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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 × 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

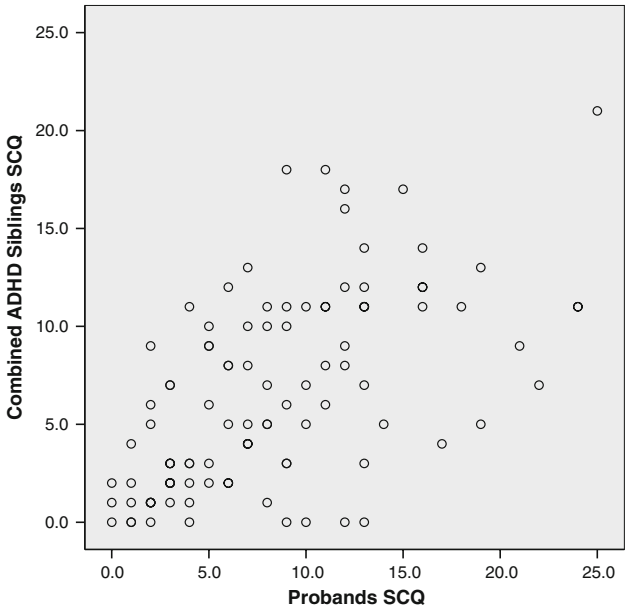

Fig. 1 Familiality of autism symptoms in sibling pairs concordant for ADHD. Autism symptoms of probands (combined type ADHD) versus autism symptoms of siblings with combined type ADHD. Pearson correlation = 0.58, number of families = 102

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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