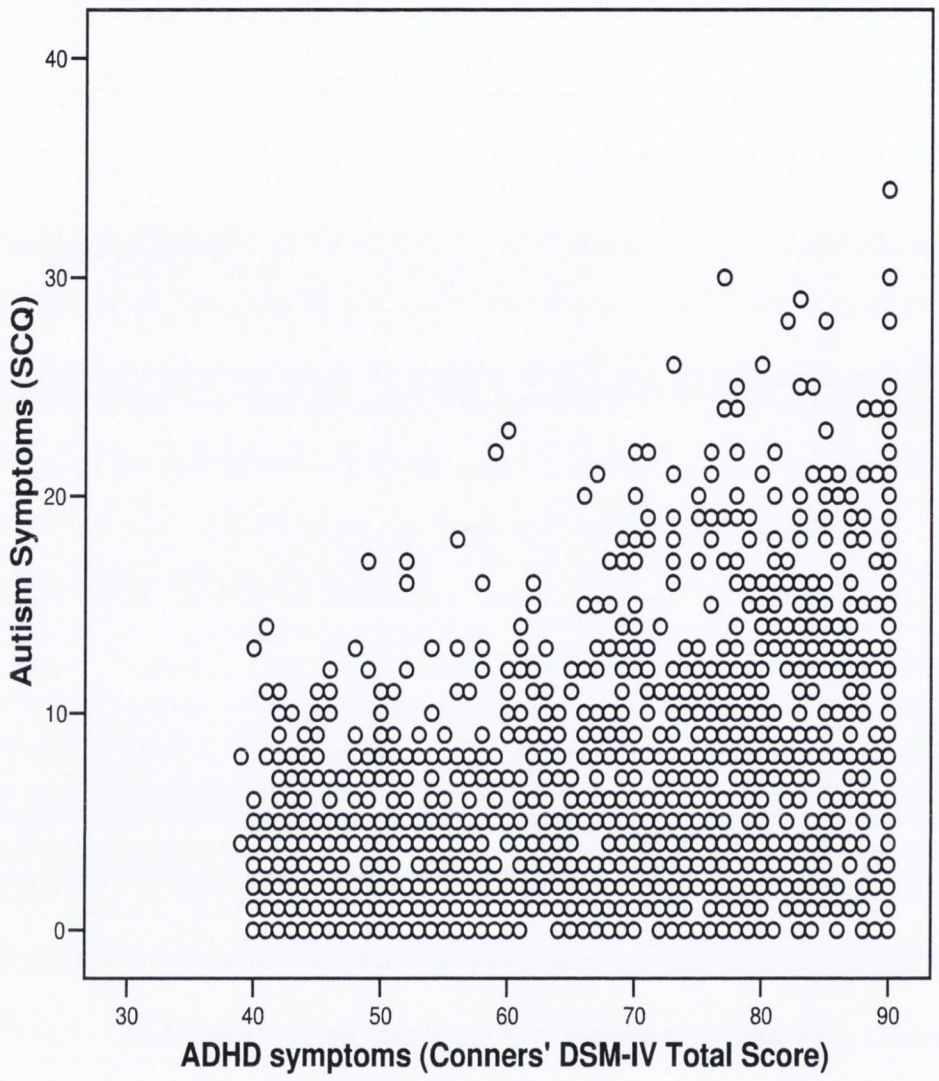

Figure 5: Autism symptoms vs. ADHD symptoms (all probands and siblings)

3.4 Measurement of familiality

3.4.1 Calculation of familiality of autism symptoms in ADHD

The correlation of autism symptoms within families was assessed graphically by examining the correlation of SCQ scores in families where there were two children, both with ADHD-CT (concordant sibling pairs). A graph was constructed where autism symptoms of probands were plotted against autism symptoms of their siblings with ADHD-CT. As can be seen from Figure 6, this graph has a linear appearance and has a Pearson's correlation of 0.58, $p<0.001$. Some families have 2 children with ADHD-CT, both of whom also have high symptoms of autism, while other families have 2 children with ADHD-CT, both of whom have low symptoms of autism. This supports the hypothesis that autism symptoms are at least in part a familial trait in ADHD, as postulated in the second hypothesis (see *Section 1.4.2*). Graphs were then constructed to show the familiality of autism symptoms in families with male-male sibling pairs (Figure 7) and families with female-female sibling pairs (Figure 8) concordant for ADHD-CT.

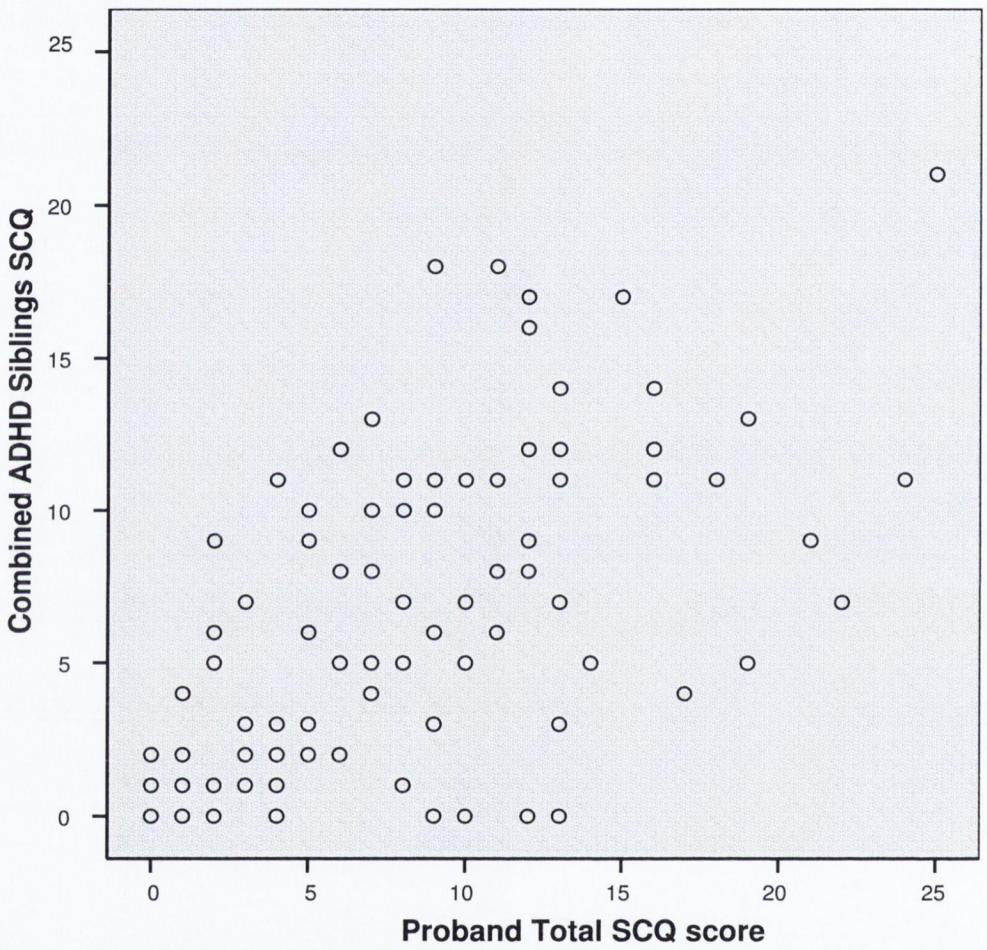

Figure 6: Familiality of autism symptoms in sibling pairs concordant for ADHD
Autism symptoms of probands (ADHD-CT) vs. Autism symptoms of siblings with ADHD-CT; Pearson correlation = 0.58, $p<0.001$, number of families = 102

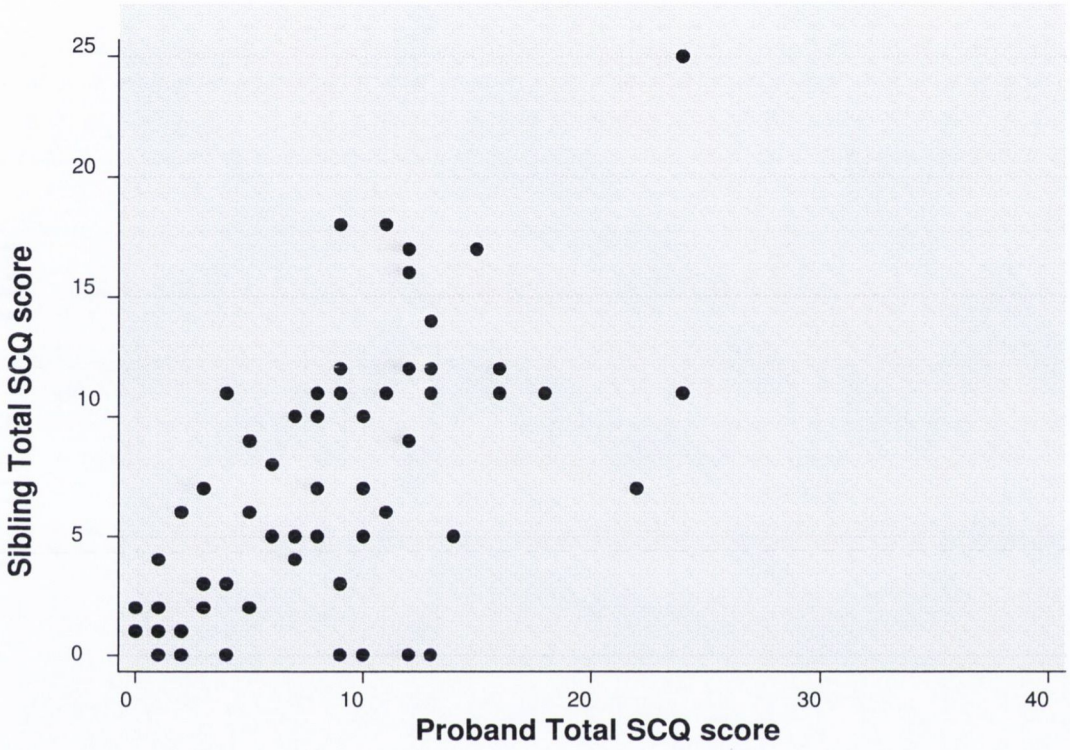

Figure 7: Familiality of autism symptoms in male-male sibling pairs concordant for ADHD, combined type. Autism symptoms of male probands (ADHD-CT) vs. autism symptoms of male siblings with ADHD-CT; Pearson correlation = 0.64, $p<0.001$, number of families = 67.

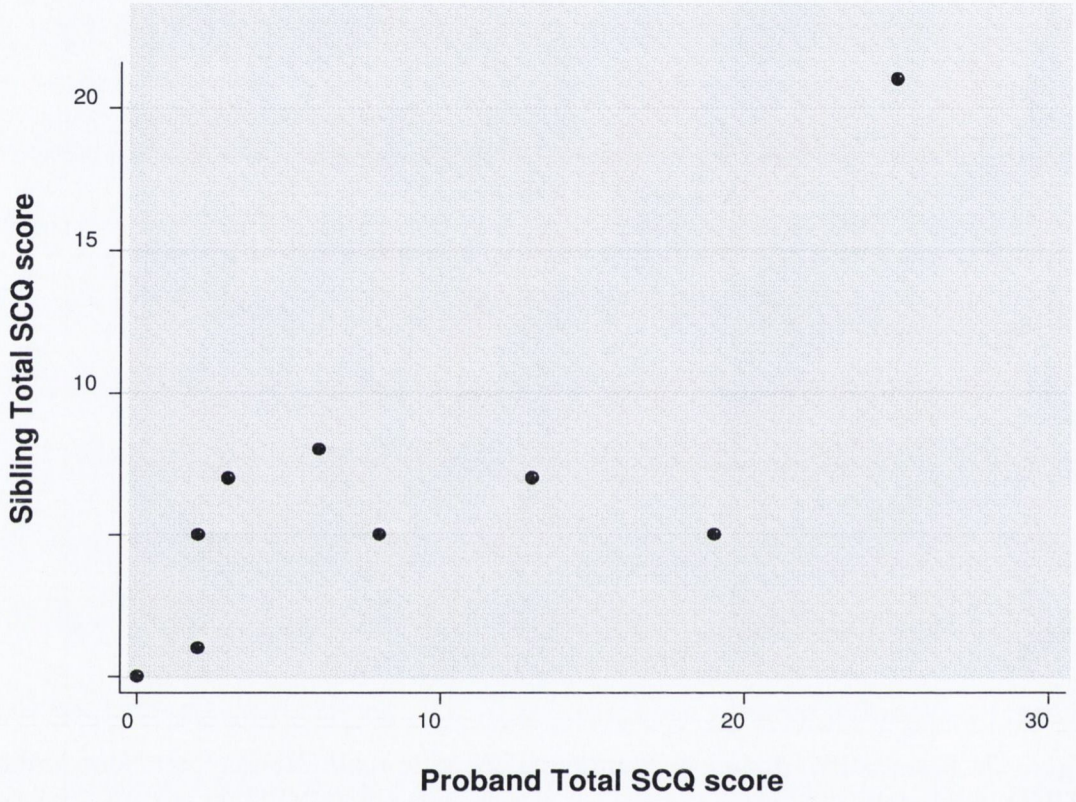

Figure 8: Familiality of autism symptoms in female-female sibling pairs concordant for ADHD, combined type. Autism symptoms of female probands (ADHD-CT) vs. autism symptoms of female siblings with ADHD-CT; Pearson correlation not calculated due to small number of families.

The correlation between autism symptoms in sibling pairs was also assessed statistically by calculation of the intraclass correlation co-efficient, or the correlation of autism symptoms within families. This calculation was performed initially for all proband and sibling pairs, irrespective of the ADHD status of the sibling, and then for probands and siblings with ADHD any type, and finally for probands and siblings without ADHD. In the analysis, the SCQ score of each proband was compared with the SCQ score of each child in the family. As some families had just one sibling, and other families had 2 or more siblings, a correction was made for the number of children in the family, so that a large family could not bias the intra-class correlation co-efficient calculated. The correlation between proband and sibling symptoms of autism was 0.37 for siblings unselected for ADHD status; 0.54 for probands and siblings with ADHD, any type and 0.32 for probands and their siblings without ADHD. Thus it can be seen that the correlation between autism symptoms of the proband and sibling is greatest when both children have ADHD (see Table 7). The correlation of autism symptoms in families with male-male sibling pairs can be seen in Table 8 and the correlation of autism symptoms in families with female-female sibling pairs can be seen in Table 9. The correlation of autism symptoms in males (0.37) is similar to that of the group as a whole (0.37), and similar to the correlation of autism symptoms in females (0.36).

The correlation of autism symptoms from the SCQ questions representing each of the three domains of autism (communication domain, reciprocal social interaction domain and repetitive behaviour and stereotyped patterns domain) was then calculated for families with male-male sibling pairs (Table 10) and for families with female-female

sibling pairs (Table 11). The correlation of symptoms of autism was stronger in the communication domain (0.47) than in the reciprocal social interaction domain (0.30) or the repetitive behaviour and stereotyped patterns domain (0.25) in families with unselected male sibling pairs. However in families with concordant male-male sibling pairs both with ADHD-CT there was a considerable correlation of symptoms from the repetitive behaviour and stereotyped patterns domain (0.42) as well as from the communication domain (0.57).

The correlation of autism symptoms was higher in the communication domain (0.45) than in the reciprocal social interaction domain (0.39) or the repetitive behaviour and stereotyped patterns domain (0.12) in families with unselected female-female sibling pairs. The number of families with concordant female sibling pairs, both with ADHD, any type (N= 14) or both with ADHD-CT (N= 9) were too small to perform intraclass correlation analyses.

Table 7: Correlation of symptoms of autism within families

Sibling group	Intraclass Correlation
Unselected sibling	0.37 (0.32-0.42)
Siblings with ADHD, any type	0.54 (0.43-0.64)
Siblings without ADHD	0.32 (0.26-0.38)

Note: Intraclass correlation co-efficient for probands with siblings (siblings either unselected, with ADHD any type, with ADHD-CT or without ADHD), and 95% confidence intervals for intraclass correlation co-efficient.

Table 8: Correlation of symptoms of autism within families with male-male sibling pairs

Sibling group	no. of families	Intraclass Correlation
Unselected sibling	404	0.37 (0.31-0.45)
Siblings with ADHD, any type	94	0.54 (0.42-0.66)
Siblings with ADHD, Combined Type	67	0.57 (0.43-0.70)
Siblings without ADHD	324	0.31 (0.23-0.40)

Note: Intraclass correlation co-efficient for male probands with male siblings (siblings either unselected, with ADHD any type, with ADHD-CT or without ADHD) and 95% confidence intervals for intraclass correlation co-efficient.

Table 9: Correlation of symptoms of autism within families with female-female sibling pairs

Sibling group	no. of families	Intraclass Correlation
Unselected sibling	53	0.36 (0.18-0.59)
Siblings with ADHD, any type	14	number too small to analyze
Siblings with ADHD, Combined Type	9	number too small to analyze
Siblings without ADHD	41	0.25 (0.08-0.54)

Note: Intraclass correlation co-efficient for female probands with female siblings (siblings either unselected, with ADHD any type, with ADHD-CT or without ADHD) and 95% confidence intervals for intraclass correlation co-efficient.

Table 10: Correlation of domains of autism symptoms within families with male-male sibling pairs

Sibling group	no. of families	Intraclass Correlation
SCQ communication domain		
Unselected sibling	404	0.47 (0.41-0.54)
Siblings with ADHD, any type	94	0.53 (0.41-0.65)
Siblings with ADHD, Combined Type	67	0.57 (0.42-0.70)
Siblings without ADHD	324	0.45 (0.38-0.53)
SCQ social reciprocal interaction domain		
Unselected sibling	404	0.30 (0.23-0.38)
Siblings with ADHD, any type	94	0.36 (0.24-0.52)
Siblings with ADHD, Combined Type	67	0.35 (0.20-0.53)
Siblings without ADHD	324	0.26 (0.18-0.36)
SCQ repetitive behaviour and stereotyped patterns domain		
Unselected sibling	404	0.25 (0.18-0.33)
Siblings with ADHD, any type	94	0.40 (0.27-0.54)
Siblings with ADHD, Combined Type	67	0.42 (0.0.27-0.59)
Siblings without ADHD	324	0.18 (0.11-0.29)

Note: Intraclass correlation co-efficient for male probands with male siblings (siblings either unselected, with ADHD any type, with ADHD-CT or without ADHD) and 95% confidence intervals for intraclass correlation co-efficient, for each subscale of SCQ.

Table 11: Correlation of domains of autism symptoms within families with female-female sibling pairs

Sibling group	no. of families	Intraclass Correlation
SCQ communication domain		
Unselected sibling	53	0.45 (0.27-0.65)
Siblings without ADHD	41	0.38 (0.18-0.62)
SCQ social reciprocal interaction domain		
Unselected sibling	53	0.39 (0.22-0.61)
Siblings without ADHD	41	0.33 (0.14-0.58)
SCQ repetitive behaviour and stereotyped patterns domain		
Unselected sibling	53	0.12 (0.01-0.50)
Siblings without ADHD	41	0.08 (<0.00-0.68)

Note: Intraclass correlation co-efficient for female probands with female siblings (siblings either unselected or without ADHD) and 95% confidence intervals for intraclass correlation co-efficient, for each subscale of SCQ. The number of families with female-female sibling pairs with ADHD, any type (N=14) and the number with female-female siblings with ADHD-CT (N=9) were too small to analyze the correlation of the domains of the SCQ.

3.4.2 Shared familial effects on ADHD and autism traits

The proportion of the correlation of autism symptoms and ADHD symptoms which are due to shared familial influences was calculated using a modified DeFries Fulker analysis according to the description in *Section 2.6.3*. Initially the phenotypic correlation of symptoms of autism with symptoms of ADHD was calculated, using the first of the group of three equations described in *Section 2.6.3*. The phenotypic correlation can be described as the increase in mean autism symptoms of probands above the mean autism symptoms of the normal population divided by the increase in mean ADHD symptoms in probands, above the mean ADHD symptoms of the normal population. For the calculation of the phenotypic correlation using the first equation in *Section 2.6.3*, each increase in mean symptoms was expressed in terms of the standard deviation of that trait in the normal population. The mean SCQ score of 3.89, SD = 2.77 for the sample of school children in this study was used to represent the normal population, with the mean SCQ score among males of 4.00, SD = 2.65 taken to represent the SCQ score of the normal male population and the mean SCQ score among females of 3.78, SD = 2.90 taken to represent the normal female population. The mean SCQ subscales for the normal control sample can be seen in Table 12.

Table 12: Mean SCQ scores and mean SCQ subscale scores of normal controls

	Gender	N	Mean	Std. Deviation
SCQ communication total	Males	73	2.01	1.60
	Females	76	2.07	1.73
SCQ repetitive behaviour and stereotyped patterns total	Males	73	0.77	1.02
	Females	76	0.91	1.33
SCQ social reciprocal interaction total	Males	73	1.11	1.25
	Females	76	0.76	1.02

Calculations of the phenotypic correlation of symptoms were performed for the group as a whole, (which included opposite sex sibling pairs and same sex sibling pairs) and for male-male sibling pairs and for female-female sibling pairs, as the normal control mean SCQ score was found to be greater for males than for females. The mean SCQ scores and mean SCQ subscale scores for male probands of male-male sibling pairs, for male siblings of male-male sibling pairs, for female probands of female-female sibling pairs and for female siblings of female-female sibling pairs can be seen in Table 13.

Table 13: Mean SCQ scores and mean SCQ subscale scores of probands and siblings in male and female sib-pairs

	Male probands who have male siblings	Male siblings of male probands	Female probands who have female siblings	Female siblings of female probands
Number	407	458	53	59
SCQ total	8.37 +/ 6.23	5.07 +/- 4.65	8.53 +/-_7.17	3.95 +/- 4.52
Communciation total	3.37 +/- 2.40	2.39 +/- 2.06	3.25 +/- 2.40	1.85 +/- 2.01
Social Reciprocal Interaction total	2.70 +/ 2.95	1.50 +/- 2.10	3.11 +/- 3.40	1.59 +/- 2.53
Repetitive Behaviours total	1.86 +/- 0.97	0.97 +/-1.59	1.74 +/- 1.82	0.42 +/- 0.68

The phenotypic correlation of autism symptoms with ADHD symptoms in probands was 0.69 for the proband group as a whole, 0.71 for male probands, and 0.54 for female probands. This indicates that autism symptoms correlate relatively well with ADHD symptoms in probands, with a greater correlation between autism symptoms and ADHD symptoms seen in male probands than in female probands.

The second step was to calculate the bivariate sibling correlation, which is the ratio of the increase in mean SCQ score of siblings above the population mean SCQ score, divided by the increase in mean ADHD symptoms in probands above the population mean ADHD score. This was calculated using the second equation described in *Section 2.6.3.* Again all increases were expressed in terms of the standard deviation of the trait in the normal population. The bivariate sibling correlation calculated in this way was 0.09 for

the group as a whole, 0.17 for male-male sibling pairs and 0.02 for female-female sibling pairs. This indicates that there is a correlation of .09 between the increase in autism symptoms in siblings and the increase in ADHD symptoms in the proband group. The correlation between the increase in autism symptoms in male siblings and the increase in ADHD symptoms in male probands was greater than the similar correlation for female sibling pairs. It can be seen that very little of the increase in autism symptoms of female siblings above the normal population was associated with an increase in the symptoms of ADHD in female probands above the normal population. In other words, there is little association between autism symptoms in female siblings and ADHD symptoms in the female proband group.

The final step was to calculate the percentage of the phenotypic correlation which was due to shared familial influences, assuming that the effect of shared environment was negligible and that siblings share on average half of their genetic make-up. This was calculated using the third equation in *Section 2.6.3,* or the ratio of the bivariate sibling correlation to the phenotypic correlation. It was found that the percentage of the correlation of autism symptoms and ADHD symptoms due to shared familial influences in the sibling pairs was 27% for the group as a whole, 49% for male - male sibling pairs and 7% for female - female sibling pairs (Table 14 and Table 15). The DeFries Fulker analysis was performed for the subscales of the SCQ for male-male sibling pairs and for female-female sibling pairs. For male sibling pairs, the shared heritability of the communication domain with ADHD symptoms was 56%, the shared heritability of the social reciprocal interaction domain with ADHD symptoms was 49% and the repetitive

behaviours domain with ADHD symptoms was 37% (Table 15). Figures were more varied for females, and it was not possible to calculate the shared heritability of the Communication domain or the Repetitive Behaviours domain due to the small sample size.

Table 14: Shared familial effects on ADHD and autism symptoms

Combined type	Phenotypic correlation	Bivariate sibling Correlation	Percentage of phenotypic correlation due to shared genetic influences
Total Sample	0.69	0.09	27%
Corrected total sample	0.70	0.15	43%

Table 15: Defries Fulker analysis of total SCQ and SCQ subscales by gender

	Phenotypic correlation	Bivariate sibling correlation	Percentage of phenotypic correlation due to shared genetic influences
Male Total SCQ	0.71	0.17	49%
Female Total SCQ	0.54	0.02	7%
Male Communication	0.37	0.10	56%
Female Communication	0.22	n/a	n/a
Male Social Reciprocal Interaction	0.55	0.13	49%
Female Social Reciprocal Interaction	0.76	0.27	71%
Male Repetitive Behaviours	0.46	0.08	37%
Female Repetitive Behaviours	0.21	n/a	n/a

In this study, the total group of probands with ADHD-CT had a male to female ratio of 9:1, but the sibling group and normal control groups each had male to female ratios of 1:1. However males had a higher mean SCQ score than females in the unselected sibling and the normal control groups. Hence the calculation of the shared heritabililty of autism symptoms and ADHD symptoms was repeated with the mean SCQ score of the normal controls and of siblings corrected to reflect a 9:1 male to female ratio. This was performed by forming two hypothetical groups of 10 children, - one group of 9 sibling males and 1 sibling female all of average SCQ score, and one group of 9 normal control males and 1 normal control female all of average SCQ score. The mean average SCQ score of each group was thus (9 x mean SCQ for males) + (1 x mean SCQ score for females) / 10. The adjusted shared familiality to take account of the 9:1 ratio of males to

females in the proband group was 43%. This figure is closer to the shared familiality calculated for male probands (49%) than the figure for female probands (7%) (Table 15).

Thus it appears that autism symptoms are partly familial, as hypothesized in the second hypothesis (see *Section 1.4.2*) and that part of that familiality is shared with the familiality of ADHD. The familiality of autism symptoms in ADHD, as measured in the intraclass correlations, is similar in males and in females, (see *Section 3.4.1*) but there is a different shared familiality with ADHD in male and female sibling pairs. The three dimensions of autism have each been shown to be partly familial, with different levels of shared familiality with ADHD found in male and female sibling pairs. This supports the third hypothesis, that *autism symptoms in children with ADHD have the same three dimensional pattern as autism symptoms in children with ASD* (see *Section 1.4.2*).

3.5 Autism symptoms and disorders comorbid to ADHD

3.5.1 Autism symptoms and oppositional defiant disorder and conduct disorder

The proband group was divided into those with and without oppositional defiant disorder. 536 probands had the disorder and 280 probands did not. Probands with comorbid oppositional defiant disorder had a significantly higher mean SCQ score than probands without comorbid oppositional defiant disorder (9.19 vs. 7.15; t = +4.67, df = 629, 95% CI = 1.19 – 2.91, $p < 0.001$). The proband group was then divided into those with and without conduct disorder, and it was found that 202 had conduct disorder and 613 did not. The mean SCQ score of those with conduct disorder was significantly greater than the mean SCQ score of those without conduct disorder. (10.56 vs. 7.81; t= +4.93, df = 288, 95% CI = 1.66 - 3.86, $p < 0.001$ (Table 16).

Table 16: Oppositional disorders and symptoms of autism in ADHD probands

	Number	Mean SCQ	S.D.
No Oppositional Defiant Disorder	280	7.15[1]	5.68
With Oppositional Defiant Disorder	536	9.19	6.41
No Conduct Disorder	613	7.81[2]	5.72
With Conduct Disorder	202	10.56	7.24

[1] t = +4.67, df = 629, 95% CI = 1.19 – 2.91, $p < 0.001$
[2] t = +4.93, df = 288, 95% CI = 1.66 - 3.86, $p < 0.001$

3.5.2 Autism symptoms and neurodevelopmental difficulties

The mean SCQ score of 164 probands with a definite motor disorder was significantly greater than the mean SCQ score of 209 probands with a possible motor disorder and 414 probands with no motor disorder (9.79 vs. 9.10 vs. 7.69; oneway analysis of variance: F =8.04, df = 2, $p<0.001$). There was no statistically significant relationship between autism symptoms in ADHD-CT and comorbid reading disorder. The finding of increased autism symptoms in those with oppositional disorders and in those with motor disorder supports the fourth hypothesis - that the presence of autism symptoms represents a specific subtype of ADHD-CT with particular phenotypic characteristics (see *Section 1.4.2*).

Table 17: Neurodevelopmental difficulties and symptoms of autism in ADHD-CT probands

	Number	Mean SCQ	S.D.
No Reading Disorder	408	8.06[1]	6.13
Possible Reading Disorder	156	8.53	6.36
Definite Reading Disorder	217	9.21	6.39
No Motor Disorder	414	7.69[2]	6.09
Possible Motor Disorder	209	9.10	6.33
Definite Motor Disorder	164	9.79	6.39

[1] Reading Disorder: oneway analysis of variance: F =2.40, df=2, p=0.09
[2] Motor Disorder: oneway analysis of variance: F =8.04, df=2, $p<0.001$

3.6 Cluster Analysis and Comorbid disorders in ADHD

3.6.1 Cluster Analysis

The latent class analysis was performed using 39 informative questions from the SCQ responses of the proband group, as described in *Section 2.6.6.* Five classes were generated which fitted the data reasonably. Thus the proband group formed 5 subgroups of children with ADHD-CT, according to their symptoms of autism. For each question from the SCQ the percentage of children in each class or cluster who had an "autism positive" response is shown in Table 9, with ++++ indicating that 80-100% of children had a positive response, +++ that 70-80% had a positive response, ++ that 60-70% had a positive response and + that 50-60% had an autism positive response. Similarly ---- indicated that 80-100% of respondents in the cluster had an "autism negative" response and – indicated that 50-60% of respondents had an "autism negative" response.

"Autism positive" responses which corresponded with all three domains of autism were noted in the proband group as a whole, as shown in Table 18. However children in cluster 1 had few "autism positive" responses on the SCQ and children in cluster 5 had "autism positive" responses in each of the three domains of autism. Children in cluster 2 had some symptoms from the communication domain and some from the repetitive and stereotyped patterns of behaviour domain. Children in cluster 4 had some symptoms from the social reciprocal interaction domain and from the communication domain of autism.

Table 18: Cluster analysis: SCQ responses for ADHD-CT probands

	ADI	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster5
Size of the clusters		31%	22.5%	21%	18.5%	7%
conversations	C	----	----	----	----	--
stereotyped utterances	C	----	++	---	---	+++
inappropriate questions	C	--	+++	--	-	++++
Pronoun reversal	C	----	---	----	----	+
neologisms	C	----	+	----	----	++
verbal rituals	R	----	-	----	----	+++
compulsions and rituals	R	----	-	----	---	+++
Inapprop. facial expression	S	----	----	----	---	--
use of other's body to commun.	S	----	---	----	----	-
Unusual preoccupations	R	----	---	----	----	-
Repetitive use of objects	R	----	+	----	---	++++
circumscribed interests	R	----	+	----	---	++
Unusual sensory interests	R	----	--	----	----	-
hand and finger mannerisms	R	----	--	----	----	--
complex body mannerisms	R	----	-	----	----	+++
self injury	-	----	--	----	---	+
Unusual attachment to objects	R	----	----	----	----	--
friends	S	---	---	--	-	+
4-5 social chat	C	----	---	-	+	+
4-5 imitation	C	----	----	--	+	-
4-5 point to express interest	C	----	----	---	--	---
4-5 gestures	C	----	--	++++	++	+
4-5 nod yes	C	----	----	--	--	----
4-5 shake head no	C	----	----	--	--	----
4-5 eye gaze	S	----	--	---	+	++++
4-5 social smile	S	----	----	----	--	+
4-5 showing and directing attention	S	----	----	----	----	---
4-5 offer to share	S	----	----	----	-	++
4-5 shared enjoyment	S	----	----	----	---	-
4-5 offer comfort	S	----	----	----	--	--
4-5 quality of social overtures	S	----	----	--	---	---
4-5 range facial expression	S	----	----	----	----	---
4-5 imitative social play	C	----	----	----	+++	++
4-5 imaginative play	C	----	----	----	+	+
4-5 interested other children	S	----	----	----	++	+++
4-5 respond to other children	S	----	----	----	-	++
4-5 attention to voice	-	----	--	----	+	++++
4-5 imaginative play peers	S	----	---	---	+++	++++
4-5 group play	S	----	--	----	+++	+++

Key: ++++80-100%; +++70-80%; ++60-70%; +50-60%;
+'s indicate presence of symptom; -'s indicate absence of symptoms; **ADI domains:** S = social reciprocal interaction domain, C = communication domain, R = repetitive behaviour and stereotyped patterns domain

3.6.2 Clinical characteristics of clusters

The clinical characteristics of probands in the five clusters can be seen in Table 19. Cluster 1 was the largest, with 31% of children and a mean SCQ score of 2.24. Clusters 2, 3 and 4 had mean SCQ scores of 10.22, 7.04 and 13.58 respectively. Cluster 5 was the smallest with 7% of the probands and a mean SCQ score of 21.4.

Significant differences in the risk of oppositional defiant disorder, conduct disorder, motor disorder and a history of perinatal complications at birth was found in the five clusters. Children in cluster 1 had a significantly lower risk, compared to all other clusters, of having all of these comorbid conditions or risk factors. Children in cluster 5 had the highest risk of having oppositional defiant disorder (77 %) and conduct disorder (44%). Children in cluster 4 had the highest risk of comorbid motor disorder (30%). Children in cluster 2 had the highest risk of having a history of perinatal complications at birth (31%). All the clusters were predominantly male as in the total sample, and had similar mean age (Table 19). The finding of different clusters according to symptoms of autism, with some children with low symptoms of autism and low prevalence of comorbid disorders and other children with high symptoms of autism and high prevalence of comorbid disorders, supports the fourth hypothesis that there are *that the presence of autism symptoms represents a specific subtype of ADHD with particular phenotypic characteristics* (see *Section 1.4.2).*

Table 19: Characteristics of clusters of ADHD-CT probands

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Mean SCQ	2.24	10.22	7.04	13.58	21.4
No of Cases	255	185	171	152	58
% Female	11	14	13	10	14
Size of Cluster	31%	22.5%	21%	18.5%	7%
Percentage with Definite Disorder:					
Oppositional Defiant Disorder[1]	58	70	62	73	77
Conduct Disorder[2]	18	25	21	32	44
Reading Disorder	23	30	31	29	30
Motor Disorder[3]	15	23	18	30	23
Perinatal Difficulties[4]	13	31	24	23	28
Pregnancy Difficulties	15	26	16	19	21
Mean age	10.51	10.93	11.12	11.24	10.71
SD of mean age	2.82	2.78	2.49	2.90	2.60

Note: Chi square analysis was performed to compare the numbers with No Disorder/Possible Disorder/Definite Disorder for each disorder in each cluster. Percentages with a Definite Disorder in each cluster are presented in this table as a summary of the data.

[1]Pearson Chi-Square = 15.05, df = 4, sig= 0.005
[2]Pearson Chi-Square = 22.88, df = 4, sig< 0.001
[3]Pearson Chi-Square = 21.61, df = 8, sig= 0.006
[4]Pearson Chi-Square = 20.40, df = 8, sig= 0.009

CHAPTER 4: DISCUSSION

4.1 Summary of findings

4.1.1 Summary of findings

Using the IMAGE sample we have investigated the relationship between autism symptoms and ADHD-CT by (1) comparing autism symptoms in children with ADHD-CT with autism symptoms in their siblings and with autism symptoms of the normal population; (2) calculating the familial correlation of autism symptoms in ADHD-CT, using proband and sibling data, and calculating the percentage of the familial correlation of autism symptoms which is shared with the familial correlation of ADHD-CT for the group, for male-male sibling pairs and for female-female sibling pairs; (3) calculating the familial correlation of each of the domains of autism symptoms in ADHD-CT, using proband and sibling data and (4) correlating autism symptoms in children with ADHD-CT with measures of ADHD and co-morbid oppositional defiant disorder, conduct disorder, motor disorder and reading disorder (5) conducting a cluster analysis of autism symptoms in probands with ADHD-CT and examining the rates of comorbid disorders in each cluster.

The results that are described in this thesis show that (1) children with ADHD-CT have more symptoms of autism than their siblings and more symptoms of autism than normal children; (2) symptoms of autism in ADHD-CT are not linearly correlated with symptoms of ADHD-CT; (3) symptoms of autism in ADHD-CT are from all three domains of autism; (4) the presence of symptoms of autism in ADHD-CT is a familial

trait, 43% of which is shared with the familiality of ADHD-CT; (5) children with comorbid oppositional defiant disorder, conduct disorder and motor disorder have more symptoms of autism than children without these disorders, and (6) children with ADHD-CT can be subdivided into 5 different clusters with different clinical characteristics according to symptoms of autism. 31% of children with ADHD-CT are in cluster 1, have low symptoms of autism and a lower risk of comorbid oppositional and neurodevelopmental disorders than children in the other clusters. In contrast, 7% of children are in cluster 5 with high symptoms of autism and a higher risk of oppositional defiant disorder and conduct disorder than children in other clusters. Children in clusters 2, 3 and 4 have intermediary levels of symptoms of autism, and intermediary risk of having comorbid oppositional and neurodevelopmental disorders. The finding that different clusters had different clinical characteristics supports the hypothesis that the presence of autism symptoms represents a specific subtype of ADHD with different clinical characteristics (see *Section 4.2.4*).

4.1.2 Symptoms of autism in children with ADHD-CT

Symptoms of autism were measured in a large sample of children with ADHD-CT, in their siblings, and in a sample of normal children. It was found that children with ADHD-CT have significantly higher symptoms of autism (mean SCQ = 8.49, SD = 6.23) than their siblings (mean SCQ = 4.42, SD = 4.18) and than normal children (mean SCQ = 3.89, SD = 2.77). Siblings who have a diagnosis of ADHD (any type) had higher symptoms of autism (mean SCQ = 6.36, SD = 5.28) than siblings without ADHD (mean SCQ = 4.01, SD = 3.79).

The mean SCQ scores described in this study are in keeping with the mean SCQ scores described in other studies. Berument et al, (1999) found that children with autism had a mean SCQ score of 23.08, SD = 8.07 while children with conduct disorder had a mean SCQ score of 14.03, SD = 5.01. In this study, children with ADHD-CT and conduct disorder were found to have a mean SCQ score of 10.56, SD = 7.24.

The mean SCQ score of normal children reported in medical literature varies from 1.69 (Farzin et al, 2006) to 4.2 at age six (Rutter et al, 1999). Normal children in this study were found to have a mean SCQ score of 3.89, which lies between the two reported scores in the literature (see *Section 4.4.2*).

4.2. Does this data prove the hypotheses of this study?

4.2.1 First hypothesis: that autism symptoms are part of the ADHD phenotype

The first hypothesis was that *autism symptoms are part of the ADHD phenotype.* If this hypothesis is correct, there would be a strong correlation between ADHD symptom scores and autism symptom scores in both probands and siblings. It was found that symptoms of autism are increased in probands with ADHD-CT (mean SCQ score = 8.49 +/- 6.23) in comparison to siblings (mean SCQ score = 4.42 +/- 4.18) or in comparison to children in the general population (mean SCQ score = 3.89 +/- 2.77). However a graphical representation of a comparison of autism symptoms with ADHD symptoms did not find a linear relationship between autism symptoms and ADHD symptoms (Figure 5). It can be seen from Figure 5 that there are some children with high ADHD symptoms who have low symptoms of autism and some children with high ADHD symptoms who have high symptoms of autism. This indicates that the measurement of autism symptoms is not purely a severity measurement for ADHD, and it is also not likely to be a measurement artefact. It appears that autism symptoms are not part of the ADHD phenotype in all cases of ADHD, but are present in some children with ADHD and not in others. This suggests that the first hypothesis *that autism symptoms are part of the ADHD phenotype* is in general, not true (see *Section 1.4.2).* This finding prompted the cluster analysis discussed later (see *Section 4.2.4*).

The relationship between autism symptoms and ADHD symptoms was further explored in the calculation of the shared familiality of autism and ADHD symptoms (using a modified DeFries Fulker method) and in particular the calculation of the phenotypic correlation of autism symptoms and ADHD symptoms in probands with ADHD-CT. A phenotypic correlation of 0.69 was found, although this figure was higher in males (0.71) than in females (0.54). This means that there is a partial correlation of autism symptoms with ADHD symptoms, but not a complete correlation. Hence this does not support the hypothesis that autism symptoms are simply part of the ADHD phenotype.

If autism symptoms were part of the ADHD phenotype, a high shared familiality between ADHD symptoms and autism symptoms would be expected. A partial correlation with ADHD symptoms has been shown, with a phenotypic correlation of 0.69 but only 27%-43% of this is due to shared familial effects. These findings are not what would be expected if autism symptoms were entirely part of the ADHD phenotype (see *Section 1.4.2*) and thus we were not able to prove our first hypothesis.

In the cluster analysis of probands, it can be seen that there are some children with ADHD-CT with low autism symptoms (Cluster 1) and some children with ADHD-CT with high autism symptoms (Clusters 2,4,5). Again this does not support the hypothesis that autism symptoms are part of the ADHD phenotype. It would appear that autism symptoms are associated with ADHD symptoms, but not in all cases.

4.2.2 Second hypothesis: that autism symptoms are familial in ADHD

Because a family sample was available, it was possible to examine the familiality of autism symptoms in ADHD-CT both graphically and numerically. It has been shown that there was a correlation of 0.37 in autism symptoms of children with ADHD-CT and their unselected siblings. In families with two children with ADHD (any type), a correlation of 0.54 was found between the autism symptoms of the two children, while in families with discordant sibling pairs, a correlation of 0.32 was found between the autism symptoms of the children. It can be seen that the more alike the children are with regard to symptoms of ADHD, the greater the correlation of their autism symptoms.

The relationship between ADHD symptoms and autism symptoms in families was further explored by performing a DeFries Fulker analysis, with a calculation of the percentage of the correlation of ADHD and of autism symptoms which is due to shared familial influences. We know that the influence of shared environment on ADHD symptoms is small (Faraone and Doyle, 2000) and that the influence of shared environment on the variance of autism symptoms in the population is small (Ronald et al, 2006). Hence it was found that 27% - 43% of the correlation between autism symptoms and ADHD symptoms in children with ADHD-CT was due to shared familial influences. This shows that only part of the correlation of autism symptoms and ADHD-CT symptoms are due to shared familial influences, and the remainder of the correlation may be due to environmental influences or to non-shared familial influences. It was also found that the percentage of the correlation of autism symptoms and ADHD symptoms which was due to shared familial influences was greater in males than in females. 49% of the correlation

of autism symptoms with ADHD symptoms for males was due to shared familial influences, but for females only 7% of this correlation was due to shared familial influences. It could be suggested that other influences, such as environmental influences or non-shared familial influences are more important in the correlation of ADHD symptoms and autism symptoms in females than in males.

The difference in the male and female shared familiality of autism symptoms in ADHD (49% vs 7%) is striking and there are several possible mechanisms that might explain the findings. Both ADHD and autism spectrum disorders are more prevalent in males than in females, and the difference in male and female shared familiality of the disorders may be related to the sex chromosomes. It is possible that genes on the Y chromosome are responsible for symptoms of both ADHD and of autism spectrum disorder, where both disorders are present in males. Such genes are not present in females, and this may explain why shared familial influences are not so important in females who have both ADHD and symptoms of ASD. Alternatively genes on the X chromosome may have a protective influence against the development of both ADHD and of ASD and thus females (who have two copies of X chromosome genes) may have a lower risk of both disorders. Another possible explanation is that there may be X-linked recessive genes which are responsible for symptoms of ADHD and of ASD – if there is one copy of this recessive genetic material, as in males, the individual may develop symptoms of ADHD and of ASD. However in the case a female who is heterozygous and hence has one copy of these recessive genes she will not develop symptoms of ADHD and of ASD.

A further possible explanation for the higher shared familiality of ADHD and ASD in males than in females is that epigenetic factors may be regulating the expression of genes for ADHD and for ASD in males but not in females. Epigenetic factors influence the expression of genes, so that only some genes are active in some cells, and gene expression can change in response to external influences. Known epigenetic factors include environmental factors, and proteins formed by other genes. It is possible that there are epigenetic factors which are turning on genes for ADHD and for ASD in males but not in females. It should be noted that males are more prone to childhood disorders and a little more prone to birth trauma than are females – perhaps the more fragile biological make-up of males and the precarious birth process in males switches on genes which may be beneficial in males, but also cause ADHD and ASD symptoms, but that this does not occur in females.

The difference in male and female shared familiality coupled with the 9:1 ratio of males to females in the study population suggested that the shared familiality calculated for the total study population should be more similar to the shared familiality for males than for females. However this was not the case when the calculations were initially performed. The adjustment of the mean SCQ scores of the normal population and the unselected sibling group to reflect the 9:1 male to female ratio of the proband group allowed the revised calculation of the percentage of the correlation of autism symptoms and ADHD symptoms which were due to shared familial influences. The revised figure of 43% is closer to the figure of 49% which was calculated for males, as would be expected. The figure 43% is likely to represent a more true reflection of the percentage of the

correlation of shared autism symptoms and ADHD symptoms which are due to shared familial influences in ADHD.

The second hypotheses - *that autism symptoms are familial in ADHD* has thus been proven, and a familial effect has been shown graphically and numerically (see S*ection 1.4.2*). It was also shown that the each of the subdomains of autism is familial in children with ADHD-CT (see *Section 4.2.3*).

4.2.3 Third hypothesis: that autism symptoms in children with ADHD have a three dimensional pattern

If this is the case, it could be expected that children with ADHD-CT have autism symptoms from each of the three domains of autism, and each of the domains of autism would be expected to be heritable, as in the normal population. The mean subscales of the SCQ representing the three domains of autism are presented for the normal control sample (Table 12) and for probands and siblings in same sex sibling pairs (Table 13). It can be seen that children from the normal control sample have some symptoms in each of the three domains of autism. Male siblings have higher SCQ subscale scores than the normal control males in each of the three domains of autism, and similarly male probands have higher SCQ subscale scores than male siblings in each of the three domains of autism (Table 13). Male probands had a mean communication SCQ score of 3.37 +/- 2.4 while their male siblings had a mean communication SCQ score of 2.39 +/- 2.06, and normal sample males had a mean communication SCQ score of 2.01 +/- 1.60. Male probands had a mean social reciprocal interaction SCQ score of 2.70 +/ 2.95 while their

male siblings had a mean social reciprocal interaction SCQ score of 1.50 +/- 2.10 and normal sample males had a mean social reciprocal interaction SCQ score of 1.11 +/- 1.25. Male probands had a mean repetitive behaviours SCQ score of 1.86 +/- 0.97 while their male siblings had a mean repetitive behaviours SCQ score of 0.97 +/-1.59, and normal sample males had a mean repetitive behaviours SCQ score of 0.77 +/- 1.02.

The cluster analysis also demonstrates that each of the three domains of autism contributes to the increased SCQ score seen in probands in comparison to siblings or the normal population. The contribution of each of the 39 informative SCQ items to the mean SCQ score of probands with ADHD-CT can be seen in Table 18, with each question labeled as to whether it represents a symptom in the communication domain, the social reciprocal interaction domain or the repetitive behaivours domain of the ADI-R. It can be seen that items from each of the three domains of autism are present in probands with ADHD-CT and that in particular, children in cluster 5 had "autism positive" responses in each of the three domains of autism.

The familiality of autism symptoms in children with ADHD was calculated for each of the three domains of autism. Initially the correlation of autism symptoms of probands with autism symptoms of unselected siblings was calculated, which was 0.37 for the total group (Table 7), 0.37 for male-male sibling pairs (Table 8) and 0.36 for female-female sibling pairs (Table 9). The correlation of symptoms from each of the three domains of autism was then calculated, for males and for females. It was found that for unselected male-male sibling pairs, the correlation of symptoms from the SCQ communication

domain was 0.47, from the social reciprocal interaction domain was 0.30 and from the repetitive behaviour and stereotyped patterns domain was 0.25. It can be seen that symptoms representing all three domains of autism are familial, although the communication domain may be contributing to the overall familiality of autism symptoms more than the social reciprocal interaction domain or the repetitive behaviour and stereotyped patterns domain. The familiality of the domains of autism was generally greater for concordant sibling pairs than for discordant sibling pairs (see Table 10).

The familiality of the three subscales of autism was calculated for females (Table 11). The correlation of symptoms from the SCQ communication domain was 0.45, from the social reciprocal interaction domain was 0.39 and from the repetitive behaviour and stereotyped patterns domain was 0.12 for unselected female-female sibling pairs. Like the male-male sibling pairs, the familiality was greater in the communication domain than in the social reciprocal interaction domain or the repetitive behaviour and stereotyped patterns domain. The familiality of the subdomains of autism for concordant female-female sibling pairs could not be calculated due to the small number (N=9) of concordant female-female sibling pairs in the sample (Table 11).

Finally the percentage of the shared familiality of autism symptoms with ADHD symptoms was calculated for each of the three domains or autism, for male and for female sibling pairs (Table 15). For male-male sibling pairs, the shared familiality was higher for the communication subscale (56%) than for the social reciprocal interaction domain (49%) and than for the repetitive behaviours domain (37%). However it can be

seen that each of the three subdomains of autism have some shared familial influences with ADHD. For females there was a higher shared famliality calculated for social reciprocal interaction (71%) than for the total SCQ score (7%). However these findings should be treated with caution, due to the small number of the female-female sibling pairs in the sample.

These analyses have thus proven the third hypothesis: that autism symptoms in children with ADHD have a three dimensional pattern (seen in the comparison of subscales of the SCQ score in probands and siblings and in the cluster analysis), and that this three dimensional pattern is heritable in children with ADHD-CT.

4.2.4 Fourth hypothesis: That the presence of autism symptoms represents a specific subtype of ADHD with particular phenotypic characteristics.

If this is the case, it would be expected that a distinct cluster of children with autism symptoms could be identified. It might also be expected that there would be certain clinical attributes associated with this subgroup of children with ADHD-CT and autism symptoms.

A cluster analysis using a latent class approach showed that children with ADHD form 5 different classes or clusters, according to their symptoms of autism. Symptoms from all three domains of autism contributed to autism traits measured in children with ADHD-

CT. 31% of the probands formed cluster 1, with very low symptoms of autism and the lowest risk of oppositional defiant disorder (58%), conduct disorder (18%), motor disorder (15%), and reading disorder (23%). Cluster 1 also had a low risk of perinatal difficulties (13%) and of pregnancy difficulties (15%). The mean SCQ score of Cluster 1 was lower than the mean SCQ score found for the normal population (2.24 vs 3.55). In contrast, children in cluster 5 had the highest symptoms of autism, and the highest risk of oppositional defiant disorder (77%) and conduct disorder (44%). The mean SCQ score of children in cluster 5 was 21.4, which is slightly lower than the mean SCQ score of a sample of children with autism (mean SCQ = 23.08), as reported by Berument et al, (1999). It must be remembered that all children with autistic spectrum disorder have been excluded prior to the analysis, so the results of the present analyses are conservative. Children in clusters 2, 3 and 4 had intermediary levels of symptoms of autism and also had intermediary levels of comorbid disorders.

The finding of distinct clusters of children with ADHD-CT with different levels of autism symptoms and different rates of comorbid disorders suggests that ADHD-CT may not be an aetiologically homogenous disorder. We have already shown that the familiality of autism symptoms is only partly shared with the familiality of ADHD symptoms (see *Section 4.2.2*). We have thus proven our fourth hypothesis *that the presence of autism symptoms represents a specific subtype of ADHD with particular phenotypic characteristics* (see *Section 1.4.2*). Cluster 1 and cluster 5 differ from each other in terms of the symptoms of developmental disorders in the children (symptoms of autism, and motor disorder) and in terms of the development of comorbid oppositional disorders. This

finding challenges the current nosological system, where all children with ADHD combined type are classified together.

The next step in the study of the phenotype of children with ADHD-CT and autism symptoms was to examine the relationship between autism symptoms and comorbid disorders in ADHD. Children with ADHD-CT and oppositional defiant disorder were found to have significantly higher symptoms of autism than children with ADHD-CT without oppositional defiant disorder (SCQ=9.19 vs SCQ=7.15). Similarly children with ADHD-CT and conduct disorder were found to have significantly higher symptoms of autism than children with ADHD-CT without conduct disorder (SCQ=10.56 vs SCQ=7.81). Children with ADHD-CT and motor disorder had significantly more symptoms of autism than those without this disorder (SCQ = 9.79 vs. SCQ = 7.69). The finding of increased symptoms of autism in children with ADHD-CT and oppositional defiant disorder, conduct disorder and motor disorder supports the hypothesis that the presence of autism symptoms in ADHD-CT represents a specific subtype of ADHD, which has specific phenotypic characteristics.

4.3 Strengths and Limitations of this study

4.3.1 Strengths of this study

This study is a large scale multi-centre study which examines the topic of autism symptoms in ADHD-CT and the familiality of autism symptoms in more detail than many previous studies have done. It is a strength of the study that such a large proband and sibling group was used, as this allowed a comparison of autism symptoms in concordant siblings pairs with autism symptoms in discordant sibling pairs. The large sample size also allowed for the comparison of male and female mean SCQ scores and a comparison of the correlation of autism symptoms in male-male sibling pairs with the correlation of autism symptoms in female-female sibling pairs. The size of the sample also allowed for a comparison of autism symptoms in those with and without oppositional defiant disorder, those with and without conduct disorder and those with and without motor disorder.

The study uses robust, well standardised measures to diagnose ADHD and to measure symptoms of autism. It is also a strength of the study that all raters for the PACS semi-structured interview were trained together and that inter-rater reliability was checked at the beginning of the study as well as midway through the data collection. The use of the SCQ to measure autism symptoms is a strength of the study, as the SCQ correlates well with the ADI-R and can measure symptoms from each of the three domains of autism. The present study uses reliable clinical measures, in comparison to the previous study of autism symptoms in children with ADHD, which did not use a standardised tool to measure autism symptoms, and did not perform a diagnostic interview to diagnose

ADHD (Clarke et al, 1999). The use of the SCQ, with the knowledge that questions were derived from the ADI-R, allowed for an analysis of the familiality of the dimensions of autism in ADHD and for the calculation of the percentage of the familiality which is shared with the familiality of ADHD for each dimension of autism. This would not have been possible if a tool to measure autism symptoms was used which did not represent the three domains of autism.

4.3.2 Limitations of this study

There are a number of possible limitations to this study. The IMAGE study sample is a large sample of families with children with ADHD, but it should be noted that the sample was ascertained for a genetics study, and not for this study of autism symptoms in ADHD. It is possible that the IMAGE ADHD sample was in some way biased with respect to symptoms of autism – perhaps the families with children with ADHD who were motivated and able to participate in a study of ADHD genetics were in some way different to the general population of families with children with ADHD. It is possible that the sample of children with ADHD collected for genetics purposes is actually enriched for autism symptoms, and this could partly account for the increased symptoms of autism found in children with ADHD and in their siblings in comparison to the general population.

The exclusion criteria for IMAGE allowed a family to be included in the study if the proband and one sibling were shown not to have autism spectrum disorder, even in the presence of another (excluded) sibling who had autism spectrum disorder. This could mean that the proband and sibling had some familial symptoms of autism and an increased genetic loading for autism spectrum disorder, although they did not have sufficient symptoms to classify them as ASD. This could have accounted for some of the increase in mean SCQ score seen in probands and in siblings in comparison to the general population. However it is unlikely that the very small number of such situations would account entirely for the findings of the study, considering that the cluster analysis showed that many children with ADHD had increased symptoms of autism in comparison to the normal population.

This study has shown that children with ADHD-CT have increased symptoms of autism, but it could be noted that those who were nominated as probands had higher symptoms of autism (mean SCQ score = 8.49 +/- 6.23) than those with ADHD-CT who were nominated as siblings (mean SCQ score = 6.78 +/- 5.27). The mean Conners' scores for each group was also calculated and it was found that probands had higher symptoms of ADHD (mean Conners' = 77.84 +/- 8.87) than siblings with ADHD-CT (mean Conners' = 75.01 +/- 11.98). It appears that the most severely affected child in many families was the identified proband, and the less severely affected child was the identified sibling, with higher ADHD symptoms and autism symptoms in the identified proband than in the siblings with ADHD-CT. The proband group may have more severe symptoms of ADHD and of autism symptoms than the general ADHD population, and hence the finding of

increased symptoms of autism in the proband group in comparison to the sibling or control group may be exaggerated in this study in comparison to the general ADHD population.

It has been suggested that SCQ score is partly dependent on the age of the child (Corsello et al, 2007) and that a different mean age in the proband group from the sibling group could account for the difference in the mean SCQ scores. However it can be seen that there was no significant difference between the mean age of the proband sample (10.9 +/- 2.8 years) and sibling sample (10.7 +/- 3.3 years), and the age range of each of the subgroups of siblings was similar (Table 4). Hence the difference in proband and sibling mean SCQ score is not due to a difference in the mean age of the groups. The normal sample group was a little younger than the other groups (8.07 +/- 2.33 years). This lower mean age in the normal sample group could be expected to cause a lower mean SCQ score in the normal sample group than in an age-matched normal sample group, if the findings of Corsello et al, (2007) can be extended to the normal population. A lower cut-off for autism spectrum disorder in younger children than in older children using the SCQ was found by Corsello et al, (2007). This suggests that the finding of a lower mean SCQ score in the normal population sample than in probands or siblings may have been influenced by age effects. However in this study the mean SCQ score was calculated for probands, siblings and controls for each of the age groups <5 years, 5-7 years, 8-10 years and >10 years, which were the age-groups studied by Corsello et al, (2007). It can be noted in this study that children with ADHD-CT and their siblings have more symptoms of autism (measured by SCQ) than the normal population in almost each age-group of

children studied (see Table 5). It can be concluded then that the findings of more symptoms of autism in the group with ADHD-CT is not due to age effects.

It has been suggested that a lower SCQ score should be used as the cut-off point when screening for autism in children in the <5 years age-group and in the 5-7 age-group than for older children (Corsello et al, 2007), and hence if Corsello's (2007) findings had been available at the time of data collection for this study, the screening for autism may have been performed differently for children <= 7years. More children aged <= 7 years would have had a PACS performed and using the information from the study of Corsello et al, (2007), it is possible that some children aged <= 7 years with autism spectrum disorder did not have the disorder diagnosed using the methods of this study. Hence there may be some young children in the proband group who have an autism spectrum disorder, which could account for some of the findings of increased symptoms of autism in children with ADHD. This would not account for all of the findings of the study as autism symptoms were shown to be increased in children with ADHD in comparison to siblings or normal controls in each age-group studied. However the finding of a lower suggested cut-off point for autism in Corsello's study is in contrast to the age related findings of Rutter et al, (1999) and age related findings of this study for the SCQ. It was found that UK adopted children had a higher mean SCQ score at 4 years of age (mean SCQ = 5.2) than at 6 years of age (mean SCQ = 4.2) (Rutter et al, 1999). In this study, it was found that the mean SCQ score of younger siblings and of younger normal children was generally higher than the mean SCQ score of older children (see Table 5). There was one exception to this finding - in the subset of 30 normal children over 10 years of age, the mean SCQ

of the normal children was 4.57 +/- 4.55, which is greater than the mean SCQ of siblings of that age-group (mean SCQ = 4.19 +/- 4.186). It is expected that this finding is spurious, related to the relatively small sample size in that age-group (N=30). It is possible that there was one or more children with autism spectrum disorder in the over 10 years age-group who were placed in mainstream school, and hence were included in the study, and which did not reflect the population as a whole. If the true mean SCQ score of children in the normal population in the >10 age-group is lower than that of siblings of that age-group, then the finding of higher symptoms of autism in children with ADHD than in the general population would be more pronounced than is reported in this study. This means also that the measures of familiality and shared familial influences on ADHD and autism symptoms in this study may be an underestimation of their true values.

A further possible limitation of the study was that the SCQ is a 40 item screening questionnaire, but that there were just 12 items on the PACS which were used to exclude children with autism spectrum disorder from the sample, who had already obtained a high score on the SCQ. If children with autism spectrum disorder were not properly excluded from the ADHD proband sample, the findings of increased symptoms of autism spectrum disorder in those with ADHD could be due to poor sample ascertainment rather than due to overlap of two disorders. It should be noted however that the exclusion of children using PACS was performed by a trained clinical researcher who performed a semi-structured interview to ascertain if symptoms of ASD were present or not, and may have asked more than one question in order to rate each of the 12 questions on the PACS. It

should also be noted that the inter-rater reliability on performance of the PACS was measured, and found to be satisfactory (Brookes et al, 2006).

The measurements of neurodevelopmental disorders including reading disorder and motor disorder were not made using a specific research tool, but the trained clinical researcher ascertained whether or not there was a definite clinical diagnosis of reading disorder and of motor disorder for each proband. Also the measurement of pregnancy difficulties and of perinatal difficulties was by retrospective report of a list of possible symptoms rather than by measurement at the time of pregnancy or birth. The retrospective measurement may not be accurate and may be associated with recall bias, which could either increase or decrease reporting of symptoms.

There were some limitations in the ascertainment of the normal sample. There was no measurement of ADHD symptoms or IQ in the normal sample studied, but as the whole school was sampled, this should increase the possibility that the normal school children sample reflected the normal population. There was also no method of definitively excluding those with autism or those with ADHD from the normal school sample of children. If the normal population sample contained more children with autism or more children with ADHD than would be expected in the normal population, then the mean SCQ score of the normal population may be lower than is reported here. This means that the effect of shared familial influences on symptoms of autism and symptoms of ADHD may be greater than is reported in this study. There was also no measure of the socio-demographic details of the schoolchildren. However the SCQ was designed to measure symptoms of autism and as such should not be influenced by socio-demographic factors.

A further possible limitation of the study is that the normal sample age-group did not match totally with the study sample age-group. It is possible that if the under 5 year old population had been excluded from the normal sample, to match the proband sample, that the mean SCQ score of the normal sample would have been less than the reported normal sample mean used in the study, as the mean SCQ score of children under 5 years of age was higher (mean SCQ = 5.5, SD = 2.91) than the mean SCQ score of children aged 5-7 years (mean SCQ = 4.24, SD = 2.89). It appears from the normal sample mean SCQ scores and from the unselected sibling sample mean SCQ scores that SCQ score reduces a little with increasing age, and so it is possible that if the older adolescent population were represented in the normal sample measured, that the mean SCQ score of the normal sample would have been even lower. If a lower mean SCQ score for the normal population was used to calculate the shared familiality of autism symptoms and ADHD symptoms, a higher shared familiality for ADHD and autism symptoms would have been found than is reported in this thesis. This means that the percentage of the shared familiality with ADHD presented in this study could be an underestimate of the true value.

4.4 The findings of this study and existing literature

4.4.1 The rate of comorbid disorders in this study and other ADHD studies

The probands participating in this study have a similar rate of comorbid oppositional defiant disorder (66%) to the population-based sample of children with ADHD described by Kadesjö and Gillberg, (2003). In that study, half of all children born in 1985 in the Karlstad community who were attending school in 1992 were assessed. The authors performed clinical observations as well as parent and teacher interviews to diagnose children with DSM-IV disorders. 60% of children with ADHD studied by Kadesjö and Gillberg, (2003) were found to have oppositional defiant disorder and the rate of conduct disorder was not assessed. The rate of developmental co-ordination disorder (47%) in the Kadesjö and Gillberg (2003) study resembled the sum of the rate of possible motor disorder (27%) and definite motor disorder (21%) in our study. Similarly 40% of the Kadesjö and Gillberg (2003) sample had a reading/writing disorder while 20% and 28% of our study sample had a possible or definite reading disorder respectively. Taylor et al, (1991) found that 43% of children with hyperkinetic disorder had motor disorder, and that 64% had speech disorder. This study has shown a rate of 48% with possible or definite motor disorder and 25% of children had a language disorder, which differs from Taylor's study (Taylor et al, 1991).

The study sample for autism symptoms in ADHD was recruited primarily for the assessment of the genetics of ADHD, but the similar rates of comorbid disorders to the rates found in the epidemiological samples described above suggest that the clinical

characteristics of the study sample are similar to the characteristics of an epidemiological sample. This suggests that the findings of the study could be gerneralised to all children with ADHD-CT. It was noted however that the rate of comorbid disorders in siblings with ADHD-CT was less than the rate of comorbid disorders in probands with combined type ADHD (see *Section 3.2.1*; Table 1 and Table 2). This may due to a severity effect – families may nominate their most severely affected child with ADHD as the proband and the less severely affected child as the sibling.

4.4.2 Use of the SCQ in control samples.

There has been limited use of the SCQ with normal children to date and validation studies of the SCQ have compared the response pattern for children with autism with the response pattern for children with other psychiatric diagnoses or disorders, (Berument et al, 1999; Lee et al, 2007; Corsello et al, 2007). The SCQ has been used to compare symptoms of autism in adopted children of UK origin with symptoms of autism in adopted children of Romanian origin (Rutter et al, 1999). The SCQ score of 52 UK adopted children was 5.2 at 4 years of age and 4.2 at 6 years of age, and it has been hypothesized that this may reflect the SCQ score of the normal population. Farzin et al, (2006) also described the use of the SCQ in normal children who were siblings of children with Fragile X, and found a mean SCQ of 1.69, SD = 2.02. Bishop and Norbury, (2002) used the SCQ in their study on autistic disorder and specific language impairment and reported that the mean SCQ score of a group of normal children was 4.77 (personal communication). The mean SCQ score for control children reported in this study is in keeping with the mean SCQ scores reported in the literature to date. The range of mean

SCQ scores reported in control samples to date may be due to the small size of some of these samples (Farzin et al, 2006; and Bishop et al, 2002), and the possibility of confounding attachment disorder in one sample (Rutter et al, 1999). The mean SCQ score for the control sample in this study may be a more accurate estimation of the true population mean SCQ score than the mean SCQ scores reported in previous studies, as this sample was ascertained from a mainstream school.

In this study, normal males were found to have a higher mean SCQ score (4.00, SD = 2.65) than normal females (SCQ = 3.78, SD = 2.90). However this finding was not statistically significant and the distribution of SCQ score in males and females from the general population followed a normal curve (see *Figures 3 and 4*). A statistically significant difference between male and female SCQ score was found for unselected siblings, and for siblings without ADHD, who may resemble the normal population. It is possible that the control sample studied was not large enough to detect a difference in the male and female mean SCQ score, but that there is a small true difference in the mean population SCQ score according to gender, as noted in the non-ADHD sibling sample.

4.4.3 Symptoms of autism in ADHD

This study has clearly shown that children with ADHD-CT have more symptoms of autism than children who do not have ADHD. The increase in symptoms of autism noted in children with ADHD in this study was previously suggested (Clarke et al,1999), (see *Section 1.3.4*). It has long been established that many children with autistic spectrum disorder fulfill diagnostic criteria for ADHD and there has been much recent interest in the similarities between pervasive developmental disorder with ADHD (see *Section 1.3.4*). Some studies have found that there are children who are eligible to be diagnosed with both autistic spectrum disorder and ADHD, but this is not possible using the current classification systems. However this study provides evidence that many children with ADHD also have symptoms of autistic spectrum disorder, but do not fulfill diagnostic criteria for an autistic spectrum disorder. This suggests that there may be some overlap between the two disorders.

It must be remembered that in this study, all children with ADHD and comorbid autistic spectrum disorder were excluded. Hence the findings are likely to be conservative. The overlap of symptoms of autism in children with ADHD would be stronger if children with a pervasive developmental disorder and ADHD had been included in the study.

4.4.4 Familiality

It has long been established that symptoms of ADHD are heritable and that symptoms of autism are heritable. It has also been shown that autism symptoms among twins in the normal population are moderately to highly heritable (Constantino and Todd, 2003). It has recently been shown that the three domains of autism in the population have a low phenotypic correlation and it has been suggested that the three domains of autism are separately inherited in the population (Ronald et al, 2006). The finding that some families have ADHD with autism symptoms and that some families have ADHD without autism symptoms is in keeping with previous literature on autism symptoms in the normal population.

4.4.5 Autism symptoms and oppositional disorders in ADHD

An association between autism symptoms in ADHD and oppositional disorders has not previously been reported, except by the author in the analysis of a subgroup of the children described in this study (Mulligan et al, WCPG, Boston, 2005; Mulligan et al, WCPG, Cagliari, 2006). However Greene et al, (1996) have shown that 22% of children with ADHD are socially disabled, and a follow-up longitudinal study found that social disability in boys with ADHD was a significant predictor of later conduct disorder and most substance use disorders (Greene et al, 1997). Hence the finding of increased symptoms of autism in children with conduct disorder and oppositional defiant disorder is in keeping with previous findings.

4.4.6 Previous studies of autistic traits and motor disorder

The description of children with ADHD-CT, increased symptoms of autism and comorbid motor disorder is similar to Gillberg's description of Deficits of Attention, Motor and Perception (DAMP) syndrome (Gillberg et al, 1982). The original description of DAMP followed an epidemiological study of children with minimal brain dysfunction, where a group of children were identified with a combination of deficits of attention and deficits of a perceptual nature, either motor clumsiness, language disorder or other perceptual difficulty, in the absence of cerebral palsy or mental impairment. It has since been estimated that approximately half of all children with DAMP also fulfilled diagnostic criteria for ADHD (Kadesjo et al, 2001; Landgren et al, 1998). Since the original DAMP studies were performed, the diagnostic symptoms of ADHD have been defined in DSM-IV and DAMP has now been redefined as a combination of ADHD and Developmental Co-ordination disorder (DCD) (Kadejso and Gillberg, 1998; Gillberg, 2003). It is reported however that many children with DAMP have other deficits or a greater academic impairment than what would be expected from a combination of symptoms seen in ADHD and DCD (Gillberg, 2003).

Like ADHD, DAMP has a prevalence of approximately 5% of school aged children (Landgren et al, 1998) and the prevalence of clinically severe DAMP is reported at 1.5% of school-aged children, (Gillberg, 2003). Boys are affected more than girls (Gillberg, 2003). The original description of children with DAMP did not include a specific assessment of autism symptoms or a discussion about autism symptoms. However in a later review article on the topic of DAMP, Gillberg (2003) clarified that many of the

children originally diagnosed with severe DAMP fitted diagnostic criteria for pervasive developmental disorder (Gillberg, 2003).

This thesis describes a group of children with a primary diagnosis of ADHD-CT, who have increased symptoms of autism and an increased risk of motor disorder and oppositional disorders. In contrast, Gillberg et al, (1982) performed an epidemiological study, which identified children with deficits of attention, motor and perception, some of whom fitted criteria for ADHD. It appears that the description of DAMP (Gillberg et al, 1982) and our description of Cluster 5 may be describing the same or a similar clinical entity, although our sample exclusively contains children with ADHD-CT, while only some of the original group of children with DAMP described by Gillberg fulfilled criteria for ADHD.

4.4.7 Previous descriptions of subgroups of ADHD

A previous latent class analysis of symptoms of ADHD in a sample of 342 children with ADHD has shown that there are 6 clusters of children with ADHD, thus challenging the DSM-IV classification system which classifies children into those with ADHD combined type, ADHD inattentive type and ADHD hyperactive type (Elia et al, WCPG, New York, 2007). However this study has shown that children with combined type ADHD can be subdivided according to their symptoms of autism, and that children in the various subgroups have different risks of comorbid disorders. This is a new finding.

4.5 Implications for clinical practice

4.5.1 ADHD as a Developmental Disorder

The finding of increased symptoms of autism in children with ADHD-CT, with increased autism symptoms associated with motor disorder, suggests that ADHD-CT could be considered a developmental disorder rather than a behavioural disorder. The finding that there are subgroups of children with "pure ADHD" and children with "ADHD and neurodevelopmental disorders" suggests that it may be appropriate to manage these two groups of children differently in the clinical setting. The concept of DAMP may be used clinically again. It may be more useful clinically to manage children with "ADHD and neurodevelopmental disorders" alongside children with ASD, as they share many symptoms in common.

4.5.2 Measurement of symptoms of autism may help identify children at risk of developing oppositional disorders

The association between autism symptoms in ADHD-CT and oppositional defiant disorder and conduct disorder may assist the early identification of children at risk of developing these disorders. However this is a cross-sectional study, and prospective studies need to be performed to ascertain if children with high symptoms of autism and ADHD-CT are more likely to develop oppositional defiant disorder and conduct disorder. If the association between autism symptoms in ADHD and oppositional defiant disorder and conduct disorder is confirmed in a prospective study, then it may be possible to identify children with social communication deficits as well as ADHD-CT in childhood using screening questionnaires, such as the SCQ and the Conners' questionnaires. A

specific intervention could then target these children, before the development of oppositional defiant disorder and conduct disorder.

4.5.3 Measurement of symptoms of autism may help identify children at risk of motor disorder

The finding of an association between increased symptoms of autism and motor disorder in some children with ADHD-CT supports the model of ADHD as a neurodevelopmental disorder, with more neurodevelopmental deficits seen in some children than in others. The association between autism symptoms in ADHD and motor disorder may assist the clinician to target occupational therapy assessments to children with increased autism symptoms. Children who have a greater possibility of having a motor disorder could be rapidly identified at intake to clinical services with the use of the SCQ or similar measure, and referred for a comprehensive occupational therapy assessment.

4.6 Implications for future research

4.6.1 Implications for future clinical research

This study has shown a relationship between autism symptoms in ADHD-CT and disorders comorbid to ADHD. It would be interesting to assess if this relationship between autism symptoms and comorbid disorders is present in all children with ADHD, including those with inattentive type and hyperactive type. It has previously been hypothesized that ADHD, inattentive type is different in aetiology to ADHD-CT (Biederman and Faraone, 2005). If the same relationship between between autism symptoms in ADHD and comorbid disorders is found in the inattentive group, it would suggest that this group is similar in aetiology to the ADHD-CT group. It would also be interesting to assess if the relationship between autism symptoms and oppositional defiant disorder, conduct disorder and motor disorder is present in children in the normal population or merely those with ADHD-CT. A study is currently underway to assess autism symptoms and other disorders in children presenting to child psychiatric services. The issue of autism symptoms in children with inattentive type ADHD will also be assessed as part of this study. A further study could be performed in the normal population, to establish if there is an association between autism symptoms in the normal population and symptoms of oppositional defiant disorder, conduct disorder and motor disorder.

The association between autism symptoms in ADHD and oppositional disorders suggests that children who are at risk of developing oppositional defiant disorder or conduct disorder could be identified early. A prospective study of outcome of children with

ADHD and with high and low autism symptoms is currently planned. If it is confirmed that children with ADHD and with increased autism symptoms are more likely to develop oppositional defiant disorder or to develop conduct disorder, then a trial of treatment with social skills training for children could be performed. Parent training has been shown to be of benefit in the treatment of oppositional disorders in ADHD. A treatment trial of intensive parent training could also be performed for children with increased symptoms of autism in ADHD.

4.6.2 Implications for future genetic research into ADHD

This study has shown that ADHD-CT might not be a homogenous disorder, but a group of disorders with subgroups of children with distinct clinical features, and in particular a group with high and a group with low symptoms of autism. Genetic studies on ADHD to date have found many genes of small effect associated with ADHD, with the odds ratio of many associated genes in the region of 1-2 (Brookes et al, 2006). It has previously been discussed in *Section 1.2.8* that difficulties in identifying genes associated with a disorder may relate to the accuracy of the description of the phenotype, and that the candidate symptom approach or the endophenotype approach may be used in the identification of genes of relevance in a disorder.

The presence of autism symptoms in ADHD-CT is not part of the ADHD phenotype but may be a subgroup of ADHD. It has been shown in this study that (1) autism symptoms are partly associated with symptoms of ADHD, (2) autism symptoms are present in

siblings of those with ADHD at higher rates than the normal population, (3) autism symptoms are familial, and (4) that some of the correlation between ADHD and autism symptoms is due to shared familial influences. The IMAGE study has already reported on the analysis of 52 genes for association with ADHD, and found nominal significance with one or more single nucleotide polymorphisms (SNP's) in 18 genes (Brookes et al, 2006). It is planned to repeat this genetic analysis in the proband group with high symptoms of autism and in the group with low symptoms of autism. It may be that the association of some of these genes with ADHD may be stronger in either the subgroup with low symptoms of autism ("pure ADHD" group) or in the subgroup with high symptoms of autism. Studies of gene environment interactions in ADHD may also be stratified according to symptoms of autism in the subjects studied.

The finding of an overlap of symptoms of autism and symptoms of ADHD suggests that there may also be an overlap in the genetic aetiology of autistic spectrum disorder and some forms of ADHD-CT. Potential overlap in the genetic findings in ADHD and autism has been suggested by previous studies (Fischer et al, 2002; Smalley et al, 2002). A genome-wide linkage scan for loci influencing ADHD performed by Fischer et al, (2002) found that two of the ADHD loci, 2q24 and 16p13 coincided with the top linkage peaks reported by the International Molecular Genetic Study of Autism Consortium genome-wide screen (IMSAC, 2001). A susceptibility locus for ADHD has also been localised at chromosome 16p13, a region which overlaps with genetic findings in autism (Smalley et al, 2002). Consequently, it was suggested that a variation in a gene on 16p13 may contribute to deficits common to autism and ADHD.

4.7 Concluding remarks

4.7.1 Concluding remarks

This study has shown that some children with ADHD-CT have increased symptoms of autism, while some children with ADHD-CT have less autism symptoms than the general population. Symptoms of autism in children with ADHD-CT have the same three dimensional structure as symptoms of autism in those with ASD. It was also noted that symptoms of autism in children with ADHD-CT are familial, with symptoms from each of the three domains familial in nature. The familiality of autism symptoms in children with ADHD-CT is partly shared with the familiality of ADHD. It has also shown that children with autism symptoms and ADHD-CT are more likely to have some of the well known disorders which are often comorbid to ADHD, including oppositional defiant disorder, conduct disorder and motor disorder. In summary, this study has shown that there may be an overlap of the disorders ADHD and autism. It has also shown that ADHD is not a homogenous disorder, but can be described as a disorder with familial subtypes which correlate with autism symptoms in ADHD and different risks of comorbid disorders. The finding of different subtypes of combined type ADHD has implications for clinical and molecular genetic studies of ADHD.

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APPENDICES

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2 Mulligan A, Richardson T, Anney RJ, Gill M. The Social Communication Questionnaire in a sample of the general population of school-going children. Irish Journal of Medical Science 2008; [Epub ahead of print]

3 DSM-IV Criteria for ADHD

4 IMAGE Protocol

5 IMAGE parent information

6 IMAGE teacher information

7 IMAGE information for children with ADHD

8 IMAGE information for brothers and sisters of children with ADHD

9 IMAGE parent questionnaires

10 IMAGE teacher questionnaires

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ORIGINAL PAPER

Autism symptoms in Attention-Deficit/Hyperactivity Disorder: A Familial trait which Correlates with Conduct, Oppositional Defiant, Language and Motor Disorders

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Abstract It is hypothesised that autism symptoms are present in Attention-Deficit/Hyperactivity Disorder (ADHD), are familial and index subtypes of ADHD. Autism symptoms were compared in 821 ADHD probands, 1050 siblings and 149 controls. Shared familiality of autism symptoms and ADHD was calculated using DeFries-Fulker analysis. Autism symptoms were higher in probands than siblings or controls, and higher in male siblings than male controls. Autism symptoms were familial, partly shared with familiality of ADHD in males. Latent class analysis using SCQ-score yielded five classes; Class 1(31%) had few autism symptoms and low comorbidity; Classes 2–4 were intermediate; Class 5(7%) had high autism symptoms and comorbidity. Thus autism symptoms

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in ADHD represent a familial trait associated with increased neurodevelopmental and oppositional/conduct disorders.

Keywords ADHD · Autism · Familiality · Oppositional disorders · Motor disorder · Language disorder

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a behavioural disorder with symptoms of hyperactivity, impulsivity and inattention (American Psychiatric Association 2000). Autism spectrum disorders (ASD), also known as Pervasive Developmental Disorders (PDD) are a group of disorders characterized by qualitative defects in social reciprocity and communication, and restricted repetitive behaviours (Lord et al. 2000), and include the disorders of autism, Asperger's syndrome and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). DSM-IV TR (American Psychiatric Association 2000) and ICD-10 (World Health Organization 1992) operational classifications separate ADHD from ASD. A primary diagnosis of ADHD can only be made if symptoms of ADHD are not accounted for by another diagnosis, such as a diagnosis of autism.

There has been recent interest in the diagnostic overlap and similarities between ADHD and ASD (Hattori et al. 2006; Luteijn et al. 2000; Reiersen et al. 2007; Reiersen and Todd 2008; Ronald et al. 2008). It has long been acknowledged that children with ADHD have social and communication difficulties as part of the ADHD complex (Greene et al. 1996; Hoza 2007; Hoza et al. 2005; Nijmeijer et al. 2008; Pelham and Bender 1982). Children with ADHD may also have pragmatic language difficulties similar to those of children with Asperger's syndrome or to children with PDD-NOS (Bishop and Baird 2001). It has been shown that the pragmatic language difficulties of children with ADHD are greater than those of normal children, but not so severe as those of children with high functioning autism (Geurts et al. 2004). Further similarities between ADHD and ASD are suggested by a study of emotional recognition and theory of mind which showed that children with ADHD could not be distinguished from those with autism or PDD-NOS (Buitelaar et al. 1999) and a study on empathic ability which showed that children with ADHD were different to children with no psychological disorder, and were similar to but less affected than those with autistic disorder (Dyck et al. 2001).

Studies which have measured symptoms of autism in children with ADHD have found that children with ADHD have significant difficulties in social interaction and communication (Clarke et al. 1999; Reiersen et al. 2007; Santosh and Mijovic 2004). It has been shown that children with ADHD have similar difficulties in communication and restrictive repetitive behaviour as children with PDD (Hattori et al. 2006) and similar social insight to children with PDD-NOS (Luteijn et al. 2000). Two types of social impairment have been described in hyperkinetic disorder: relationship difficulty related to environmental stressors and social communication deficits which related to symptoms of PDD (Santosh et al. 2004). As autism symptoms are part of a dimensional trait in the population (Constantino and Todd 2005), it could be expected that children with ADHD may have some symptoms of autism, as in the general population. However it has been shown that symptoms of autism in children with ADHD exceed those of the general population (Hattori et al. 2006; Reiersen et al. 2007) and significant correlations between symptoms of ADHD and symptoms of autism spectrum disorder have been shown in the general population (Ronald et al. 2008).

The reverse finding has also been extensively reported—that children with ASD have increased levels of ADHD symptoms (Arnold et al. 2003; Gadow et al. 2006; Goldstein and Schwebach 2004; Hattori et al. 2006; Lee and Ousley 2006; Yoshida and Uchiyama 2004). However, the mechanisms underlying this phenotypic overlap between ADHD and PDD are poorly understood.

There are several possible explanations for the presence of symptoms of autism in ADHD (Caron and Rutter 1991; Neale and Kendler 1995). The first is that autism symptoms, as measured by a particular rating scale are in fact ADHD symptoms, but that the rating scale is not sufficiently specific. A second possibility is that ADHD and autism are overlapping disorders which may share some common aetiology, with ADHD and autism symptoms co-existing in all or most cases, ie a single 'joint' phenotype. A third explanation is that the presence of autism symptoms describes a subgroup of children with ADHD which has its own clinical characteristics and aetiology. The possibility of a common shared genetic aetiology has been suggested by a community twin study of ADHD symptoms and symptoms of autism, which showed that symptoms of both disorders correlate in the general population (Ronald et al. 2008).

In the present study, symptoms of autism are examined in a large set of families consisting of at least one sibling pair participating in the International Multi-centre ADHD Genetics (IMAGE) study (Brookes et al. 2006). We set out to test three hypotheses. The first hypothesis is that children with ADHD have more symptoms of autism than children from the general population. The second is that autism symptoms in children with ADHD are familial. If this is the case, we predict high levels of autism symptoms, not only in probands with ADHD, but also in their unselected

siblings, compared to controls and a high correlation between autism symptom scores in probands and siblings. The third hypothesis is that children with ADHD and comorbid autism symptoms represent a specific subtype of ADHD with specific clinical characteristics.

Methods

Participants

The IMAGE Study Sample

Caucasian subjects were recruited to the IMAGE study, with ethical approval from twelve European centres (Brookes et al. 2006). Researchers at each of the sites liaised with local child psychiatry clinics, and invited families with a child aged 5–17 years with a clinical diagnosis of combined type ADHD to participate in the study, with parental consent. In total 2067 families were invited to participate and expressed initial interest in the study. 1339 of these families completed the PACS interview and questionnaires, and 1084 families had a child who met the research criteria of combined type ADHD, with symptoms confirmed in the home and school setting, with clinical impairment. Each participant family consisted of a child with a diagnosis of DSM-IV combined subtype ADHD (ADHD-CT), one or more full siblings aged 5 to 17 years and one or both parents, with each family member invited to donate a blood or saliva sample for DNA collection. Parental consent was required for each participant family. Exclusion criteria included the presence of a diagnosis of ASD, epilepsy, IQ < 70, brain injury, genetic disorder or metabolic disorder associated with hyperactivity or inattention. If either the proband or sibling was excluded, the whole family was excluded from the study. The final number of participating families for the study of autism symptoms in ADHD was then 821.

Measures

Symptoms of ADHD were measured in probands and siblings using the Long Version of the Conners' Parent and Teacher Rating Scales (Conners 2001) and the Parent and Teacher versions of the Strengths and Difficulties Questionnaire (SDQ) (Goodman et al. 2004). The parent and teacher rated SDQ was also used to measure clinical impairment. The Parental Account of Children's Symptoms (PACS) (Taylor et al. 1986) semi-structured interview was performed for each child (proband or sibling) who scored above the screening cut-off T score for ADHD (a T score of 63 or above for 'DSM IV Symptoms: Total' in the Conners' Parent or Teacher Rating Scales). Interviewers were trained in the performance of the PACS and inter-rater reliability assessments were performed (Brookes et al. 2006). The Hypescheme data capture system (Curran et al. 2000) was used to apply a standardised algorithm to symptoms listed from the PACS interviews, SDQ parent and teacher data and Conners' parent and teacher data, thus generating DSM-IV diagnoses of ADHD (inattentive type, hyperactive-impulsive type, and combined type), conduct disorder, and oppositional defiant disorder. IQ was assessed in probands and siblings using four subtests of the Wechsler Intelligence Scale for Children-Revised (Wechsler 1991) or Wechsler Adult Intelligence Scale-Revised (Wechsler 1981) as appropriate, with a prorated estimation of full scale IQ (Sattler 1992). Interviewers were trained to assess for the presence of language disorder, motor disorder and reading disorder in the PACS interview, and to classify each of these conditions as a 'Definite Disorder,' 'Possible Disorder' and 'No Disorder.' For each disorder (language, motor and reading) the child was given a score of 0 for no disorder, 1 for a possible disorder, and 2 for a definite disorder. By combining these, a neurodevelopmental score of 0–6 was assigned to each ADHD proband. Perinatal risk factors and were classified as 'Definite Disorder' if any of the risk factors listed in the Hypescheme Glossary were definitely present (birth weight less than 1.5 kg, gestational age less than 29 weeks, apgar score less than 2 at 5 minutes, special care baby unit for more than 24 hours, severe infection, severe metabolic disturbance (hypoglycaemia, acidosis, hypocalcaemia), seizures/convulsions in the first month of life). Pregnancy risk factors were classified as 'Definite Disorder' if any of the risk factors listed in the Hypescheme Glossary were definitely present (antepartum hemorrhage, pre-eclamptic toxaemia, hypertension, diabetes, severe infection, smoking more than 20 cigarettes per day for at least 3 months of the pregnancy, use of benzodiazepines, anticonvulsants or any other drugs thought to be associated with ADHD in the offspring).

Symptoms of autism were assessed in probands and siblings using the lifetime version of the parent-rated Social Communication Questionnaire (SCQ), (Rutter et al. 2003) which is a questionnaire developed as a companion tool to the Autism Diagnostic Interview—Revised (ADI-R), using many items from the ADI-R (Lord et al. 1994). The SCQ consists of 40 yes/no questions answered by the chief care-giver and has been validated in clinical populations. (Berument et al. 1999; Bölte et al. 2008; Chandler et al. 2007; Corsello et al. 2007; Lee et al. 2007). The scale has good validity in differentiating ASD from non-ASD in children 4 years and older, has a correlation of 0.71 with the ADI-R, (Berument et al. 1999) and is independent from IQ (Chandler et al. 2007; Rutter et al. 2003). High correlations between the autism domains of the SCQ and the

autism domains of the ADI-R have been shown, with a correlation of 0.82 for Reciprocal Social Interaction, 0.73 for Communication and 0.89 for the Restricted, Repetitive, and Stereotyped Patterns of Behaviour domain. (Bishop and Norbury 2002). An SCQ-score of 15 or more on the lifetime version suggests the presence of a PDD, with a sensitivity of 0.85 and a specificity of 0.75. A cut-off score of 22 is required to differentiate autism from other PDD's, with a sensitivity of 0.75 and specificity of 0.60 (Berument et al. 1999). As the sample was ascertained for genetic studies of ADHD, families were excluded if the proband or sibling had a diagnosis of ASD. Children with ADHD who fulfilled criteria for ASD were excluded as follows: those who scored 15 or more on the SCQ or scored 4 or less in pro-social scale of the SDQ were assessed using the autism schedule of the PACS, which yields a DSM-IV diagnosis of ASD, or no ASD. The subsequent PACS diagnosis was used as an exclusion criterion.

Normal Population Sample

Parents of 149 children of mixed gender (73 males and 76 females) aged 5–12 years attending a mainstream state funded primary school in Ireland completed the SCQ. The school serves a predominantly Caucasian mixed urban and rural community with all socio-economic groupings represented.

Procedure

Children with a clinical diagnosis of ADHD were assessed using the PACS semi-structured interview, parent and teacher Conners' rating scale, parent and teacher SDQ and parent rated SCQ. Siblings were assessed using the same questionnaires, and also the PACS semi-structured interview if they were suspected to have ADHD or if the sibling had a T score of 63 or above for 'DSM IV Symptoms: Total' in the Conners' Parent or Teacher Rating Scales. All participating children and one or both parents had a blood test or saliva swab taken for the IMAGE study. Data was recorded at anonymously at each site, and was sent electronically to a central database at the London site. Data was analysed using either SPSS (SPSS Inc, IL, USA) or the STATA statistical package (Stata Inc, TX USA) as outlined below.

Statistical Analysis

Comparison of Autism Symptoms in ADHD-CT Probands and Siblings with and ithout ADHD

The mean SCQ-scores of the proband group and of the sibling group were calculated. The sibling group was then subdivided into those with ADHD (either hyperactive-impulsive, inattentive or combined subtype), and those without ADHD. The mean SCQ-score of each subgroup of siblings was calculated. A random effects model controlling for family status (sibling or proband) and for gender was constructed to compare SCQ-scores within families. A random effects model was used as we were interested in comparing probands and siblings within each family (Rabe-Hesketh and Skrondal 2005). As the variable family is a random effect a random effects approach was adopted to the analysis. Proband SCQ scores were compared with (a) the SCQ-scores of siblings unselected for ADHD status, (b) the SCQ scores of siblings with ADHD any type and (c) the SCQ-scores of siblings without ADHD, using the within family random effects model.

Measurement of Familiality: Sibling Intra-class Correlation of Autism Symptoms

The correlation between SCQ-scores in the proband and SCQ-scores in the sibling was estimated by calculation of the intra-class correlation coefficient. This was calculated between probands and (a) siblings unselected for ADHD status, (b) siblings with ADHD, any type and (c) siblings without ADHD.

DeFries-Fulker Analysis of Familial Influences on Autism Symptoms in ADHD

A modified method of DeFries-Fulker analysis (Andreou et al. 2007; DeFries and Fulker 1985; Purcell and Sham 2003) was used to analyse the effect of shared familial influences on symptoms of autism and symptoms of ADHD in our data. DeFries-Fulker analysis uses a comparison of the proband and sibling mean symptom scores with the mean scores of the population. If the effect of familial influences is small, the sibling mean will be the same as or resemble the population mean, and the correlation between the sibling and proband mean scores will be small. However if the sibling mean varies substantially from the population mean, it is likely that this variation is due to familial influences shared with the proband. As probands and siblings share on average half of their genetic make-up, the effect of genetic influences on the variance of a disorder will be twice the correlation between the sibling and proband deviations from the normal population scores.

Bivariate analysis was used to estimate (a) the correlation of autism symptoms with ADHD symptoms in probands (phenotypic correlation (R_p)), (b) the correlation between autism symptoms in the sibling group and ADHD symptoms in the proband group (bivariate sibling correlation (R_{bvs})) and (c) the percentage of the phenotypic correlation which is due to shared familial influences (F). The following equations were used to calculate these

measures respectively: R_p = (mean SCQ of probands − mean SCQ of normal population)/(mean Conners' DSM-IV:Total T score of probands − mean Conners' DSM-IV:Total T score of normal population), with each difference expressed in units of the standard deviation of the normal population; R_{bvs} = (mean SCQ of siblings − mean SCQ of normal population)/(mean Conners' DSM-IV:Total T score of probands − mean Conners' DSM-IV:Total T score of normal population), with each difference expressed in units of the standard deviation of the normal population. $F = (2 \times R_{bvs})/R_p = 2x$ (mean SCQ of siblings − mean SCQ of normal population)/(mean SCQ of probands − mean SCQ of normal population).

The percentage of the phenotypic correlation which is due to shared familial influences (F) describes the percentage of the phenotypic correlation of autism with ADHD symptoms which is due to familial influences, assuming that (a) the variation in symptoms of autism from the population mean is due to genetic influences, and the effect of the shared environment is small or negligible and (b) the variation in symptoms of ADHD from the population mean is due to genetic influences, and the effect of the shared environment is small or negligible. The third equation can be interpreted as describing the percentage of the correlation between autism symptoms and ADHD symptoms which are due to shared familial influences.

Latent Class Analysis of SCQ Symptoms in Probands with ADHD

We wished to determine if we could divide the sample of ADHD probands into different groups on the basis of their SCQ-score. A latent class analysis was performed on probands with ADHD using 39 informative questions from the SCQ in order to form clusters. In the simplest form the model can be considered as follows: we assume that there is an underlying latent class variable x with a number of categories where these categories correspond to the clusters or latent classes. The model can be expressed using (unconditional) probabilities of belonging to each cluster or latent class. For example, suppose we have two variables, A and B, and we hypothesise that there are three clusters or latent classes. We can write an expression for the probability of getting a response i from item A and response j from item B and belonging to class t as follows:

$$\pi_{ijt} = \pi_t^x \pi_{it}^{Ax} \pi_{jt}^{Bx}$$

where $t = 1,2,3$; π_t^x is the probability of being in cluster/latent class t; π_{it}^{Ax} the conditional probability of obtaining ith response to item A for members of class t; π_{jt}^{Bx} the conditional probability of obtaining jth response to item B for members of class t.

Each case can be a member of one and only one cluster or class and we assume that conditional on the latent class membership the variables A and B are independent. In latent class terminology this is referred to as local independence. The package Latent Gold 4.0 (Statistical Innovations, MA, USA) was used to test and fit these models (Vermunt and Magidson 2000).

The percentage of probands in each cluster that had oppositional defiant disorder (ODD), conduct disorder (CD), language disorder (LD), reading disorder (RD) and motor disorder (MD) was then calculated.

Comparison of Autism Symptoms in ADHD with and Without Comorbid Disorders

For two-level variables such as CD and ODD, the total proband group was subdivided into two groups: (a) not-present and (b) present. The mean SCQ-score of each group was compared using the independent t-test. For three level variables such as LD, RD and MD, probands were subdivided into three groups: (a) not-present, (b) possible and (c) definite. Mean SCQ-scores were compared using one-way analysis of variance. All analysis was performed using SPSS 15.0.

Results

Comparison of Autism Symptoms Between ADHD Probands and Siblings

821 families with a proband with ADHD-CT and one or more siblings were studied, representing a total of 1871 children. There were 182 siblings with ADHD and 868 siblings who did not have ADHD. Mean SCQ-scores for probands, the total sibling group (unselected for their ADHD status), the group of siblings with ADHD, the group of siblings without ADHD and the normal control group are presented in Table 1. It can be seen that symptoms of autism were higher in probands with ADHD than in siblings or controls, and that male siblings had a higher mean SCQ score than control children, regardless if the siblings had ADHD or not. This was not the case for female siblings of those with ADHD, suggesting that there is a stronger familial mechanism for autism symptoms in males than in females.

A random effects model controlling for status (sibling or proband) and for gender was used to compare autism symptoms within families. A significant effect of family status was found, with a higher mean SCQ-score in probands than siblings unselected for ADHD status (size of effect = 3.67–5.68, $p < 0.001$) (Table 2). The difference between the mean SCQ-score of probands and siblings was

Table 1 Comparison of SCQ scores in probands, siblings and normal controls

Group	Number	Mean SCQ	SD
All probands	821	8.49	6.23
Probands male	723	8.48	6.22
Probands female	98	8.54	6.40
All unselected siblings	1050	4.42	4.18
Unselected siblings male	522	5.23[a]	4.65
Unselected siblings female	527	3.61	3.49
All non-ADHD siblings	868	4.01	3.79
Non-ADHD siblings male	406	4.71[b]	4.20
Non-ADHD siblings female	461	3.39	3.28
All siblings ADHD any type	182	6.36	5.28
Siblings ADHD any type male	116	7.04[c]	5.62
Siblings ADHD any type female	66	5.17	4.42
All siblings combined type ADHD	111	6.78	5.27
Siblings combined type ADHD Male	79	6.92	5.47
Siblings combined type ADHD Female	32	6.44	4.83
All normal controls	149	3.89	2.77
Normal controls male	73	4.00	2.65
Normal controls female	76	3.78	2.90

Note: [a] A significant difference between male and female SCQ score was noted for the unselected sibling group ($t = 6.355$, df = 966.5, $p < .00195\%$ CI = 1.11–2.11), [b] siblings without ADHD ($t = 5.10$, df = 763.5, $p < .001$, 95% CI = 0.81–1.82), and [c] siblings with ADHD any type ($t = 2.49$, df = 162.1, $p = .014$, 95% CI = 0.39 = 3.36)

greater between probands and siblings without ADHD (size of effect = 3.98–6.23, $p < 0.001$) than probands and siblings with ADHD any type (size of effect = 0.9–2.54, $p < 0.001$) (Table 2). There was also a significant effect of gender, with the mean SCQ-score in males higher than in females for all sets of sibling comparison. In the comparison with unselected siblings and siblings without ADHD there was a significant interaction between gender and status suggesting that the difference between the genders depended on the family status of the case. The analyses suggest that the difference between males and females was larger for siblings than for probands. There was no significant interaction between gender and family status for the comparison with siblings with ADHD any type.

If the autism trait, as measured by SCQ, is not simply a measure of ADHD, it should be independently familial within ADHD families. In other words probands with ADHD with autism symptoms would be more likely to have siblings with autism symptoms and probands with ADHD without autism symptoms would be more likely to have siblings without autism symptoms.

Measurement of Familiality

Sibling Intra-class Correlation of Autism Symptoms

A graph comparing autism symptoms in sibling pairs concordant for ADHD-CT is shown in Fig. 1. This demonstrates a linear relationship between autism symptoms in the proband and autism symptoms in their siblings with ADHD-CT (Pearson's Correlation = 0.58).

The relationship between SCQ in probands and SCQ in their siblings was further explored by calculation of the intra-class correlation co-efficient for the SCQ-score, which is a measure of symptom correlation within a family. This comparison was performed between probands and (a) siblings unselected for ADHD status (b) siblings with ADHD, any type and (c) siblings without ADHD. The intra-class correlation co-efficient for each comparison was 0.37, 0.54 and 0.32 respectively (see Table 2).

DeFries-Fulker Analysis of Familial Influences on Autism Symptoms in ADHD

Familial influences were calculated using the mean SCQ-score of the normal population sample and the mean SCQ-score of the sibling group, unselected for ADHD status. The mean SCQ-score of 149 children from the normal

Table 2 Comparison of autism symptoms (SCQ) in probands with autism symptoms in siblings

Sibling group	Effect	Significance	Size of effect	Intraclass correlation
Unselected sibling	Status*	$p < 0$ .001	3.67–5.68	0.37
	Gender	$p < 0$ .001	1.22–2.36	
	Status* gender	$p = 0.014$	0.29–2.60	
Siblings with ADHD, any type	Status	$p < .001$	0.90–2.54	0.54
	Gender	$p < .001$	1.07–3.40	
Siblings without ADHD	Status	$p < .001$	3.98–6.23	0.32
	Gender	$p < .001$	0.79–2.05	
	Status* gender	$p = .029$	0.14–2.73	

* A random effects model controlling for status (sibling or proband) and for gender was constructed to compare SCQ scores within families. Proband SCQ scores were compared with (a) unselected sibling SCQ scores, (b) SCQ scores of siblings with ADHD and (c) SCQ scores of siblings without ADHD, using the within family random effects model

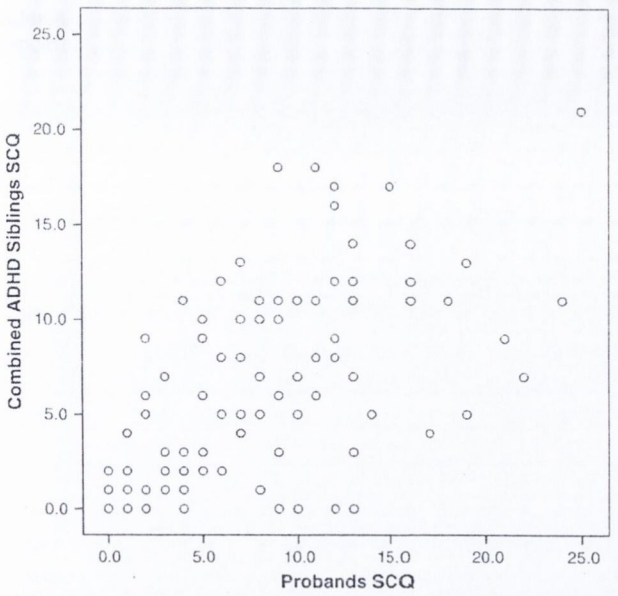

Fig. 1 Familiality of autism symptoms in sibling pairs concordant for ADHD. Autism symptoms of probands (combined type ADHD) versus autism symptoms of siblings with combined type ADHD. Pearson correlation = 0.58, number of families = 102

population (73 males and 73 females) was 3.89, SD 2.77. As an effect of gender on SCQ-score was found in siblings (Table 1), and the ratio of males and females in the proband group differed from the ratio in the sibling and in the control groups, calculations were performed for male probands and female probands. The correlation of SCQ-score with parent rated Conners'-score in probands was calculated (phenotypic correlation), with each value compared with that of the normal population. The phenotypic correlation was found to be 0.63 for males and 0.49 for females (see Table 3). The bivariate sibling correlation (the correlation between autism symptoms in siblings and ADHD symptoms in probands) was calculated as 0.175 for males and could not be calculated for females, due to the lower mean SCQ score of unselected female siblings than the normal female population. The percentage of phenotypic correlation due to shared familial influences was 56% for males and similarly could not be calculated for females (see Table 3). This suggests that for males, a large proportion of the correlation between ADHD and autism symptoms as measured by the SCQ is due to familial influences shared between ADHD and autism symptoms.

Latent Class Analysis of SCQ Symptoms in Probands with ADHD-CT

We performed a latent class analysis to determine if responses to the 39 informative questions on the SCQ identified one or more clusters of children within the ADHD proband group. The latent class analysis suggested that 5 clusters fitted the data. SCQ responder pattern by cluster is summarised in Table 4—the higher the number of symbols, the more prevalent (+) or less prevalent (−) the symptom. 31% of children were in cluster 1, and demonstrated few or no symptoms of autism, with a mean SCQ-score of 2.2 (Table 5). If the SCQ was simply detecting ADHD symptoms then cluster 1 should not be formed. Clusters 2, 3 and 4 had mean SCQ-scores of 10.2, 7.0 and 13.6 respectively. Cluster 2 represented 22.5% of the sample and children had symptoms which corresponded with the repetitive and stereotyped behaviours domain of the ADI-R, such as circumscribed interests and the repetitive use of objects. 21% of children were in cluster 3 and also displayed some symptoms which corresponded with the communication domain of the ADI-R such as lack of the use of gestures in the 4–5 year age-group. 18.5% of children were in cluster 4 and had some symptoms which corresponded with the communication and social reciprocal interaction domains of the ADI-R, such as a reduced ability to use gestures, play with imagination or join in group play at the age of approximately 4–5 years of age. Finally children in cluster 5 represented 7% of the sample, had a mean SCQ-score of 21.4, and had symptoms in all three domains of the ADI-R, especially social reciprocal interaction symptoms in the 4–5 year age-group. Children in cluster 5 had the greatest prevalence of oppositional defiant disorder (77%), conduct disorder (44%) and language disorder (25%). Children in cluster 1 had the lowest prevalence of oppositional defiant disorder (58%), conduct disorder (18%), motor disorder (15%) and language disorder (7%). All clusters were predominantly male.

Table 3 Shared familial effects on ADHD and autism symptoms

ADHD proband Group	Phenotypic correlation	Bivariate sibling correlation	Percentage of phenotypic correlation due to shared genetic influences
Male probands	0.63	0.175	56%
Female probands	0.49	–	–

Comparison of Autism Symptoms in ADHD with and Without Comorbid Disorders

We examined comorbid oppositional and neurodevelopmental disorders for association with SCQ-score. Probands with ODD, CD, language disorder, motor disorder, and the composite neurodevelopmental difficulties score had significantly higher mean SCQ-scores than probands without these disorders (Table 6).

Table 4 Cluster analysis: SCQ responses for ADHD probands

	ADI	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster5
Size of the clusters		31%	22.5%	21%	18.5%	7%
Conversations	C	–	–	–	–	–
Stereotyped utterances	C	–	++	–	–	+++
Inappropriate questions	C	–	+++	–	–	++++
Pronoun reversal	C	–	–	–	–	+
Neologisms	C	–	+	–	–	++
Verbal rituals	R	–	–	–	–	+++
Compulsions and rituals	R	–	–	–	–	+++
Inapprop. facial expression	S	–	–	–	–	–
Use of other's body to commun.	S	–	–	–	–	–
Unusual preoccupations	R	–	–	–	–	–
Repetitive use of objects	R	–	+	–	–	++++
Circumscribed interests	R	–	+	–	–	++
Unusual sensory interests	R	–	–	–	–	–
Hand and finger mannerisms	R	–	–	–	–	–
Complex body mannerisms	R	–	–	–	–	+++
Self injury	–	–	–	–	–	+
Unusual attachment to objects	R	–	–	–	–	–
Friends	S	–	–	–	–	+
4–5 social chat	C	–	–	–	+	+
4–5 imitation	C	–	–	–	+	–
4–5 point to express interest .	C	–	–	–	–	–
4–5 gestures	C	–	–	++++	++	+
4–5 nod yes	C	–	–	–	–	–
4–5 shake head no	C	–	–	–	–	–
4–5 eye gaze	S	–	–	–	+	++++
4–5 social smile	S	–	–	–	–	+
4–5 showing and directing attention	S	–	–	–	–	–
4–5 offer to share	S	–	–	–	–	++
4–5 shared enjoyment	S	–	–	–	–	–
4–5 offer comfort	S	–	–	–	–	–
4–5 quality of social overtures	S	–	–	–	–	–
4–5 range facial expression	S	–	–	–	–	–
4–5 imitative social play	C	–	–	–	+++	++
4–5 imaginative play	C	–	–	–	+	+
4–5 interested other children	S	–	–	–	++	+++
4–5 respond to other children	S	–	–	–	–	++
4–5 attention to voice	–	–	–	–	+	++++
4–5 imaginative play peers	S	–	–	–	+++	++++
4–5 group play	S	–	–	–	+++	+++

Key: ++++80–100%; +++70–80%; ++60–70%; +50–60%

+'s indicate presence of symptom; −'s indicate absence of symptoms

ADI domains: S = social reciprocal interaction domain, C = communication domain, R = repetitive behaviour and stereotyped patterns domain

Discussion

Our study has shown that children with ADHD display significantly more symptoms of autism than their siblings or normal controls, (mean SCQ = 8.49, 4.42 and 3.89, respectively), having taken account of the effects of gender. All three domains of autism (social reciprocal interaction, communication and repetitive behaviours) contribute to this finding. These data are in keeping with previous studies (Berument et al. 1999; Farzin et al. 2006; Reiersen et al. 2007; Rutter et al. 1999) although reported SCQ-scores in normal controls vary from 4.2 (Rutter et al. 1999) to 1.69 (Farzin et al. 2006).

In the DeFries Fulker analysis we show that symptoms of autism in ADHD are partly related to symptoms of ADHD, with a correlation of 0.63 between increased

Table 5 Characteristics of clusters of ADHD probands

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Mean SCQ	2.24	10.22	7.04	13.58	21.4
No of cases	255	185	171	152	58
% Female	11	14	13	10	14
Size of cluster (%)	31	22.5	21	18.5	7
Percentage with definite disorder					
Oppositional defiant disorder[a]	58	70	62	73	77
Conduct disorder[b]	18	25	21	32	44
Speech disorder[c]	7	16	9	19	25
Reading disorder	23	30	31	29	30
Motor disorder[d]	15	23	18	30	23
Perinatal difficulties[e]	13	31	24	23	28
Pregnancy difficulties	15	26	16	19	21

Note: Chi square analysis was performed to compare the numbers with No Disorder/Possible Disorder/Definite Disorder for each disorder in each cluster. Percentages with a Definite Disorder in each cluster are presented in this table as a summary of the data

[a] Pearson Chi-Square = 15.05, df = 4, sig = 0.005

[b] Pearson Chi-Square = 22.88, df = 4, sig < 0.001

[c] Pearson Chi-Square = 26.28, df = 8, sig < 0.001

[d] Pearson Chi-Square = 21.61, df = 8, sig = 0.006

[e] Pearson Chi-Square = 20.40, df = 8, sig = 0.009

Table 6 Comorbid disorders and symptoms of autism in ADHD probands

	Number	Mean SCQ	S.D.
No oppositional defiant disorder	280	7.15[a]	5.68
With oppositional defiant disorder	536	9.19	6.41
No conduct disorder	613	7.81[b]	5.72
With conduct disorder	202	10.56	7.24
No speech disorder	588	8.00[c]	5.98
Possible speech disorder	97	9.10	7.15
Definite speech disorder	102	10.87	6.54
No reading disorder	408	8.06[d]	6.13
Possible reading disorder	156	8.53	6.36
Definite reading disorder	217	9.21	6.39
No motor disorder	414	7.69[e]	6.09
Possible motor disorder	209	9.10	6.33
Definite motor disorder	164	9.79	6.39
No neurodevelopmental difficulties	228	7.21[f]	5.90
Some neurodevelopmental difficulties	418	8.59	6.25
Definite neurodevelopmental difficulties	131	10.40	6.47

[a] t = + 4.67, df = 629, 95% CI = 1.19–2.91, $p < 0.001$

[b] t = + 4.93, df = 288, 95% CI = 1.66–3.86, $p < 0.001$

[c] Speech Disorder: oneway analysis of variance: $F = 9.83$, df = 2, $p < 0.001$

[d] Reading Disorder oneway analysis of variance: $F = 2.40$, df = 2, $p = 0.09$

[e] Motor Disorder: oneway analysis of variance: $F = 8.04$, df = 2, $p < 0.001$

[f] Summary of Neurodevelopmental Difficulties: oneway analysis of variance: $F = 11.15$, df = 2, $p < 0.001$

symptoms of autism and increased symptoms of ADHD in males and a correlation of 0.49 in females. However the correlation was not complete, implying that autism symptoms may be partly independent of symptoms of ADHD. This is supported by the cluster analysis where the non-linear relationship between the two traits suggests that the SCQ is measuring, at least in part, a different trait to that measured by the Conners' rating scale, and that the overlap of symptoms is not due to measurement artefact. The presence of high symptoms of autism in some children with ADHD and low symptoms of autism in others suggests that autism symptoms potentially index a subgroup of ADHD.

Our data suggests that autism symptoms in ADHD are familial over and above the familiality of ADHD symptoms. The correlation of autism symptoms between sibling pairs was higher where there were two children in the family with ADHD (correlation of 0.54) than when there was one child with ADHD and an unaffected sibling (correlation of 0.32). The familial nature of autism symptoms in the general population has previously been shown (Constantino and Todd 2005), but our study shows that the correlation in autism symptoms is greater when both siblings have ADHD than if only one has ADHD. We calculated that 56% of the correlation between autism symptoms and ADHD symptoms in male probands was due to familial influences shared between the two disorders. We thus support our second hypothesis that ASD symptoms in ADHD are familial and we have shown that the comorbidity of ADHD and autism symptoms is due, in part, to

shared familial risk factors, but the difference between that calculated using male probands and female probands is striking. For a family with a male child with ADHD and co-morbid autism symptoms, a second child with ADHD is also likely to have co-morbid autism symptoms, whereas this is not the case for a family with a female child with ADHD and autism symptoms, suggesting differences in aetiology according to sex. The influence of gender, however, should be regarded as preliminary, given the large predominance of male patients in our sample. It has previously been shown that environmental (i.e. non-genetic) factors have only limited effect on the variance of both autism and ADHD symptoms (Ronald et al. 2006; Faraone et al. 2005). Therefore, to a large extent, in this study familiality may be assumed to equal heritability. It should be noted that the exclusion of children with ADHD and co-morbid ASD from the sample could result in the lower figure calculated for shared familial influences of ADHD and autism symptoms than was found in the twin study by Ronald et al. 2008.

Our finding that autism symptoms in ADHD are familial, with only a part of the familiality directly shared with the familiality of ADHD may indicate the presence of distinct genetic subtypes of ADHD, with and without autism symptoms. Our latent class analyses appear to be in line with this. 31% of children with ADHD-CT had very few symptoms of autism, in keeping with the normal population and had a lower prevalence of comorbid disorders than those with higher symptoms of autism. The remaining four clusters, comprising 69% of the sample had more symptoms of autism than the normal population, and these children had a higher prevalence of comorbid disorders in ADHD. The cluster with the highest mean SCQ-score (21.4) had the highest prevalence of co-morbid oppositional defiant disorder, conduct disorder, language disorder and motor disorder. This finding supports our third hypothesis—that the comorbidity of ADHD and autism symptoms is a specific subtype of ADHD and that this subtype has specific phenotypic characteristics.

The presence of autism symptoms in children with ADHD may have direct clinical implications and may be an important risk factor for the presence of impairing comorbidities. In the present study we found that children with ODD or CD have more autism symptoms than children without these co-morbid disorders. It has previously been shown that 22% of children with ADHD are socially disabled, on a measure of social functioning (Greene et al. 1996) and that those who are socially disabled have increased rates of disruptive disorders and substance misuse disorders, in comparison to those with ADHD without social disability (Greene et al. 1997). The association between autism symptoms in ADHD and both ODD and CD may have implications for the course of ADHD from early childhood to later childhood. An assessment of symptoms of autism at initial presentation may identify children at increased risk of developing ODD/CD. Intensive parent training and family based interventions of proven efficacy in antisocial disorders such as the Webster-Stratton programme (Scott et al. 2001; Webster-Stratton and Hancock 1998) could be planned for the child. Future research could compare the efficacy of child-based social skills training with parenting programmes in the prevention of progression to ODD/CD in those with high autism symptoms in ADHD.

We have shown that children with ADHD-CT who also have motor disorder or language disorder have higher autism symptom scores than those without these disorders. Language disorder in ADHD and communication problems as seen in ASD may share the same dimension. It is also possible that motor disorder in ADHD, which is usually associated with motor clumsiness, and repetitive behaviour in ASD could share the same dimension. Our latent class analysis further demonstrated that there is a subgroup of children (cluster 5) with ADHD-CT, as well as social and communication deficits as indexed by the SCQ and an increased prevalence of motor and language disorders. This subgroup of children also has an increased prevalence of conduct disorder. While it has been well accepted that ADHD is associated with language disorder (Faraone et al. 1998) and with motor disorder (Kadesjo and Gillberg 2001) there has been limited interest in autism symptoms in relation to these disorders in ADHD. The findings of motor disorder and language disorder in association with autism symptoms and ADHD in this study are not unlike Gillberg's description of Deficits of Attention, Motor and Perception (DAMP) syndrome (Gillberg et al. 1982). However, the original description of perceptual, motor and attentional deficits by Gillberg was in relation to an epidemiological study, where a screening questionnaire for minimal brain dysfunction was used to identify children with attentional, perceptual, conduct or motor difficulties. Hence children described as having DAMP may or may not also have ADHD. In contrast, this study describes a group of children who have ADHD who have symptoms consistent with DAMP and also have high autism trait scores. Kadesjo has shown that approximately half of all children with ADHD meet criteria for DAMP (Kadesjo and Gillberg 2001). In his 2003 review Gillberg states "in those with severe DAMP autism features were extremely common, amounting to what would nowadays be diagnostic status for 'autism spectrum disorder' in no less than two-thirds of cases," in reference to children diagnosed with severe DAMP in the 1970's (Gillberg 2003; Gillberg et al. 1983). It appears to us that our cluster 5, and to a lesser extent, possibly clusters 2, 3 and 4, and the diagnosis of DAMP are describing similar clinical entities.

Conclusions

This study has shown that (a) there are more symptoms of autism in children with ADHD than in their siblings or normal controls; (b) symptoms of autism are partly independent of symptoms of ADHD; (c) symptoms of autism in ADHD are familial with some of that familiality shared with the familiality of ADHD in males; (d) there are two extreme types of ADHD according to autism symptoms—Cluster 1 with low autism symptoms, a low prevalence of language disorder and motor disorder and low prevalence of conduct disorder and Cluster 5 with high autism symptoms, increased prevalence of language disorder and increased prevalence of conduct disorder; (e) children with ADHD and oppositional defiant disorder and conduct disorder have more autism symptoms and (f) children with ADHD and language disorder, motor disorder or increased neurodevelopmental difficulties have more autism symptoms than children with ADHD without these disorders. These findings may have implications for the clinical management of children with ADHD in that children with few autism symptoms might be less likely to develop disruptive behavioural disorders while children with many symptoms of autism might need more intensive medical and psychosocial support. Our findings also have implications for future genetic research in ADHD, which may need to take into account the presence of autism symptoms as a potentially important co-variable.

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ERRATUM

Autism Symptoms in Attention-Deficit/Hyperactivity Disorder: A Familial Trait which Correlates with Conduct, Oppositional Defiant, Language and Motor Disorders

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The following is a corrected version of Table 4:

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Table 4 Cluster analysis: SCQ responses for ADHD probands

Size of the clusters	ADI	Cluster 1 31%	Cluster 2 22.5%	Cluster 3 21%	Cluster 4 18.5%	Cluster 5 7%
Conversations	C	−−−−	−−−−	−−−−	−−−−	−−
Stereotyped utterances	C	−−−−	++	−−−	−−−	+++
Inappropriate questions	C	−−	+++	−−	−	++++
Pronoun reversal	C	−−−−	−−−	−−−−	−−−−	+
Neologisms	C	−−−−	+	−−−−	−−−−	++
Verbal rituals	R	−−−−	−	−−−−	−−−−	+++
Compulsions and rituals	R	−−−−	−	−−−−	−−−	+++
Inapprop. facial expression	S	−−−−	−−−−	−−−−	−−−	−−
Use of other's body to commun.	S	−−−−	−−−	−−−−	−−−−	−
Unusual preoccupations	R	−−−−	−−−	−−−−	−−−−	−
Repetitive use of objects	R	−−−−	+	−−−−	−−−	++++
Circumscribed interests	R	−−−−	+	−−−−	−−−	++
Unusual sensory interests	R	−−−−	−−	−−−−	−−−−	−
Hand and finger mannerisms	R	−−−−	−−	−−−−	−−−−	−−
Complex body mannerisms	R	−−−−	−	−−−−	−−−−	+++
Self injury	−	−−−−	−−	−−−−	−−−	+
Unusual attachment to objects	R	−−−−	−−−−	−−−−	−−−−	−−
Friends	S	−−−	−−−	−−	−	+
4–5 social chat	C	−−−−	−−−	−	+	+
4–5 imitation	C	−−−−	−−−	−−	+	−
4–5 point to express interest	C	−−−−	−−−−	−−−	−−	−−−
4–5 gestures	C	−−−−	−−	++++	++	+
4–5 nod yes	C	−−−−	−−−−	−−	−−	−−−−
4–5 shake head no	C	−−−−	−−−−	−−	−−	−−−−
4–5 eye gaze	S	−−−−	−−	−−−	+	++++
4–5 social smile	S	−−−−	−−−−	−−−−	−−	+
4–5 showing and directing attention	S	−−−−	−−−−	−−−−	−−−−	−−−
4–5 offer to share	S	−−−−	−−−−	−−−−	−	++
4–5 shared enjoyment	S	−−−−	−−−−	−−−−	−−−	−
4–5 offer comfort	S	−−−−	−−−−	−−−−	−−	−−
4–5 quality of social overtures	S	−−−−	−−−−	−−	−−−	−−−
4–5 range facial expression	S	−−−−	−−−−	−−−−	−−−−	−−−
4–5 imitative social play	C	−−−−	−−−−	−−−−	+++	++
4–5 imaginative play	C	−−−−	−−−−	−−−−	+	+
4–5 interested other children	S	−−−−	−−−−	−−−−	++	+++
4–5 respond to other children	S	−−−−	−−−−	−−−−	−	++
4–5 attention to voice	−	−−−−	−−	−−−−	+	++++
4–5 imaginative play peers	S	−−−−	−−−	−−−	+++	++++
4–5 group play	S	−−−−	−−	−−−−	+++	+++

Key: +'s indicate presence of symptom; −'s indicate absence of symptoms; ++++ indicates symptom present in 80–100%; +++ indicates symptom present in 70–80%; ++ indicates symptom present in 60–70%; + indicates symptom present in 50–60%; −−−− indicates symptom absent in 80–100%; −−− indicates symptom absent in 70–80%; −− indicates symptom absent in 60–70%; − indicates symptom absent in 50–60%

ADI domains: S = social reciprocal interaction domain, C = communication domain, R = repetitive behaviour and stereotyped patterns domain

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ORIGINAL ARTICLE

The Social Communication Questionnaire in a sample of the general population of school-going children

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Abstract
Background The social communication questionnaire (SCQ) for autistic spectrum disorder was previously validated in clinical populations.
Aims To describe the distribution of SCQ-scores in the general child population, and identify if traits from all domains of autism are present.
Methods The SCQ was completed by parents of children attending a mixed-gender primary school of 240 children.
Results Total SCQ scores ranged from 1 to 20, with a mode 1 and corrected mean of 3.89, SD = 2.77. SCQ items corresponding to all three domains of autism were found in the sample. Some items on the SCQ were answered as "autism-positive" for up to 41.8% of children in the general population sample.
Conclusions The SCQ has a wide range in the general population, with traits from all three domains of autism. Some items in the SCQ do not discriminate children with autism from other school-going children.

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Keywords Pervasive developmental disorder · Social Communication Questionnaire · General population · Dimensions of autism · Autism

Introduction

The social communication questionnaire (SCQ), formerly known as the Autism Screening Questionnaire is a 40 item questionnaire completed by caregivers and was developed as a screening tool for autistic spectrum disorder in children [1]. A definitive research diagnosis of autistic spectrum disorder can be made by a trained therapist using the autism diagnostic observation schedule (ADOS) with the child [2, 3] or using the autism diagnostic interview-revised (ADI-R) with a caregiver [4]. Each of these is time consuming and requires a trained therapist with expertise in the clinical assessment of children with autism. The SCQ was developed using questions from the ADI-R, and was designed to be used as a companion tool. It is less time consuming to complete than the ADI-R and is completed by the caregiver without a therapist and can be a used to screen children for possible autistic spectrum disorder. Those with high scores on the SCQ can be further assessed using the ADI-R, the ADOS or both the ADI-R and ADOS. There are two versions of the SCQ, the current version which assesses the child's behaviour at the time of the assessment and the preceding 3 months and the Lifetime version, which assesses for symptoms throughout the child's life. The Lifetime version was used in this study, and contains a series of questions about the child's behaviour at age 4–5 years. A high correlation of 0.71 has been found between the SCQ and the ADI-R [5].

The SCQ has been previously validated against various clinical populations, with the SCQ score of children with

autistic spectrum disorder confirmed using the ADI [6] or ADI-R [4] compared with the SCQ scores of children with other psychiatric diagnoses. It was found that a score of 15 or more was suggestive of a pervasive developmental disorder, with a sensitivity of 0.85 and specificity of 0.75. A score of 22 or more was suggestive of autism [5]. A more recent validation study in children with autism and children with other disorders found that younger children scored lower than older children on the SCQ. It was suggested that a lower cut-off point of 12 would be useful to discriminate non-ASD from ASD in children aged less than 8 years [7]. A validation study of the SCQ in the 3–5 year age-group attending special schools also found that a lower cut-off score was appropriate for the assessment for autistic spectrum disorder in this younger age-group [8].

The SCQ has been validated and used in many clinical samples, but to date there has not been a report on the use of the SCQ in a sample representing the general population. A comparison study of SCQ scores of adopted children from the UK with that of adopted children from Romania [9] has been cited to represent the general population [10], although the sample was not specifically taken from the general population. UK adopted children, generally non-autistic, were found to have a mean SCQ score of 5.2 at age 4 and of 4.2 at age 6 [9]. A sibling control study of fragile X syndrome found that male siblings had a mean SCQ score of 1.69 and SD of 2.02 [11]. The sibling sample had a mean age of 10.38 and it could be hypothesised that the difference in the lower mean SCQ score of this study in comparison to the previous study of adopted children is related to the different mean age of the sample.

The aims of this study are (1) to describe the mean and standard deviation of the Social Communication Questionnaire when used in children from the general population, (2) to ascertain if the SCQ score is related to the age and gender of the child and (3) to identify if children from the general population have some symptoms in all domains of the autistic spectrum.

Method

The sample

The SCQ was given to all parents of children attending a mainstream Irish primary school of 240 pupils aged 5–13 years of mixed gender. The school is situated in a rural area close to a new suburb of a large town in the Dublin metropolitan area, and serves both the rural and urban community. The demographics of the area are mixed with middle class, some working class and some migrant families living in the catchment area of the school. The questionnaire was distributed to the pupils by their teachers, accompanied by an information letter about the study and the possibility of publication of the results. Parents were requested to complete the questionnaire anonymously and return the questionnaire blank if they did not consent to participate.

Statistical analysis

The mean SCQ score and standard deviation was calculated for the sample of children from the general population. The group was divided into four groups according to age (<5 years, 5–7 years, 8–10 years, >10 years) and the mean SCQ score of each group was calculated and compared using one way analysis of variance. The SCQ score was correlated with the age of the child. The mean SCQ score of males was compared with the mean SCQ score of females, using an independent sample's t test.

The response pattern to the 40 items of the questionnaire was examined. The response patterns of items from the questionnaire which corresponded with each of the ADI domains of autism were examined. Data was analysed using the SPSS statistical package.

Results

Response rate and demographics

A total of 240 questionnaires were distributed and 182 were returned. Fourteen questionnaires were returned blank, implying that the parent(s) did not consent to participate in the study. Four were returned for whom the gender could not be established, and were excluded. Eleven questionnaires were incomplete and were excluded. In total, 75.8% of the parents returned the questionnaire either complete, partly complete or blank. A total of 153 questionnaires completed by parents of 76 males and 77 females were included in the final analysis. The children ranged from age 4 to age 12 with a mean age of 8.14 (SD = 2.35) years. There were seven children less than 5 years old, 55 children aged 5–7 years, 59 children aged 8–10 years and 30 children aged above 10 years.

Distribution of SCQ scores

The range and distribution of the total SCQ scores of the 153 children can be seen in Fig. 1. The data had a range of 0–20, a mode of 1 and a mean of 4.22, SD = 3.45. The distribution was not normal, and was skewed to the right (skewness = 1.59, kurtosis = 3.94).

Figure 2 shows that there were four outliers in the sample, each of whom had total SCQ scores more than two

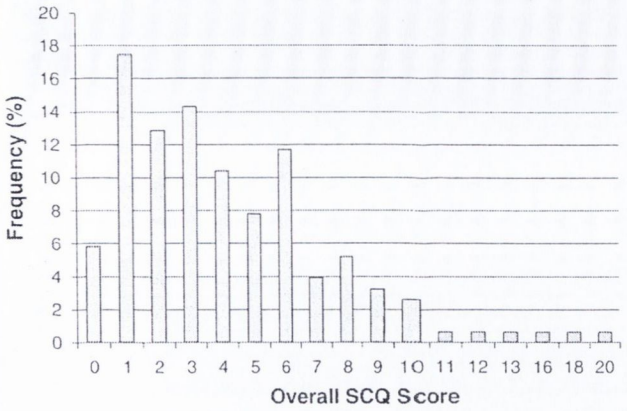

Fig. 1 The range and distribution of total SCQ scores

standard deviations above the mean total SCQ score for the sample. The corrected mean of the sample without the outlier values was 3.89, SD = 2.77, and the corrected sample was normally distributed. (skewness = 0.67, kurtosis = − 0.27).

The mean SCQ scores of children in the various age groups can be seen in Fig. 3. One way analysis of variance did not find a significant effect of age group on SCQ score. A Pearson's correlation showed that there was not a statistically significant correlation between age and overall SCQ score; $r = 0.008$, $P > 0.05$.

The mean SCQ score was higher in males (4.46, SD = 3.48) than in females (3.99, SD = 3.42). However,

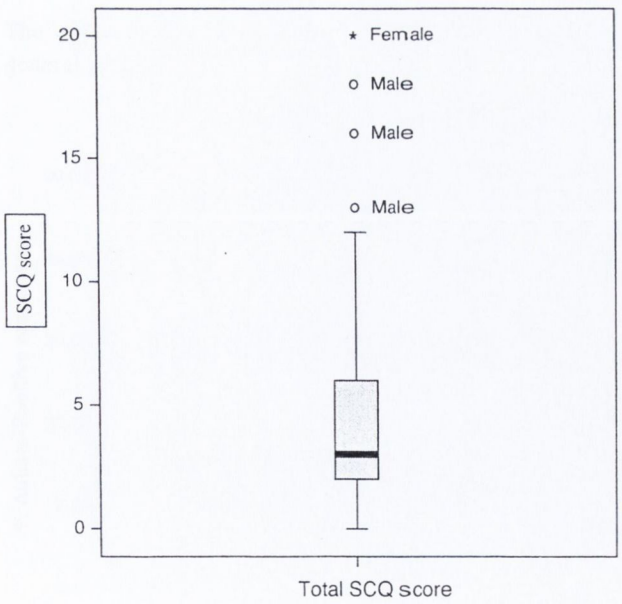

Fig. 2 Boxplot indicating the range of total SCQ scores and outliers. The box indicates the median value, the 75th percentile abd the 25th percentile. Four outliers which are more than 1.5 times the interquartile range from the median are marked

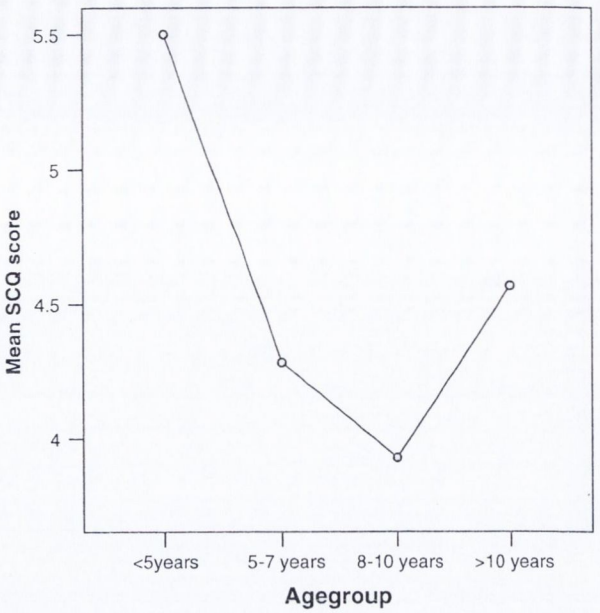

Fig. 3 Relationship between mean SCQ score and age group. Age-group *<5* years: mean SCQ = 5.14, SD = 2.91. Age-group *5–7* years: mean SCQ = 4.24, SD = 2.89. Age-group *8–10* years: mean SCQ = 3.97, SD = 3.43, Age-group *>11* years: mean SCQ = 4.57, SD = 4.55. One way analysis of variance: $F = 0.366$, $df = 3$, sig = 0.78

an independent sample *t*-test found that this difference was not statistically significant; $t(151) = 0.85$, $P > 0.05$, two-tailed.

Response pattern to SCQ items

The percentage of "autism-positive" responses to each of the 39 informative SCQ questions was examined in all of the completed questionnaires (Fig. 4). There was considerable variation in the individual questions of the SCQ in terms of the percentage of autism positive-responses. This varied from just 0.7% "autism-positive" for the question: "Can you have a to and fro 'conversation' with her/him that involves taking turns or building on what you have said?" to 41.2% "autism positive" for the question "Has he/she ever used odd phrases or said the same thing over and over in almost exactly the same way? That is, either phrases she/he has heard other people use or the ones she/he has made up?" (question 3) and 41.8% "autism-positive" for the question "When she/he was 4-to-5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted?" (Question 23).

SCQ questions 2–40 were divided into those which corresponded with the Communication domain of the ADI-R, the Social Reciprocal Interaction domain and the Repetitive Behaviour and Stereotyped patterns domain on the ADI-R, with each question relabelled with a C, S or R,

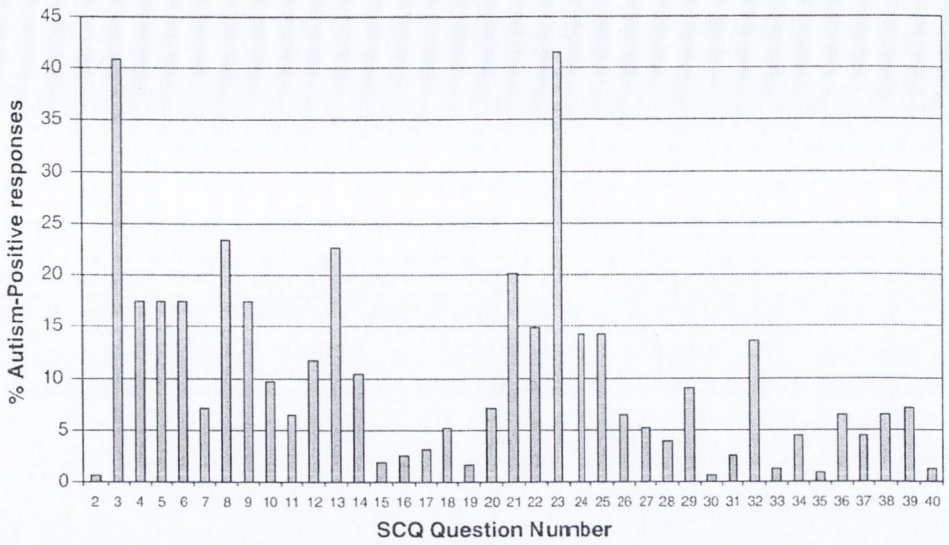

Fig. 4 Percentage of autism-positive responses across individual questions of the SCQ

as appropriate. Questions which did not correlate with a question from the ADI-R were marked with a U.

The percentage of "autism positive" responses to questions from each domain of the ADI-R can be seen in Figs. 5, 6 and 7.

Discussion

Range and distribution of SCQ scores in the general population

The mean SCQ score of this sample representing the general population was 4.22, which is similar to the mean SCQ score of 4.2 reported for UK adopted children aged 6 years [9]. However a wide range of SCQ scores was found in the sample, with a range of 0–20. The distribution was not normal, as reflected by the mode of 1 and the mean score of 4.22, SD = 3.45. However when four outlier values were excluded, the mean was 3.89, SD = 2.77 and the distribution was normal. The recalculated mean score of 3.89, SD = 2.77 is more likely to reflect the true mean of the general population.

Three children in the sample (1.8%) had a total SCQ score which was greater than the cut-off of 15, which is recommended for identifying pervasive developmental disorder from other psychiatric disorders in children [5]. It is possible that there are some children with pervasive developmental disorder attending the mainstream school studied. Alternatively this finding may be due to the reported specificity of 0.75 for the SCQ at a cut-off of 15, and some false positive findings are expected [5]. Lower specificity levels of 0.62 and 0.71 at a cut-off of 15 were recently reported in two subsequent validation studies using the SCQ in clinical populations [7, 12]. It can be expected that there will be some false positive results if a sample from the general population are tested using the SCQ.

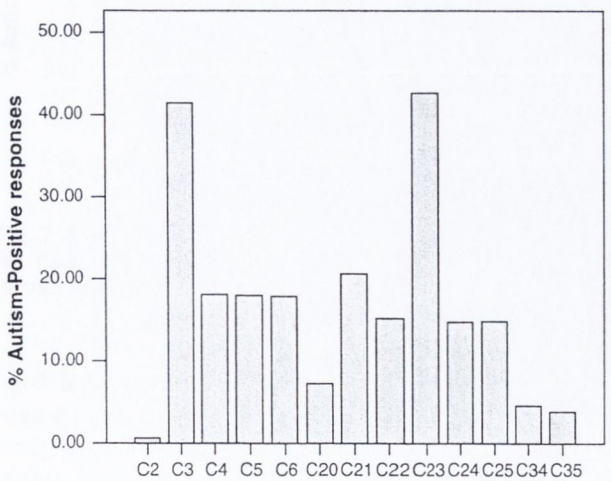

Fig. 5 Responses pattern to SCQ questions which correspond with the Communication domain of the ADI-R (questions 2, 3, 4, 5, 6, 20, 21, 22, 23, 24, 25, 34 and 35)

Effect of age and gender on SCQ scores

No significant effect of gender or age was found on mean SCQ scores in this study. However, there appeared to be a non-significant effect of age on SCQ score in our study, with the mean SCQ score of 4 year old children higher than the mean SCQ score of children in older age-groups. Similarly Rutter et al. [9] found a higher mean SCQ score in adopted children aged 4 years than in adopted children

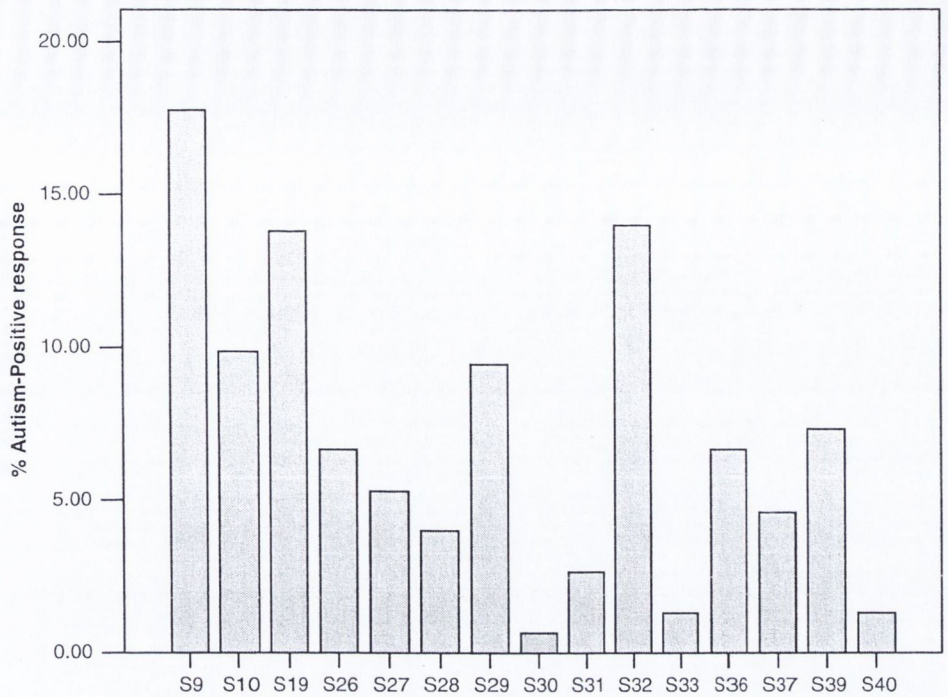

Fig. 6 Responses pattern to SCQ questions which correspond with the Reciprocal Social Interaction domain of the ADI-R (questions 9, 10, 19, 26, 27, 28, 29, 30, 31, 32, 33, 36, 37, 39 and 40)

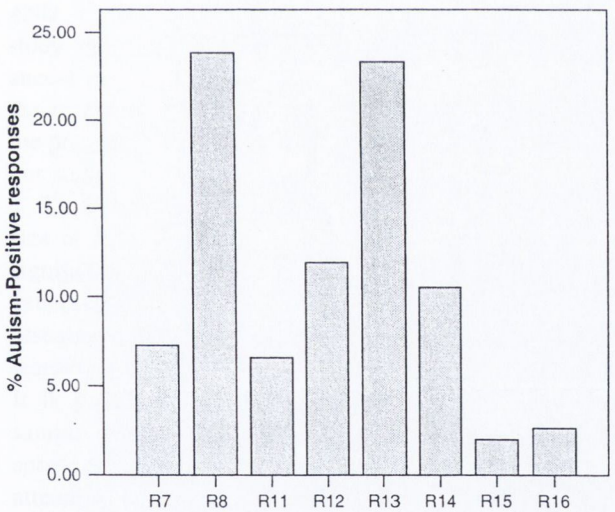

Fig. 7 Responses pattern to SCQ questions which correspond with the Restricted, Repetitive, and Stereotyped Patterns of Behaviour domain of the ADI-R (questions 7, 8, 11, 12, 13, 14, 15 and 16)

aged 6 years (5.2 vs. 4.2) . Although our findings with regard to age were not significant, our study and Rutter's study suggest that very young schoolchildren may have a higher SCQ score than the older children.

In contrast to this, recent validation studies on the SCQ have suggested that younger children may have a lower SCQ score than older children, and suggested that a lower cut-off point for the identification of autistic spectrum disorder could be used in younger children [7, 8]. The age-groups used in our study mimicked the age-groups in a recent study which examined the validity of the SCQ in various age-groups [7]. However, the findings of the validation studies are in contrast with the trend shown in our study and in contrast with Rutter's study [9], both of which suggest that 4 year old children from the general population may have a higher mean SCQ score than children aged 6 years. It is clear that further studies on the effect of age on SCQ score are required.

Traits from three domains of autism are present in the general population

The SCQ was designed primarily as a screening tool for epidemiological research and is considered a useful tool to differentiate between pervasive developmental disorder and other non-autistic disorders [5]. It is explained in "The Social Communication Questionnaire Manual" that the questionnaire identifies symptoms which are rare in the unaffected population, and hence validation studies were performed against the clinical population rather than the general population [1]. This study has examined the SCQ in the general population, and has shown that there is a wide range of SCQ symptoms in the general population,

although the mean SCQ score is low. It was also shown that the general population had some "autism positive" responses on the SCQ from each of the three domains of autism. This finding is in keeping with Constantino's [13] finding that autistic symptoms are part of a continuum in the population.

This study has also shown that some "autistic" symptoms assessed using the SCQ questions were rarely found in the general population while other symptoms were found at a relatively high frequency. In particular, it was found that question 3 (the presence of stereotyped utterances) and question 23 (the presence of gestures) was answered as "autism positive" for over 40% of the general population sample studied. Both these items have corresponding questions in the ADI-R Communication domain. It is clear that these two questions are not useful in discriminating children with autistic spectrum disorder from other children. This suggests that the specificity of the SCQ may be increased if these two questions were not included.

A recent validation study of the SCQ examined item validity, and whether or not each question was useful in discriminating children with ASD from those with other disorders [12]. It was found that 15 of the 39 informative items of the SCQ discriminated between ASD and non-ASD, which is much lower than the findings of the original study [5]. Question 3 (the presence of stereotyped utterances) was useful in discriminating ASD from non-ASD in the recent item validation study (unlike our study), while the presence of gestures (question 23) was not useful, as in our study.

There are certain limitations to our study; the sample size of 153 children may not be large enough to identify significant gender differences or age differences in the general population. The children did not undergo a clinical assessment for other disorders, such as conduct disorder or learning disability which may influence the SCQ score [5]. It is possible that one or more of the children in the sample had a clinical disorder, such as a mild autistic spectrum disorder which did not prevent the child from attending a mainstream school, which would account for the four outlying total SCQ values. Alternatively these values may represent artificially increased SCQ scores due to recall bias for parents of children greater than 10 years old (all children with outlying SCQ scores were in the >10 years age-group, and the SCQ has many questions about the child when 4–5 years of age). However, by including all children attending a mainstream school in the sample, the study should reflect the general population. If a future study on the SCQ score in the general population was being performed, it would be useful to screen all participants for ASD, conduct disorder, learning disability and other disorders associated with an increased SCQ score. It would also be useful to compare results on the SCQ score in the general child population with results using the ADI-R. It may also be useful to conduct a study examining the frequency of autism-positive responses for the individual items of the SCQ, with children with pervasive developmental disorders and the general population comparatively.

In summary, the SCQ has a wide range when used in the general population of school aged children, although most children have a very low SCQ score. Items on the SCQ which relate to all three domains of autism are present in the general population. However, there are two items on the SCQ which are frequently present in the general population, and hence these two questions are not useful in discriminating autistic spectrum disorder from the general population.

Acknowledgments We would like to thank all the parents who completed the SCQ questionnaires, and the teachers who helped to co-ordinate the return of questionnaires. We would also like to thank Myra O'Regan, statistician for her invaluable advice on statistical analysis. We would like to acknowledge the International Multicentre ADHD Genetics Project (IMAGE), a multisite international effort supported by NIH Grant R01MH62873 to SV Faraone, which assisted in the electronic storage of the data.

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DSM-IV Criteria for ADHD

I. Either A or B:

A. Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:

Inattention

1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
2. Often has trouble keeping attention on tasks or play activities.
3. Often does not seem to listen when spoken to directly.
4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
5. Often has trouble organizing activities.
6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
7. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
8. Is often easily distracted.
9. Is often forgetful in daily activities.

B. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:

Hyperactivity/ Impulsivity

1. Often fidgets with hands or feet or squirms in seat.
2. Often gets up from seat when remaining in seat is expected.
3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
4. Often has trouble playing or enjoying leisure activities quietly.
5. Is often "on the go" or often acts as if "driven by a motor".
6. Often talks excessively.
7. Often blurts out answers before questions have been finished.
8. Often has trouble waiting one's turn.
9. Often interrupts or intrudes on others (e.g., butts into conversations or games).

II. Some symptoms that cause impairment were present before age 7 years.

III. Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).

IV. There must be clear evidence of significant impairment in social, school, or work functioning.

V. The symptoms do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder. The symptoms are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Based on these criteria, three types of ADHD are identified:

1. ADHD, *Combined Type*: if both criteria 1A and 1B are met for the past 6 months
2. ADHD, *Predominantly Inattentive Type*: if criterion 1A is met but criterion 1B is not met for the past six months

3. ADHD, *Predominantly Hyperactive-Impulsive Type*: if Criterion 1B is met but Criterion 1A is not met for the past six months.

(American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000)

International Multi-center ADHD Genetics Project (IMAGE)

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Funded by the National Institute of Mental Health (NIMH)

Background

Family and twin studies have clearly demonstrated the importance of genetic influences on ADHD. Furthermore recent findings suggest that genes influencing ADHD have already been identified. This study is designed to further this work by creating a resource for identifying the genes involved and performing a genome scan to identify the location of novel genes involved. This will be achieved in two ways. The first is to create a cell line and clinical data resource for molecular genetic studies of ADHD, both now and in the future. The second is to perform a genetic linkage study to identify regions of the human genome that contain genes that influence the risk for ADHD. At the same time we will search for genetic association with genes that lie within linkage regions or are good a priori candidates for involvement in ADHD.

ADHD is one of the commonest behavioural disorders in childhood, that often continues to effect individuals as adults. ADHD is known to cause considerable disruption of educational and social development and as a result is often treated with stimulant medication, which reverses the major symptoms of the disorder. If we can find out more about the genetic and environmental causes of ADHD, we will be in a better position to help people. This may be in the form of improved recognition and diagnosis, improved preventative measures and improved treatments.

Conduct of Project

Location

Department of Psychiatry, Trinity College Dublin and components of the South Western Area Health Board

Subjects

Children with ADHD aged 5-15 years, their brothers or sisters aged 5-15 years and both biological parents

Number

65 families consisting of one child with ADHD, plus one or more of their siblings and both parents. (from a multi-centre project total of 400)
65 families consisting of two children with ADHD, and both parents (from a multi-centre project total of 400)

Exclusion criteria

Aged under 5 and over 15 years of age, in foster care, structural brain damage, genetic disorders associated with ADHD symptoms (e.g. fragile-X), epilepsy in the last year, autism and IQ less than 70, **not** of Caucasian/European descent.

Recruitment

(1)We will recruit families who have already provided DNA and clinical information in our current study of ADHD genetics.

(2) We will recruit from families that contact us directly from anywhere in Ireland
(3) We will seek additional permissions from other ethics committees to recruit from other areas/organizations

Design, methodology and techniques

The first part of this project is to identify 65 children with ADHD aged 5-16 years, who have one or more siblings in the same age group, and 65 sib-pairs both with ADHD. These families will be recruited from three main sources:

1) First, we have already identified 200 children with ADHD who have already provided blood samples for DNA extraction, and clinical information on ADHD. This cohort was identified as part of our ongoing study of ADHD genetics, funded by the HRB and the Wellcome Trust. Participating families will be informed of this new study in a Study Newsletter. Families will then be sent the letter of invitation and information sheets for this project. They will then be contacted by telephone and if following discussion of the project they agree to participate, we will arrange an interview either in their own home or at the Department of Psychiatry, or some other suitable location.
2) Second, we propose to recruit new cases from child psychiatry clinics in the South Western Area Health Board region. These will be contacted initially by the clinical team in charge of their care and asked if they are willing to be contacted by our research team. If they agree, then the clinical team will send out the letter of invitation and information sheets. They will then be contacted by telephone and if following discussion of the project they agree to participate, we will arrange an interview either in their own home or the Department of Psychiatry.

Each family must consist of one child aged 5-15 years with a diagnosis of ADHD, one or more siblings also aged 5-15 years, and one or both biological parents who are willing to take part in the study. We will initially send out the letter of invitation and information sheets to each family. Following this we will contact families by phone to discuss the project and ensure they fulfil the entry requirements for the study. If families wish to take part in this study we will send by mail a questionnaire booklet that needs to be completed for all children taking part in the study, whether they have ADHD or not. At the same time we will arrange for an interview either in their own home or at the Department of Psychiatry. At the interview, we will use a standardised ADHD diagnostic interview for the child with ADHD that takes about 1 hour to complete and a shorter version of the same interview for each additional sibling that takes around 30 minutes to complete. We will check through the questionnaire data and help families where there are any queries or it has not been completed properly. Finally, we will take a blood sample from all individuals taking part in the study – ADHD probands, siblings and parents. At the interview parents will be asked for permission to contact a teacher for each child taking part in the study. Designated teachers will be sent teacher versions of the same rating scales that the parents are completing.

Blood sampling: We require a blood sample from each participant. 10-20 mls will be taken by a trained phlebotomist or paediatric nurse or psychologist with training in taking blood from children. We will use local anaesthetic cream, which numbs the skin and greatly reduces the mild discomfort associated with having blood taken. Blood samples will be divided into two. Half will be sent to the NIMH designated cell line repository in the United States where permanent cell lines will be established. The other half will be sent to our laboratory in the Department of Genetics, TCD so we can proceed immediately to the gene mapping work and to ensure that we have a back-up sample of DNA for cell lines that fail to be established (expected in approx. 2% of cases).

Clinical information: We will gather parent and teacher rating scale and parent interview information on each child taking part in the study. For children with a medical record of ADHD we will examine clinical case records, provided by their doctor in the Child Clinic. The scales used are standard ADHD/hyperactivity rating scales used in other studies.

(1) Strengths and difficulties questionnaire (SDQ)
(2) Conners revised-long scales
(3) In addition parents will be asked to provide basic demographic information and to complete a short adult ADHD rating scale about themselves.
The parent interview will be the Parental Adolescent and Child Schedule (PACS). This is aimed at producing reliable symptom information for the ADHD diagnosis and common co-morbid syndromes (anxiety, depression, Tourettes, oppositional defiant disorder and conduct disorder). The hyperactivity sections of the PACS will be used for children who are not thought to have ADHD. All clinical information will used to complete an operational criteria checklist for ADHD symptoms called Hypescheme.

Selection of families for linkage study: The clinical data will enable us to identify two types of families: (1) Children with ADHD plus a sibling with a high score on the ADHD rating scales (2) Children with ADHD plus a sibling with a low score on the ADHD rating scales. Both these types of sibling-pairs are informative for Quantitative Trait Loci (QTL) linkage analysis. Families that are not informative for linkage will be used for association mapping which is the main method for final identification of the genes that influence risk for ADHD and for the analysis of candidate genes for the disorder.

Molecular analysis: We will be genotyping the families with a set of 400 DNA markers that are routinely used to scan for linkage. In addition, we will use association methods on the entire sample to screen genes that are thought to influence risk for ADHD by virtue of their chromosomal location or knowledge of their likely function. The molecular (laboratory work) components of this study will be shared with Dr. Phil Asherson's group at the Institute of Psychiatry in London. This means that DNA will be sent to London, where they will perform half of the genotyping proposed for this study.

Anonymity: All blood samples DNA and clinical information will be anonymised by being given a code number. This means that no names, address or other personal identifiers will be attached to the clinical information and samples. We will keep names, addresses and other personal identifiers on a separate database that will only be accessible to identified key staff in the TCD research group. The cell lines and information in the United States will only have the code numbers.

Study Power

This is a multi-site study with nine other European groups. We are the only group from Ireland. We will be contributing 130 families to a combined dataset of 2,000 families. This study has been calculated to have very good the power to detect genes that contribute 10% to total genetic variance (out of the total of 80% genetic variance) and moderate power to detect genes contributing 5% variance. The sample also has the power to detect genes contributing 1-2% to genetic variance – these very small gene effects may turn out to be important and can be detected using association analysis.

Ethical Considerations (NOTE 3E)

- We have followed the UK MRC guidelines for the collection and storage of biological material.
- ADHD is known to have important genetic influences and finding the genes involved is expected to help us in our understanding of this disorder. There is a need for improved treatment and diagnosis and this research will be important in achieving these goals. ADHD is a childhood diagnosis so the research must be performed on children.
- There is no personal harm that can come from the analysis of the information and blood samples that are being donated for this research.
- We are restricting the study to white Caucasians of European descent. The reasons for this are well documented and are due to the variation of allele frequencies in different populations, that can give rise to false positive and negative data in these types of study. The genes involved are expected to act in all populations, but it will considerably complicate the analysis by combining samples from different ethnic groups.

- Blood samples are required to make a permanent Cell and DNA Bank for genetic studies of ADHD. This is an essential requirement of the proposal. In addition, blood is the usual method of obtaining DNA and ensures that good, high quality DNA is obtained. In this study blood will only be taken by a trained doctor, paediatric nurse, paediatric psychologist or phlebotomist and a local anaesthetic cream used which removes the sensation of a needle jab. Samples stored in the Cell and DNA Bank will be made available to other research groups, who are studying the genetic causes of ADHD. The release of these samples will be for the sole purpose of research into the genetic influences on ADHD. This will ensure that the information provided will be available to other scientists who will be looking at the genetic causes of ADHD.
- The ADHD cell line and DNA Bank will be looked after by the National Institute of Mental Health in the United States. According to the written protocol, DNA from the cell lines would be made available to any qualified scientist, as determined by their review committee – both scientific and ethical review is required to ensure that the samples are only used to search for the genes that influence risk for ADHD. This may include scientists from both academia and industry.
- Because the NIMH repository (ADHD DNA Bank) will not receive any names, the DNA released will be totally anonymous.
- Anybody receiving data from the repository will sign a contract with NIMH. That contract will require them to send back to the NIMH any genetic data they produce from the DNA, so that all knowledge obtained from these samples will be in the public domain. That data will be made available to other scientists and will not subject to restricted access for commercial purposes.
- It is possible that some scientists who access the DNA and clinical information will work for commercial companies. These companies may be able to design new ways of diagnosing and treating ADHD based in findings from these samples and profits may arise from this to the company of individual scientists. If this occurs there is no plan to compensate the families taking part in this research or their heirs.

Benefits of the study

There will be no short-term benefits. In the medium to long term we expect to find the genes involved in ADHD. This may lead to improved diagnosis and prediction of clinical outcome. New drug treatments may stem from the identification of novel drug targets. New environmental and psychological interventions may be discovered from knowledge of the gene-environment interactions involved. There is potential for prevention by knowing more about the causes of ADHD.

Consents (NOTE 3I)

Information sheets will be provided for both adults, children with ADHD, siblings who are not thought to have ADHD and teachers. Information sheets will sent with a letter of invitation to take part in the study. A member of the research team will phone to discuss the project and ensure that the information is fully understood. If the family wish to take part and agree to an interview, the information will be discussed and parents will be asked to sign their consent at the bottom of the information sheets. Children who have sufficient understanding and intelligence to understand was is proposed will also be asked to give their own consent if they wish to take part. Although it is not a requirement, it is considered good practice for parents to give consent as well (MRC guidelines), so we will ask one parent to counter-sign the child information sheet and consent form. If children are unable to understand the information because they do not have sufficient understanding or intelligence, they will not be required to sign their own consent. However, in the event of a follow-up study, they will be asked for consent to the continued use of the samples once they are old enough to understand. One copy of the information sheet and consent form will be kept by the families and one copy will be kept by the research team. The following information sheets with consents are available.

1/ Parent information sheet
2/ Child with ADHD information sheet
3/ Child without ADHD information sheet
4/ Teacher information sheet
5/ In addition, we attach a DNA information sheet, which answers questions that we are frequently asked about other uses of DNA.

UNIVERSITY OF DUBLIN
TRINITY COLLEGE

DEPARTMENT OF PSYCHIATRY
Image Project
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TRINITY CENTRE
FOR HEALTH SCIENCES

ST. JAMES' HOSPITAL
JAMES' STREET
DUBLIN 8
IRELAND

PHONE:

Information sheet for parents

The International Multi-centre ADHD Genetics project (IMAGE)
An International Resource For The Study Of ADHD Genetics

We would like to invite you to take part in this project that is designed to find out about the genetic causes of attention deficit hyperactivity disorder (ADHD). We would be grateful if you would read this information sheet and, if you agree to take part in this study, sign the consent form at the bottom.

PURPOSE OF THE IMAGE PROJECT

The IMAGE project aims to identify the genetic causes of attention deficit hyperactivity disorder (ADHD). This study will use modern genetic techniques, and match the findings to a detailed clinical examination, to try to find out which genes are contributing to the symptoms of ADHD.

The IMAGE project is funded by the National Institute of Mental Health (NIMH), the main government research funding body for mental health in the United States. NIMH would like to help scientists learn more about how genes effect the development of ADHD. They are therefore funding the IMAGE Project, to gather medical information and genetic material, or DNA, from individuals who seem to have ADHD, as well as from their brothers, sisters and parents. In order to make this research possible, NIMH will store the medical information and DNA in a central place in New Jersey, called a repository.

NIMH will fund the IMAGE project and will also make the medical information and DNA available as an international resource to other scientists in the future who want to do genetic research on ADHD. Use of these materials would first need to be reviewed and approved by NIMH. This includes review by one or more independent ethical committees to ensure that your DNA and clinical information will only be used to benefit individuals who have ADHD.

Since you or a member of your family appear to have ADHD, we are contacting

you to see if you and other members of your family are willing to contribute medical information and blood samples to the repository for use in genetic studies of ADHD.

IMPORTANCE OF THE IMAGE PROJECT

ADHD is a common behaviour, which affects many children. ADHD is recognised as a major cause of childhood problems with schoolwork and relationships with friends and family, and may go on to have long-term consequences in adulthood. In order to develop the best and most effective treatments for ADHD we need to have a very detailed understanding of what the causes are. Research has shown that genetic influences are particularly important in the development of ADHD, although this does not mean that the behaviour is caused by genetic factors alone. Our research program is designed to look for the genes involved.

WHO CAN TAKE PART IN THE IMAGE PROJECT

We are asking children aged between 5 and 15 years of age who are thought to have ADHD, their siblings (brothers and sisters) and both parents, to take part in this study. We require at least one sibling to take part in addition to your child who is being treated for ADHD.

PROCEDURES

If you agree to participate, we will ask your doctor at the Child ADHD Clinic to complete a clinical data sheet on your child who is thought to have ADHD and we will ask you to complete a booklet of questionnaires. We will also request the name and address of one of your child's teachers who will be sent a similar set of questionnaires to complete. Finally we would like to refer to clinical notes provided by your doctor at the child clinic.

We will also request the same questionnaire information for each sibling aged 5–15 years who takes part in the study.

Following these initial assessments, we will gather more detailed information on your children. This will involve an interview with you, which takes about two hours.

BLOOD SAMPLING

We will require a blood sample from each individual taking part in this study. Although this study is designed to find the genes that increase risk for ADHD, we require blood samples from the brothers and sisters of children with ADHD, so that we can look for differences between those with high and low levels of hyperactivity. The information from children without ADHD is as important for this study as information from children with ADHD. Blood samples are needed from parents so that we can tell which of your genes your children are

sharing and which of your genes your children are not sharing.

If you agree to participate, we will draw a small sample of blood (about 20 mls, or four teaspoons full) from each person. The sample will be divided and sent to the cell repository in the United States and to the laboratory in Trinity College Dublin. The blood samples that are sent to the repository will be used to create cell lines, which are living tissue. By storing blood cells in this way, we will be creating a permanent resource for the study of genes involved in ADHD.

RISKS

There are no more than minimal medical or psychological risks associated with this research. A local anesthetic cream that numbs the skin will reduce any mild pain associated with having blood drawn through a vein. You may experience mild discomfort, bruising, and/or other bleeding at the site where the needle is inserted. Sometimes people get dizzy or feel faint when their blood is drawn.

BENEFITS

DNA from your sample will be used to look for the genes involved in ADHD and related behaviours. Although you personally will not receive any direct benefit from this project, individuals who develop ADHD in the future, their family members, and future generations may benefit if we can locate the genes involved.

Because the meaning of research results are not usually fully understood results on individual families will not be made available to subjects or their doctors. If later on, diagnostic tests or new ways to treat ADHD are discovered, this information should be obtained from your own doctor or ADHD clinic. We do not expect to discover any information of direct clinical relevance to the condition or treatment of your child during the next few years.

COSTS AND COMPENSATION

There are no costs to subjects in this research project. In line with current guidelines on the collection of samples for research, we are asking you to donate the information and blood samples as a gift. We will however be able to reimburse you for reasonable costs incurred such as travel and time off work.

Some scientists who obtain your DNA and medical information may work with a private company. However all data produced from these materials will be made public and available in the public domain. Some companies may have a financial interest in using information found from studying DNA. This includes developing commercial products that may later help others by improving the diagnosis and treatment of ADHD. These companies may patent products or sell discoveries based on this research. Some of the scientists who study your DNA and medical information may get some financial benefit from this work. There are no plans to provide any compensation to you or your heirs should this occur.

financial benefit from this work. There are no plans to provide any compensation to you or your heirs should this occur.

CONFIDENTIALITY

We will keep confidential your name and any other personal information we learn about you. This information will not be sent to the repository in the United States, or known to other scientists in Europe or elsewhere.

We will take the following steps to ensure confidentiality. A research number will be assigned to you and your name will not be used. DNA and medical information collected will be stored at the repository in a coded way, to keep your identity a secret. The only people who will have access to your individual identity are the research team at Trinity College Dublin (Professor Michael Gill and his research staff). The results from the analysis of your DNA will not be released or shared in any way with your relatives, with insurance companies, or any third party not involved in research. When results of this study are published, your name will not be used.

WITHDRAWAL FROM THE RESEARCH PROJECT

You have the right to leave the study at any time without giving any reason, and without penalty. If you wish to leave the study, contact the Project Co-ordinator, Professor Michael Gill, or any member of the research team. We will tell the repository to remove your medical information and genetic material. We will keep your identity a secret by using a code number. The repository can use this code number to remove your medical information and genetic material, without ever knowing your name or other personal information. By using this code number, the repository will tell scientists to remove your data from their research. These scientists will not know your name or other personal information we learn about you.

PARTICIPATION IS VOLUNTARY

You do not have to be in this study if you don't want to be. Signing the consent form does not commit you or any member of your family to participate in this research. You will not lose any benefits or access to treatment that you are otherwise entitled to if you don't want to be in this study.

WHAT DO I DO NOW ?

If you wish to take part in the IMAGE project would you please sign your consent at the end of this information sheet.

If your children are able to understand what the study involves they should read or have explained to them the child information sheet. If they wish to take part they should sign their own consent at the bottom of the sheet. We will also ask you to confirm that you are willing for them to take part by adding, which you can do by signing the child information sheet as well. If any of your children are not yet able to understand what is involved, we will only require your consent for them to participate.

ANY QUESTIONS ?

If you have any questions about the IMAGE project please feel free to contact the Project Co-ordinator (Professor Michael Gill) on 608 2241. You may also contact us by e-mail at gquinn@tcd.ie or by mail at the Image Project, Department of Psychiatry, Trinity College Dublin.

To be completed by parents

- I have read (or been read to) the information about the IMAGE project.
- I understand the information and what taking part in this study involves.
- I am willing to participate in the project, but I feel under no obligation to do so.
- I understand that the information collected in the study will be kept strictly confidential and will only be made available to qualified scientists.
- I understand that I can withdraw from the study at any stage without giving an explanation, and withdrawal will not affect the treatment of any member of my family.

Mother

Signed: ..... **Date: .....**

Father

Signed: ..... **Date: .....**

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The International Multi-centre ADHD Genetics project (IMAGE)
An International Resource For The Study Of ADHD Genetics

Information sheet for teachers

We would like to ask for your help in the IMAGE project that is designed to find out about the genetic causes of attention deficit hyperactivity disorder (ADHD). We would be grateful if you would read this information sheet and, if you agree to take part in this study, sign the consent form at the bottom.

WHY ARE WE CONTACTING YOU?

You have been designated by the parents of one of the children taking part in this study, as someone who can provide additional information for this project. Assessment by teachers on individual children taking part in the study is an important part of the research assessment.

PURPOSE OF THE IMAGE PROJECT?

The IMAGE project aims to identify the genetic causes of attention deficit hyperactivity disorder (ADHD). This study will use modern genetic techniques, and match the findings to a detailed clinical examination, to try to find out which genes are contributing to the symptoms of ADHD.

The IMAGE project is funded by the National Institute of Mental Health (NIMH), the main government research funding body for mental health in the United States. NIMH would like to help scientists learn more about how genes effect the development of ADHD. They are therefore funding the IMAGE Project, to gather medical information and genetic material, or DNA, from individuals who seem to have ADHD, as well as from their brothers, sisters and parents. In order to make this research possible, NIMH will store the information and DNA in a central place in New Jersey, called a repository.

NIMH will fund the IMAGE project and will also make the medical information and DNA available as an

international resource to other scientists in the future who want to do genetic research on ADHD. Use of these materials would first need to be reviewed and approved by NIMH. This includes review by one or more independent ethical committees to ensure that your DNA and clinical information will only be used to benefit individuals who have ADHD.

WHY IS THE IMAGE PROJECT IMPORTANT?

ADHD is a common behaviour, which affects many children. ADHD is recognised as a major cause of childhood problems with schoolwork and relationships with friends and family, and may go on to have long-term consequences in adulthood. In order to develop the best and most effective treatments for ADHD we need to have a very detailed understanding of what the causes are. Research has shown that genetic influences are important in the development of ADHD, although this does not mean that the behaviour is caused by genetic factors alone. Our research program is designed to look for the genes involved.

PROCEDURES

We are gathering information on the behaviour of children who are thought to have ADHD, as well as their brothers and sisters whether they are thought to have ADHD or not. Parents of children who agree to take part are completing questionnaires and being interviewed. We also require a blood sample from each individual taking part in this study. Although this study is designed to find the genes that increase risk for ADHD, we also require blood samples from the brothers and sisters of children who are thought to have ADHD. The information from children without ADHD is as important for this study as information from children with ADHD.

Information from teachers who know children taking part in this study is also very important. We have therefore asked parents to designate a teacher for this purpose. We are asking designated teachers to complete a questionnaire on each child who is taking part.

BENEFITS AND COMPENSATION

The DNA and information gathered will be used to look for the genes involved in ADHD and related behaviours. Although those taking part will not receive any direct benefit from this project, individuals who develop ADHD in the future, their family members, and future generations may benefit if we can locate the genes involved.

Some scientists who use the DNA and information may work with a private company. However all data produced from these materials will be made public and available in the public domain. Some companies may have a financial interest in using information found from studying DNA. This includes developing commercial products that may later help others by improving the diagnosis and treatment of ADHD. These companies may patent products or sell discoveries based on this research. Some of the

scientists who use these materials may get some financial benefit from this work. There are no plans to provide any compensation to you or the families taking part in this research should this occur.

CONFIDENTIALITY

We will keep confidential your name and other personal details. This information will not be sent to the repository in the United States, or known to other scientists in Europe or elsewhere. Each individual will be given a code number, which will be attached to the information before it is shared with anyone else.

ANY QUESTIONS?

If you have any questions about the IMAGE project please feel free to contact the Project Co-ordinator (Professor Michael Gill) on 608 2241. You may also contact us by e-mail at gquinn@tcd.ie or by mail at the Image Project, Department of Psychiatry, Trinity Centre for Health Sciences, St. James' Hospital, Dublin 8.

To be completed by teachers giving participating in this study

- I have read and understand the information about the IMAGE project
- I am willing to participate in the project, but I feel under no obligation to do so.
- I understand that the information collected in the study will be kept strictly confidential and will only be made available to qualified scientists.

Signed: ..... **Date: .....**

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The International Multi-centre ADHD Genetics Project (IMAGE)
An International Resource For The Study Of ADHD Genetics

Information sheet for children being treated for ADHD

We would like to invite you to take part in the IMAGE project. In this project we wish to discover the genetic causes of attention deficit hyperactivity disorder (ADHD). We would be pleased if you would read this information sheet and, if you agree to take part in this study, sign the consent form at the bottom.

a) What is the IMAGE Project?

The IMAGE project will look at the genetic causes of attention deficit hyperactivity disorder, known as ADHD, in children and young adults. We will set up a resource of DNA and information that can be used now and in the future by scientists who wish to find out about the genetic causes of ADHD.

b) Why is the IMAGE project important?

ADHD effects many children and often causes problems both at home and at school. If we can find out more about the causes, we will be more able to help people with ADHD.

c) What are the causes of ADHD?

Research has shown that both genes and environment are important causes of ADHD. In this research we will be looking for the genes involved.

d) Who can take part in the IMAGE project?

Anyone aged between 5 and 15 years of age who has been treated for ADHD, their brothers and sisters and their parents.

e) What happens in the project?

Your parents and one of your teachers will be asked to complete a list of questions about you, describing behaviour relating to ADHD. We will also talk to one of your parents about your ADHD and will look at your medical notes provided by your doctor. Finally, we will take a blood sample so that we can study your DNA.

g) Who will be asked to give a blood sample?

Everyone taking part in this study will need to give a blood sample. This will include yourself, any of your brothers or sisters taking part and your parents.

h) What happens to the blood sample?

The blood sample will be sent to New Jersey in the United States. Blood cells will be stored so that we can extract DNA for research both now and in the future.

i) Who will benefit from this project?

Although you will not be directly helped by this project, people who develop ADHD in the future and their families may gain better help if we can find the genes that cause ADHD.

j) Who can use my information and blood sample?

Your DNA and information will be made available to scientists who wish to find out about the genetic causes of ADHD. This is a resource that will be available

to scientists around the world. Any research findings from these samples will be made available to the public.

Some scientists work for commercial companies. It is possible that these companies and some of the scientists may make money from this work by developing new ways to help people who have ADHD. If this happens there are no plans to pay you or your family.

k) Confidentiality

We will keep secret your name and address. We will use a code number on the information and the blood sample that is kept in the United States. This means that the only people who know your name and address are the research team at Trinity College Dublin and your own doctor. It will not be possible for anyone else to know where the DNA and information came from.

l) You do not need to take part if you do not want to

You do not have to take part in this project if you do not want to, but we hope you will be able to help in this research. You may withdraw from the study without explanation at any time, without affecting your ongoing treatment.

m) What do I do now?

If you wish to take part in this study would you please sign this information sheet to give your consent. It is usual to ask parents to give their consent for young people, so we will ask one of your parents to sign the form as well.

Any questions?

If you have any questions about the IMAGE project please feel free to contact the Project Co-ordinator (Michael Gill) on 608 2241. You may also contact us by e-mail at gquinn@tcd.ie or by mail at the Image Project, Department of Psychiatry, Trinity Centre for Health Sciences, St. James' Hospital, James' Street, Dublin 8

Consent to take part in the IMAGE Project

To take part in this project would you and one of your parents please sign your names in the space below.

- I have read (or been read to) the information about the IMAGE project and understand what I have read.
- I am willing to participate in the project, but I feel under no obligation to do so.
- I understand that the information collected in the study will be kept strictly confidential and will only be made available to qualified scientists.
- I understand that I can withdraw from the study at any stage without giving an explanation. This will not effect my medical treatment.

Child

Signed: ..... **Date:** .....

Parent

Signed: ..... **Date:** .....

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The International Multi-centre ADHD Genetics Project (IMAGE)
An International Resource For The Study Of ADHD Genetics

Information sheet for the brothers and sisters of children being treated for ADHD

We would like to invite you to take part in the IMAGE project. In this project we wish to discover the genetic causes of attention deficit hyperactivity disorder (ADHD). We would be grateful if you would read this information sheet and, if you agree to take part in this study, sign the consent form at the bottom.

a) What is the IMAGE Project?

The IMAGE project will look at the genetic causes of attention deficit hyperactivity disorder, known as ADHD, in children and young adults. We will set up a resource of DNA and information that can be used now and in the future by scientists who wish to find out about the genetic causes of ADHD.

b) Why is the IMAGE project important?

ADHD effects many children and often causes problems both at home and at school. If we can find out more about the causes,

we will be more able to help people with ADHD.

c) What are the causes of ADHD?

Research has shown that both genes and environment are important causes of ADHD. In this research we will be looking for the genes involved.

d) Who can take part in the IMAGE project?

Anyone aged between 5 and 15 years of age who has been treated for ADHD, their brothers and sisters and their parents.

e) What happens in the project?

Although you are not thought to have ADHD, information about you is as important for this research as that from your brother or sister who has been treated for ADHD.

We will ask your parents and one of your teachers to complete a list of questions about your ability to attend to things (focus your mind) and your activity levels. We will also talk to one of your parents about the same things. Finally, we will take a blood sample so that we can study your DNA. We will compare your DNA with DNA from your brother or sister who is thought to have ADHD.

g) Who will be asked to give a blood sample?

Everyone taking part in this study will need to give a blood sample. This will include yourself if you take part, any of your brothers or sisters taking part and your parents.

h) What happens to the blood sample?

The blood sample will be sent to New Jersey in the United States. Blood cells will be stored so that we can extract DNA for research both now and in the future.

i) Who will benefit from this project?

Although you will not be directly helped by this project, people

who develop ADHD in the future and their families may gain better help if we can find the genes that cause ADHD.

j) Who can use my information and blood sample?

Your DNA and information will be made available to scientists who wish to find out about the genetic causes of ADHD. This is a resource that will be available to scientists around the world. All research on these samples will be available to the public.

Some scientists work for commercial companies. It is possible that these companies and some of the scientists may make money from this work by developing new ways to help people who have ADHD. If this happens there are no plans to pay to you or your family.

k) Confidentiality

We will keep secret your name and address. We will use a code number on the information and the blood sample that is kept in the United States. This means that the only people who know your name and address are the research team at Trinity College Dublin. It will not be possible for anyone else to know where the DNA and information came from.

l) You do not need to take part if you do not want to

You do not have to take part in this project if you do not want to, but we hope you will be able to help in this research. You may withdraw from the study without explanation at any time. This will not effect your medical treatment now or in the future.

m) What do I do now?

If you wish to take part in this study would you please sign this information sheet to give your consent. It is usual to ask parents to give their consent for young people, so we will ask one of your parents to sign the form as well.

Any questions?

If you have any questions about the IMAGE project please feel free to contact the Project Co-ordinator (Professor Michael Gill) on 608 2241. You may also contact us by e-mail at gquinn@tcd.ie or by mail at the Image Project, Department of Psychiatry, Trinity Centre for Health Sciences, St. James' Hospital, Dublin 8.

Consent to take part in the IMAGE Project

To take part in this study would you and one of your parents please sign your names in the space below.

- I have read (or been read to) the information about the IMAGE project and understand what I have read.
- I am willing to participate in the project, but I feel under no obligation to do so.
- I understand that the information collected in the study will be kept strictly confidential and will only be made available to qualified scientists.
- I understand that I can withdraw from the study at any stage without giving an explanation. This will not effect my medical treatment.

Child

Signed: ..... **Date:** .....

Parent

Signed: ..... **Date:** .....

Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

Child's Name:_____ Gender: M F (Circle One)

Birthdate:_____/_____/_____ (Month / Day / Year) Age:_____ School Grade:_____

Parent's Name:_____ Today's Date:_____/_____/_____ (Month / Day / Year)

Instructions: Below are a number of common problems that children have. Please rate each item according to your child's behavior in the last month. For each item, ask yourself "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1. Angry and resentful	0	1	2	3
2. Difficulty doing or completing homework	0	1	2	3
3. Is always "on the go" or acts as if driven by a motor	0	1	2	3
4. Timid, easily frightened	0	1	2	3
5. Everything must be just so	0	1	2	3
6. Has no friends	0	1	2	3
7. Stomach aches	0	1	2	3
8. Fights	0	1	2	3
9. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)	0	1	2	3
10. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
11. Argues with adults	0	1	2	3
12. Fails to complete assignments	0	1	2	3
13. Hard to control in malls or while grocery shopping	0	1	2	3
14. Afraid of people	0	1	2	3
15. Keeps checking things over again and again	0	1	2	3
16. Loses friends quickly	0	1	2	3
17. Aches and pains	0	1	2	3
18. Restless or overactive	0	1	2	3
19. Has trouble concentrating in class	0	1	2	3
20. Does not seem to listen to what is being said to him/her	0	1	2	3
21. Loses temper	0	1	2	3
22. Needs close supervision to get through assignments	0	1	2	3
23. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
24. Afraid of new situations	0	1	2	3
25. Fussy about cleanliness	0	1	2	3
26. Does not know how to make friends	0	1	2	3
27. Gets aches and pains or stomachaches before school	0	1	2	3
28. Excitable, impulsive	0	1	2	3
29. Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
30. Has difficulty organizing tasks and activities	0	1	2	3
31. Irritable	0	1	2	3
32. Restless in the "squirmy sense"	0	1	2	3
33. Afraid of being alone	0	1	2	3
34. Things must be done the same way every time	0	1	2	3
35. Does not get invited over to friends' houses	0	1	2	3
36. Headaches	0	1	2	3
37. Fails to finish things he/she starts	0	1	2	3

Items continued on back page...

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Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
38. Inattentive, easily distracted	0	1	2	3
39. Talks excessively	0	1	2	3
40. Actively defies or refuses to comply with adults' requests	0	1	2	3
41. Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	0	1	2	3
42. Has difficulty waiting in lines or awaiting turn in games or group situations	0	1	2	3
43. Has a lot of fears	0	1	2	3
44. Has rituals that he/she must go through	0	1	2	3
45. Distractibility or attention span a problem	0	1	2	3
46. Complains about being sick even when nothing is wrong	0	1	2	3
47. Temper outbursts	0	1	2	3
48. Gets distracted when given instructions to do something	0	1	2	3
49. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
50. Forgetful in daily activities	0	1	2	3
51. Cannot grasp arithmetic	0	1	2	3
52. Will run around between mouthfuls at meals	0	1	2	3
53. Afraid of the dark, animals, or bugs	0	1	2	3
54. Sets very high goals for self	0	1	2	3
55. Fidgets with hands or feet or squirms in seat	0	1	2	3
56. Short attention span	0	1	2	3
57. Touchy or easily annoyed by others	0	1	2	3
58. Has sloppy handwriting	0	1	2	3
59. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
60. Shy, withdrawn	0	1	2	3
61. Blames others for his/her mistakes or misbehavior	0	1	2	3
62. Fidgeting	0	1	2	3
63. Messy or disorganized at home or school	0	1	2	3
64. Gets upset if someone rearranges his/her things	0	1	2	3
65. Clings to parents or other adults	0	1	2	3
66. Disturbs other children	0	1	2	3
67. Deliberately does things that annoy other people	0	1	2	3
68. Demands must be met immediately — easily frustrated	0	1	2	3
69. Only attends if it is something he/she is very interested in	0	1	2	3
70. Spiteful or vindictive	0	1	2	3
71. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools or toys)	0	1	2	3
72. Feels inferior to others	0	1	2	3
73. Seems tired or slowed down all the time	0	1	2	3
74. Spelling is poor	0	1	2	3
75. Cries often and easily	0	1	2	3
76. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
77. Mood changes quickly and drastically	0	1	2	3
78. Easily frustrated in efforts	0	1	2	3
79. Easily distracted by extraneous stimuli	0	1	2	3
80. Blurts out answers to questions before the questions have been completed	0	1	2	3

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Strengths and Difficulties Questionnaire

P4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth .....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes - minor difficulties	Yes - definite difficulties	Yes - severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

SOCIAL COMMUNICATION QUESTIONNAIRE: LIFETIME VERSION©

(Formerly ASQ)

This questionnaire should be used in conjunction with its accompanying manual (Rutter, M., Bailey, A., & Lord, C.)

CONFIDENTIAL

QUESTIONNAIRE ON BEHAVIOR AND SOCIAL COMMUNICATION

Name: _____

Date of Birth: _____

Today's date: _____

Completed by: _____

Thank you for taking the time to complete this questionnaire. A few questions ask about several related types of behavior; please tick yes if any one of these was present. Although you may be uncertain about whether some behaviors were present or not, please do answer 'yes' or 'no' to every question on the basis of what you think.

		YES	NO
1.	Is she/he now able to talk using short phrases or sentences? **If NO, proceed to question 8**	☐	☐
2.	Can you have a to and fro 'conversation' with her/him that involves taking turns or building on what you have said?	☐	☐
3.	Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way? That is, either phrases she/he has heard other people use or the ones she/he has made up?	☐	☐

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		YES	NO
4.	Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	☐	☐
5.	Has she/he ever got her/his pronouns the wrong way round (i.e. saying 'you' or 'she/he' for 'I'?)	☐	☐
6.	Has she/he ever used words that she/he seemed to have invented or made up her/himself, or ever put things in odd, indirect ways, or used metaphorical ways of saying things? For example, saying 'hot rain' for 'steam'?	☐	☐
7.	Has she/he ever said the same thing over and over in exactly the same way, or insisted on you saying the same things over and over again?	☐	☐
8.	Has she/he ever had things that she/he seemed to have to do in a very particular way or order, or rituals that she/he insisted you go through?	☐	☐
9.	Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	☐	☐
10.	Has she/he ever used your hand like a tool, or as if it were part of her/his own body (e.g. pointing with your finger, putting your hand on a doorknob to get you to open the door)?	☐	☐
11.	Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (eg traffic lights, drainpipes or timetables)?	☐	☐
12.	Has she/he ever seemed to be more interested in parts of a toy or an object (eg spinning the wheels of a car), rather than using the object as it was intended?	☐	☐

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		YES	NO
13.	Has she/he ever had any special interests that were unusual in their intensity but otherwise appropriate for her/his age and peer group (eg trains, dinosaurs)?	☐	☐
14.	Has she/he ever seemed to be unusually interested in the sight, feel, sound, taste or smell of things or people?	☐	☐
15.	Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	☐	☐
16.	Has she/he ever had any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	☐	☐
17.	Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	☐	☐
18.	Has she/he ever had any objects (other than a soft toy or comfort blanket) that she/he had to carry around?	☐	☐
19.	Does she/he have any particular friends or a best friend?	☐	☐

For the following behaviors, please focus on the time period between the 4th and 5th birthdays. You may find it easier to remember how things were at that time by focusing on key events, such as starting school, moving house, Christmas time or any events that are particularly memorable for you as a family. If your child is not yet four years old, please consider his or her behaviour in the last 12 months.

20.	When she/he was 4-to-5, did she/he ever talk with you just to be friendly (rather than to get something)?	☐	☐
21.	When she/he was 4-to-5, did she/he ever spontaneously copy you (or other people), or what you were doing (such as hoovering, gardening, mending things)?	☐	☐

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		YES	NO
22.	When she/he was 4-to-5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	☐	☐
23.	When she/he was 4-to-5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted?	☐	☐
24.	When she/he was 4-to-5, did she/he nod her/his head to mean "yes"?	☐	☐
25.	When she/he was 4-to-5, did she/he shake her/his head to mean "no"?	☐	☐
26.	When she/he was 4-to-5, did she/he usually look at you directly in the face when doing things with you or talking with you?	☐	☐
27.	When she/he was 4-to-5, did she/he smile back if someone smiled at her/him?	☐	☐
28.	When she/he was 4-to-5, did she/he ever show you things that interested her/him to engage your attention?	☐	☐
29.	When she/he was 4-to-5, did she/he ever offer to share things other than food with you?	☐	☐
30.	When she/he was 4-to-5, did she/he ever seem to want you to join in her/his enjoyment of something?	☐	☐
31.	When she/he was 4-to-5, did she/he ever try to comfort you if you were sad or hurt?	☐	☐

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		YES	NO
22.	When she/he was 4-to-5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	☐	☐
23.	When she/he was 4-to-5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted?	☐	☐
24.	When she/he was 4-to-5, did she/he nod her/his head to mean "yes"?	☐	☐
25.	When she/he was 4-to-5, did she/he shake her/his head to mean "no"?	☐	☐
26.	When she/he was 4-to-5, did she/he usually look at you directly in the face when doing things with you or talking with you?	☐	☐
27.	When she/he was 4-to-5, did she/he smile back if someone smiled at her/him?	☐	☐
28.	When she/he was 4-to-5, did she/he ever show you things that interested her/him to engage your attention?	☐	☐
29.	When she/he was 4-to-5, did she/he ever offer to share things other than food with you?	☐	☐
30.	When she/he was 4-to-5, did she/he ever seem to want you to join in her/his enjoyment of something?	☐	☐
31.	When she/he was 4-to-5, did she/he ever try to comfort you if you were sad or hurt?	☐	☐

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		YES	NO
32.	When she/he was 4-to-5, when she/he wanted something or wanted help, did she/he look at you and use gestures with sounds or words to get your attention?	☐	☐
33.	When she/he was 4-to-5, did she/he show a normal range of facial expressions?	☐	☐
34.	When she/he was 4-to-5, did she/he ever spontaneously join in and try to copy the actions in social games – such as The Mulberry Bush or The Farmer's in his Den?	☐	☐
35.	When she/he was 4-to-5, did she/he play any pretend or make-believe games?	☐	☐
36.	When she/he was 4-to-5, did she/he seem interested in other children of approximately the same age whom she/he did not know?	☐	☐
37.	When she/he was 4-to-5, did she/he respond positively when another child approached her/him?	☐	☐
38.	When she/he was 4-to-5, if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you?	☐	☐
39.	When she/he was 4-to-5, did she/he ever play imaginative games with another child in such a way that you could tell they understood what each other was pretending?	☐	☐
40.	When she/he was 4-to-5, did she/he play co-operatively in games that needed some form of joining in with a group of other children, such as hide and seek or ball games?	☐	☐

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Conners' Teacher Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

Student's Name:_____ Gender: M F
(Circle One)

Birthdate:_____/_____/_____ Age:_____ School Grade:_____
Month Day Year

Teacher's Name:_____ Today's Date:_____/_____/_____
Month Day Year

Instructions: Below are a number of common problems that children have in school. Please rate each item according to how much of a problem it has been in the last month. For each item, ask yourself "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUC TRUE (Very Often Very Frequen
1. Defiant	0	1	2	3
2. Restless in the "squirmy" sense	0	1	2	3
3. Forgets things he/she has already learned	0	1	2	3
4. Appears to be unaccepted by group	0	1	2	3
5. Feelings easily hurt	0	1	2	3
6. Is a perfectionist	0	1	2	3
7. Temper outbursts; explosive, unpredictable behavior	0	1	2	3
8. Excitable, impulsive	0	1	2	3
9. Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	0	1	2	3
10. Sassy	0	1	2	3
11. Is always "on the go" or acts as if driven by a motor	0	1	2	3
12. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)	0	1	2	3
13. Is one of the last to be picked for teams or games	0	1	2	3
14. Is an emotional child	0	1	2	3
15. Everything must be just so	0	1	2	3
16. Restless or overactive	0	1	2	3
17. Fails to finish things he/she starts	0	1	2	3
18. Does not seem to listen to what is being said to him/her	0	1	2	3
19. Actively defies or refuses to comply with adults' requests	0	1	2	3
20. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
21. Poor in spelling	0	1	2	3
22. Has no friends	0	1	2	3
23. Timid, easily frightened	0	1	2	3
24. Keeps checking things over and over	0	1	2	3
25. Cries often and easily	0	1	2	3
26. Inattentive, easily distracted	0	1	2	3
27. Has difficulty organizing tasks or activities	0	1	2	3
28. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
29. Has difficulty waiting his/her turn	0	1	2	3
30. Not reading up to par	0	1	2	3

Items continued on back page...

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Conners' Teacher Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
31. Does not know how to make friends	0	1	2	3
32. Sensitive to criticism	0	1	2	3
33. Seems over-focused on details	0	1	2	3
34. Fidgeting	0	1	2	3
35. Disturbs other children	0	1	2	3
36. Talks excessively	0	1	2	3
37. Argues with adults	0	1	2	3
38. Cannot remain still	0	1	2	3
39. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
40. Lacks interest in schoolwork	0	1	2	3
41. Has poor social skills	0	1	2	3
42. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
43. Likes everything neat and clean	0	1	2	3
44. Fidgets with hands or feet or squirms in seat	0	1	2	3
45. Demands must be met immediately—easily frustrated	0	1	2	3
46. Blurts out answers to questions before the questions have been completed	0	1	2	3
47. Spiteful or vindictive	0	1	2	3
48. Short attention span	0	1	2	3
49. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools, or toys)	0	1	2	3
50. Only pays attention to things he/she is really interested in	0	1	2	3
51. Shy, withdrawn	0	1	2	3
52. Distractibility or attention span a problem	0	1	2	3
53. Things must be done the same way every time	0	1	2	3
54. Mood changes quickly and drastically	0	1	2	3
55. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
56. Poor in arithmetic	0	1	2	3
57. Does not follow through on instructions and fails to finish schoolwork (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
58. Easily distracted by extraneous stimuli	0	1	2	3
59. Restless, always up and on the go	0	1	2	3

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Strengths and Difficulties Questionnaire

T4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name ..... Male/Female

Date of Birth .....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that this child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes - minor difficulties	Yes - definite difficulties	Yes - severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress the child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with the child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
PEER RELATIONSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐

- Do the difficulties put a burden on you or the class as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Class Teacher/Form Tutor/Head of Year/Other (please specify:)

Thank you very much for your help

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