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Published in:
Journal of Abnormal Child Psychology

DOI:
[10.1007/s10802-008-9282-0](https://doi.org/10.1007/s10802-008-9282-0)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Nijmeijer, J. S., Hoekstra, P. J., Minderaa, R. B., Buitelaar, J. K., Altink, M. E., Buschgens, C. J. M., Fliers, E. A., Rommelse, N. N. J., Sergeant, J. A., & Hartman, C. A. (2009). PDD Symptoms in ADHD, an Independent Familial Trait? *Journal of Abnormal Child Psychology*, 37(3), 443-453.
<https://doi.org/10.1007/s10802-008-9282-0>

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PDD Symptoms in ADHD, an Independent Familial Trait?

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Published online: 3 December 2008

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Abstract The aims of this study were to investigate whether subtle PDD symptoms in the context of ADHD are transmitted in families independent of ADHD, and whether PDD symptom familiarity is influenced by gender and age. The sample consisted of 256 sibling pairs with at least one child with ADHD and 147 healthy controls, aged 5–19 years. Children who fulfilled criteria for autistic disorder were excluded. The Children's Social Behavior Questionnaire (CSBQ) was used to assess PDD symptoms. Probands, siblings, and controls were compared using analyses of variance. Sibling correlations were calculated for CSBQ scores after controlling for IQ, ADHD, and

comorbid anxiety. In addition, we calculated cross-sibling cross-trait correlations. Both children with ADHD and their siblings had higher PDD levels than healthy controls. The sibling correlation was 0.28 for the CSBQ total scale, with the CSBQ stereotyped behavior subscale showing the strongest sibling correlation ($r=0.35$). Sibling correlations remained similar in strength after controlling for IQ and ADHD, and were not confounded by comorbid anxiety. Sibling correlations were higher in female than in male probands. The social subscale showed stronger sibling correlations in elder than in younger sibling pairs. Cross-sibling cross-trait correlations for PDD and ADHD were weak and not-significant. The results confirm that children with ADHD have high levels of PDD symptoms, and further suggest that the familiarity of subtle PDD symptoms in the context of ADHD is largely independent from ADHD familiarity.

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Keywords ADHD · Autism · PDD · Comorbidity ·
Children's social behavior questionnaire

Introduction

Apart from the defining symptoms of inattention, hyperactivity, and/or impulsivity, many children with attention deficit/hyperactivity disorder (ADHD) show problems in social functioning. Although children with ADHD generally do not lack interest in other people, they often fail to properly attune their behavior to other persons and to constantly changing social environments. The key characteristic of the social behavior of a substantial number of children with ADHD can be described as an apparent lack of a full comprehension of the consequences of their behaviors to others (Nijmeijer et al. 2008). This character-

istic resembles the lack of reciprocity that is one of the defining attributes of the social behavior of children with pervasive developmental disorders (PDD). The similarities in social difficulties suggest a certain degree of overlap between the two disorders, despite their strict segregation in both the Diagnostic and Statistical Manual of Mental Disorders IV-text revision (DSM-IV-TR; American Psychiatric Association 1994) and the International Statistical Classification of Diseases (ICD-10; World Health Organisation 1992). This potential overlap is supported by findings of the presence of symptoms of PDD in children with ADHD, and vice versa. The PDD symptoms that are reported to occur most frequently and in a majority of children with ADHD are impairments in social interaction, especially the inability to conceive other individuals' feelings and thoughts (Buitelaar et al. 1999, Clark et al. 1999, Santosh and Mijovic 2004). Symptoms of communication problems, and stereotyped and repetitive behaviors, have been reported to occur frequently as well in children with ADHD (Clark et al. 1999, Santosh and Mijovic 2004). A striking finding is that children with ADHD have higher scores on measures of PDD not only in comparison to healthy control children, but also compared to children with psychiatric disorders other than ADHD (Buitelaar et al. 1999, Santosh and Mijovic 2004). Especially children with the DSM-IV combined subtype have been recently shown to have elevated levels of PDD-symptoms, with nearly one third of boys and three-fourth of girls with combined type ADHD meeting clinical cut-offs for autistic symptomatology (Reiersen et al. 2007).

It has been well established that both ADHD and PDD have a strong genetic background (for reviews see Faraone et al. 2005, Freitag 2007). Interestingly, two studies in community twin samples have reported that variation in ADHD behaviors partially explain variation in PDD behaviors (Constantino et al. 2003, Ronald et al. 2008). In the most recent of the two, Ronald et al. (2008) found genetic influences on autistic and ADHD behaviors in a community twin sample to be overlapping, with PDD and ADHD traits showing a genetic correlation of around 0.50. These studies add to two other findings indicating that PDD and ADHD originate from similar underlying deficits. First, apart from symptom overlap, overlap in Theory of Mind and executive function deficits between the two disorders has been identified (Buitelaar et al. 1999, Geurts et al. 2004, Happé et al. 2006, Jonsdottir et al. 2006, Nyden et al. 1999, Ozonoff and Jensen 1999, Yuill and Lyon 2007). This may point to a shared underlying endophenotype between ADHD and PDD. Second, genetic linkage findings have partially suggested the same genetic regions of interest between the two disorders (Bakker et al. 2003, Ogdie et al. 2003, Smalley et al. 2002, Yamagata et al. 2002).

Interestingly, the three PDD symptom domains have been suggested to originate from distinct genetic influences

in both general population samples (Ronald et al. 2006a, Ronald et al. 2005, Ronald et al. 2006b) and clinical samples (Georgiades et al. 2007, Kolevzon et al. 2004), although the opposite has been found as well (Dyck et al. 2006, Goin-Kochel et al. 2008). Thus far, the potential differential heritability of the PDD dimensions in the context of ADHD has not been investigated.

Furthermore, in studies regarding the overlap between PDD and ADHD gender has rarely been taken into account. Given the higher prevalence of PDD in boys, one would expect lower levels of PDD in girls with ADHD. This was indeed what was found for autistic symptoms in the international IMAGE sample (Mulligan et al. 2008). However, clinically relevant PDD symptomatology in children with ADHD has also been found to be more prevalent in girls than in boys (Reiersen et al. 2007).

Another understudied topic is how age influences PDD symptoms in children with ADHD. Although social problems are associated with ADHD from early childhood through adolescence and young adulthood (Nijmeijer et al. 2008) this has not yet been investigated for PDD symptoms as such.

In the present study, these issues have been addressed using phenotypic data of Dutch children with ADHD and one of their siblings, which were collected as part of the IMAGE project. Children with autism were excluded from participation, which resulted in a sample where all variation in PDD severity except for the most severe end was represented. Most presently available PDD screening instruments are insufficient for assessing milder, more subtle PDD symptoms, as they are designed to screen for severe forms of PDD. Therefore, in the Dutch IMAGE sample the Children's Social Behavior Questionnaire (Hartman et al. 2006) was used. The CSBQ is particularly suited to measure the continuous distribution of PDD traits in the population as well as in clinical groups other than PDD (Hartman et al. 2006, Luteijn et al. 2000).

The questions we sought to answer in this study are: Firstly, can we confirm previous findings of elevated levels of PDD symptomatology in children with ADHD? Secondly, can we confirm the familiarity of PDD symptoms in children with ADHD? If so, does subtle PDD symptom familiarity depend on ADHD familiarity? Thirdly, does this familiarity differ for different PDD dimensions? And fourthly, are similar results found for boys and girls with ADHD, respectively, and for younger and elder sibling pairs?

Methods

Subjects

This study reports on data from Dutch participants of IMAGE. IMAGE is a collaborative study in eight European

countries (Belgium, Germany, Ireland, Israel, Spain, Switzerland, the Netherlands, and the United Kingdom) that aims to identify genes that increase the risk of ADHD using linkage and association strategies. All probands in IMAGE were aged 5 to 17 at the time of entry into the study, and are of European Caucasian descent. Entry criteria for the probands were a clinical diagnosis of DSM-IV combined subtype of ADHD and having one or more full siblings aged 5–19 available for ascertainment of clinical information and DNA collection. Exclusion criteria applying to both probands and siblings included an IQ < 70, autism (see next section for a detailed description of assessment), epilepsy, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. Whenever possible, families withdrew stimulant medication for 1 week prior to research assessment to allow for more accurate ascertainment of information on recent ADHD symptom characteristics and severity. For this study, probands with at least one sibling (regardless of his/her ADHD-status) were recruited from families referred to several participating academic child psychiatric outpatient clinics, or from the members of the Dutch Parents' Association. They had undergone clinical evaluations by a pediatrician or child psychiatrist in the recent past. CSBQ data were available for 256 families. For this study, only one sibling was selected at random in case families with two or more participating siblings.

Additional control families were recruited from mainstream primary and high-schools from the same geographical regions as the participating families with an ADHD proband. Principals were asked permission to contact the parents of their pupils. Parents who gave permission received questionnaires by mail. Control children had to obtain non-clinical scores (i.e., <63) on both the Conners' parent and the Conners' teacher ADHD/DSM-IV total-subscale. The control sample consisted of sibpairs and singletons, aged 5 to 19. From each pair, one sibling was selected with preference given to boys over girls.

The final sample was formed by 256 DSM-IV ADHD combined type probands (219 boys) and 256 siblings (131 boys), and 147 control children (89 boys). Characteristics of these groups can be found in Table 1.

Diagnostic Instruments

Children already diagnosed with ADHD as well as their siblings were screened using the standard IMAGE procedures as described by Brookes et al. (2006). Briefly, screening questionnaires, i.e., the parent and teacher Conners' rating scales, long forms (Conners 1996), and the parent and teacher Strength and Difficulties Questionnaires (Goodman 1997), were used to identify children with ADHD-symptoms. T-scores ≥ 63 on any Conners' ADHD/DSM-IV subscale and scores >90th percentile on the parent

Table 1 Characteristics for probands, siblings, and controls

Characteristic	Probands (n=256)	Siblings (n=256)	Controls (n=147)	ANOVA's	η_p^2	p
	Mean (SD)	Mean (SD)	Mean (SD)			
Age	11.3 (2.6)	10.9 (3.5)	11.2 (3.0)	F(2,650)=1.03		0.36
IQ	98.3 (12.5)	102.0 (11.6)	106.6 (9.9)	F(2,646)=23.04	0.07	<0.001 ^a
ADHD-symptom-scores						
Conners' DSM-IV total	76.5 (8.7)	55.3 (12.3)	46.5 (4.4)	F(2,656)=539.82	0.62	<0.001 ^b
DSM-IV inattentive	70.7 (8.4)	54.1 (11.8)	46.4 (5.0)	F(2, 656)=367.88	0.53	<0.001 ^b
DSM-IV hyperactive-impulsive	78.7 (9.1)	55.6 (12.8)	47.3 (4.8)	F(2, 656)=555.36	0.63	<0.001 ^b
PDD-symptoms						
CSBQ-total	72.0 (13.1)	57.5 (12.8)	46.4 (6.2)	F(2,656)=257.05	0.44	<0.001 ^b
Tuned	92.8 (12.6)	58.1 (12.5)	46.6 (7.4)	F(2,656)=252.77	0.44	<0.001 ^b
Social	62.1 (15.5)	54.5 (14.3)	47.5 (6.5)	F(2,656)=56.95	0.15	<0.001 ^b
Orientation	73.4 (15.4)	55.7 (13.3)	46.3 (5.8)	F(2,656)=230.90	0.41	<0.001 ^b
Understanding	69.4 (13.7)	57.8 (13.4)	48.0 (7.4)	F(2,656)=145.3	0.31	<0.001 ^b
Stereotyped	68.4 (18.9)	53.1 (13.6)	47.8 (7.7)	F(2, 656)=109.15	0.25	<.001 ^b
Change	61.7 (16.1)	52.5 (11.5)	48.8 (9.3)	F(2,656)=54.43	0.14	<0.001 ^c
Gender						
	N (%)	N (%)	N (%)	Kruskal-Wallis		
Boy	219 (85.5)	131 (51.2)	89 (60.5)	H(2)=71.04		<0.001 ^d
Girl	37 (14.5)	125 (49.8)	58 (39.5)			

ADHD attention-deficit/hyperactivity disorder, ANOVA analysis of variance, CSBQ child social behavior questionnaire, DSM-IV diagnostic and statistical manual of mental disorders, 4th edition, PDD pervasive developmental disorders

^a probands < siblings < controls (p<0.001)

^b probands > siblings > controls (p<0.001)

^c probands > siblings > controls (p<0.01)

^d probands > siblings (p<.001), siblings = controls

or teacher SDQ-hyperactivity scale were considered as clinical. Concerning all patients already diagnosed with ADHD and siblings scoring clinically on the parent or teacher Conners' or SDQ, a semi-structured, standardized, investigator-based interview was administered separately for each child; the Parental Account of Childhood Symptoms (PACS; Taylor 1986). The PACS covers DSM-IV symptoms of ADHD, conduct disorder, oppositional defiant disorder, anxiety, mood, and other internalizing disorders. The most prevalent comorbid disorders in probands as assessed by the PACS were oppositional defiant disorder (152 probands, 59.3%) and anxiety disorder (147 probands, 57.4%). 45 probands (17.6%) had no comorbid disorder.

A standardized algorithm was applied to the PACS to derive each of the 18 DSM-IV ADHD-items, providing operational definitions for each behavioral symptom. These were combined with items that scored 2 or 3 on the ADHD/DSM-IV total-subscale from the Conners' Teacher Rating Scale-Revised: Long Form (Conners' teacher), to generate the total number of items from the DSM-IV symptom checklist. Situational pervasiveness was defined as some symptoms occurring within two or more different situations from the PACS interview, as well as the presence of one or more symptoms scoring two or more from the ADHD/DSM-IV total subscale of the teacher rated Conners'.

Children were excluded from participation in IMAGE when classical or atypical autism was diagnosed. This was regarded to be present in case of a clinical score (i.e., ≥ 15) on the SCQ and the presence of PDD symptoms in at least two out of three DSM-IV autism domains, together with a developmental delay in at least one autism domain before the age of 3, as assessed by the section on autistic disorder of the PACS interview. Weight was given especially to symptoms that distinguish PDD from ADHD, and a lack of relationships with peers alone was not sufficient for social impairment of the autistic type. The mean SCQ scores in the final sample were 9.2 (sd 5.6) for probands and 5.4 (sd 4.4) for siblings. No SCQ data were available for controls. Reported SCQ scores in normal controls range from 4.2 (Rutter et al. 1999) to 1.69 (Farzin et al. 2006).

Measures

PDD Symptoms

The CSBQ contains 49 items scored on a 3-point Likert-scale. It contains items that refer directly to DSM-IV criteria for autism, but it also represents less severe variations of these criteria as well as PDD associated problems, such as problems in executive functioning and disruptive behavior. Because of this it also captures behavior problems as seen in children with milder variants of PDD. Age and gender specific T-scores were used for all

analyses in this paper, and were calculated based on a general population sample of 2,507 Dutch children aged 5 to 17 who have been described in the Dutch CSBQ manual (Hartman et al. 2007a, 2007b). CSBQ items are grouped in six subscales called "not optimally tuned to the social situation" (tuned; 11 items addressing emotional overreacting and stubbornness/disobedience), "reduced contact and social interest" (social; 12 items), "orientation problems in time, place, or activity" (orientation; 8 items), "difficulties in understanding of social information" (understanding; 7 items), "fear of and resistance to changes" (change; 3 items), and "stereotyped behavior" (stereotyped; 8 items). Estimates for internal, test-retest, and inter-rater reliability, and for convergent and divergent validity were good (Hartman et al. 2006). The CSBQ appears to differentiate between autism and PDDNOS on the one hand, and PDDNOS and ADHD on the other (Geurts et al. 2008, Hartman et al. 2006). Furthermore, to assess the content validity of the CSBQ, it has previously been compared to an autism screening instrument, the Autism Behavior Checklist (ABC; Krug 1980). A strong correlation of 0.75 was found between the total scores of both questionnaires in a large Dutch population sample (Luteijn et al. 2000) confirming that what the CSBQ measures correlates strongly with what more stringent autism measures pick up. In the present sample, the Pearson's correlation between the SCQ and CSBQ (raw) total score was 0.52 ($p < .01$), indicating that these questionnaires assess similar but not identical behaviors.

Two CSBQ subscales, i.e., the tuned and the orientation subscale, tap dysfunctional social behaviors that are conceptually closely related to the ADHD dimensions hyperactivity/impulsivity and attention problems, respectively. These behaviors occur frequently in children with PDD, as is recognized in DSM-IV as well. By including these subscales in the analyses it will be possible to investigate whether the relation between ADHD and PDD symptoms is carried mainly by these behaviors, or also by more PDD specific behaviors represented in the other subscales.

ADHD-symptoms

The Conners' parent rating scale, long form was applied as a measure of ADHD symptom severity. Items are scored on a four-point Likert scale. Analyses were carried out using T-scores for the DSM-IV symptoms subscales, i.e., the inattentive, the hyperactive-impulsive and the total scale. The latter is calculated by adding up the inattentive and hyperactive-impulsive subscales. We used the DSM-IV scales because these most closely reflect the current ADHD definition, whereas other scales contain some items that are ADHD-related, but somewhat less ADHD specific. For the

9 siblings who were 18 or 19 at the time of data-collection we applied the 15–17 year age norms.

Anxiety

The anxious–shy scale of the Conners' parent rating scale, long form, was used to assess anxiety, which is a potential confounding factor of the association between ADHD and PDD. T-scores were used for this scale as well, which consists of 6 items scored on a four-point Likert scale.

Intelligence

Full-scale IQ was estimated by four subtests of the Wechsler Intelligence Scale for Children — Third Version (WISC-III) or Wechsler adult intelligence scale—Third version (WAIS-III) depending on the child's age: Vocabulary, Similarities, Block Design, and Picture Completion (Wechsler 2000, Wechsler 2002). The subtests are known to correlate between 0.90–0.95 with full-scale IQ (Groth-Marnat 1997). As the WISC-III is not officially suited for 5 year-olds, data from these children (1 proband and 9 siblings) were excluded from the analyses where IQ was included as a covariate.

Analyses

Group differences in age, IQ, and T-scores on the CSBQ and the Conners' parent DSM-IV symptom subscales between probands, siblings, and controls were assessed with univariate analyses of variance (ANOVAs). Effect sizes η^2 0.01, 0.06 and 0.14 were considered small, medium and large, respectively, following Cohen's standard (1988). To test whether subtle PDD symptoms occur more frequently in children with ADHD and their siblings than in controls, the following contrasts were defined: probands versus siblings, and siblings versus controls. The Kruskal–Wallis test, followed by Mann–Whitney tests, was used to determine differences in gender distribution between probands, siblings and controls.

The relation between ADHD severity and PDD severity was assessed by calculating Pearson's correlations between Conners' parent total scores and CSBQ subscale scores in probands (phenotypic correlations). Correlations were also calculated between the CSBQ subscales and the inattentive and hyperactive-impulsive Conners' parent subscales, respectively, to investigate whether the relation between ADHD and PDD symptoms was driven by either ADHD component.

The familiarity of PDD symptoms was estimated by calculating Pearson's correlations between proband and sibling scores (sibling correlations) on the CSBQ scales. To

investigate whether findings were robust these analyses were repeated after partialling out variance based on differences in IQ between siblings. For these analyses IQ was included as a covariate in a model in which the subjects' CSBQ subscale score was the dependent variable. The residuals of this analysis were used to calculate sibling correlations.

To further evaluate the familiarity of PDD symptoms, we expanded these analyses by adding the Conners' parent DSM-IV-total score to the covariates. Correlations between siblings were calculated for the residuals of this model. From these analyses, there are two possible outcomes. First, if including the covariate does not eliminate or diminish the sibling correlations, then the covariate does not uniquely account for the familiarity of the other measure. Second, if including the covariate diminishes the sibling correlation, a common genetic mechanism could be shared by both measures. A similar approach can be found in articles by Szatmari et al. (2008) and Raskind et al. (2000). These analyses were repeated with the Conners' parent DSM-IV inattentive and hyperactive-impulsive scale instead of the total scale. Furthermore, sibling correlations were calculated for the residuals of a model in which the Conners' parent anxious-shy scale was included as a covariate in addition to IQ and the Conners' parent DSM-IV-total score. This was done to verify whether anxiety confounds the association between ADHD and PDD symptom familiarity.

The relation between ADHD and PDD symptom familiarity was further tested by calculating cross-sibling cross-trait correlations (cross-correlations). If ADHD and PDD share familial influences, sibling Conners' parent DSM-IV symptom scores should be correlated with proband CSBQ scores.

Sibling correlations were calculated separately for male and female probands, and for younger and elder sibling pairs, respectively. For the latter, a median-split based on proband age was made. Siblings were divided in younger siblings (<11 years) and elder siblings (≥ 11 years), based on the proband age median. Age concordant pairs (i.e., both siblings and proband either under or above the median split) were formed, with 88 younger and 65 elder sibling pairs. To determine whether sibling pairs with male and female probands, and younger and elder sibling pairs, respectively, showed different correlations, Fisher's z-score transformations and t-tests were calculated using freely available software (Preacher 2002).

All other analyses were carried out using Statistical Package for the Social Sciences Version 15. We used an alpha of 0.01 to indicate statistical significance for all analyses on the full sample, and an alpha of 0.05 for the analyses of male and female probands and younger and elder sibling pairs, respectively.

Results

Table 1 presents general characteristics and symptom scores of probands, siblings, and controls. ADHD probands had the lowest IQ, followed by their siblings. Controls had the highest IQ. The percentage of males was higher in the proband group than in the sibling and control group, which in turn had similar male to female distributions. All T-scores on the CSBQ scales and the Conners' parent DSM-IV-symptoms scales showed significant group differences, with large effect sizes for all scales. Planned contrasts indicated that probands had more subtle PDD and ADHD symptoms than siblings, and that siblings had more PDD and ADHD symptoms than controls.

Phenotypic correlations between the PDD and ADHD symptom scores are presented in Table 2. Correlations between CSBQ subscales and the Conners' parent DSM-IV-symptom scores were all statistically significant, with the exception of that between the CSBQ social and the Conners' parent DSM-IV hyperactive impulsive scale. The CSBQ total score correlated 0.40 ($p < 0.001$) with the Conners' parent DSM-IV-total score. As expected, the tuned and the orientation subscales correlated the strongest with the Conners' parent DSM-IV-total score, namely 0.38 ($p < 0.001$) and 0.42 ($p < 0.001$), respectively. CSBQ subscales that measure core problems of PDD, i.e., social, understanding, stereotyped and change, showed somewhat lower correlations with the Conners' parent DSM-IV total score (between 0.16 and 0.27). These positive correlations confirm the association of PDD with ADHD symptoms. Correlations between the CSBQ and the Conners' parent DSM-IV inattentive and hyperactive-impulsive scales, respectively, showed no apparent differences in strength for all but the social and orientation subscales (see Table 2). These appeared to correlate stronger with the Conners' parent inattentive than with the hyperactive-impulsive subscale (0.23 and 0.46 for the inattentive, and 0.08 and 0.27 for the hyperactive-impulsive scale, respectively).

Table 3 shows sibling correlations for the CSBQ subscales. Considering the sibling correlations for the T-scores (second column), evidence of familiarity was found. All but two of the PDD subscales showed significant correlations, with the CSBQ total symptom scores corre-

lating 0.28 ($p < 0.001$). The CSBQ subscale that showed the strongest sibling correlation was the stereotyped subscale, $r = 0.35$, $p < 0.001$.

Subsequently, sibling correlations for the CSBQ subscale scores were calculated correcting for IQ. Results can be found in the third column of Table 3. Inclusion of IQ in the analyses did not appear to change the strength of the cross-correlations. Furthermore, cross-correlations of the CSBQ total score, and the subscales orientation and stereotyped remained significant after correcting for the Conners' parent DSM-IV-total score. See Table 3, fourth column for the exact strength of the correlations. The results of the familiarity analyses were similar when the Conners' parent inattentive or hyperactive-impulsive subscale were used instead of the total scale (see Table 3, fifth and sixth columns). Anxious-shy behavior did not appear to be a confounding factor in the familiarity of PDD symptoms in children with ADHD, as can be seen in the last column of Table 3.

The independence of the ADHD and PDD symptom familiarity was also suggested by the cross-correlations between proband PDD symptoms and sibling ADHD scores, which were all very weak and non-significant (see Table 4).

In Table 5 characteristics of the probands used for the subgroup analyses based on gender and age can be found. Female probands showed significantly higher T-scores than male probands for almost all ADHD and PDD subscales. The exception was the CSBQ tuned subscale, which did not differ significantly between boys and girls. Small effect sizes were found for all differences in CSBQ subscale scores. A large effect size was found for the Conners' DSM-IV total scale, and a medium effect size for the hyperactive-impulsive scale. Differences between scores of probands of younger and elder sibling pairs were significant for the CSBQ tuned, social and orientation subscale (small effect sizes), and the Conners' DSM-IV hyperactive-impulsive scale (medium effect size), with younger probands scoring higher on the first two scales, and elder on the latter two.

When sibling correlations were calculated for male and female probands separately, male probands generally showed weaker sibling correlations than female probands

Table 2 Within proband correlations between PDD symptoms and ADHD symptoms

	CSBQ-total	Tuned	Social	Orientation	Understanding	Stereotyped	Change
Conners' DSM-IV total	0.40*	0.38*	0.16**	0.42*	0.27*	0.24*	0.26*
DSM-IV inattentive	0.40*	0.32*	0.23*	0.46*	0.25*	0.25*	0.25*
DSM-IV hyperactive-impulsive	0.30*	0.35**	0.08	0.27*	0.21*	0.19*	0.21*

ADHD attention-deficit/hyperactivity disorder, CSBQ children's social behavior questionnaire, DSM-IV diagnostic and statistical manual of mental disorders, 4th edition, PDD pervasive developmental disorders

* $p < 0.001$, ** $0.001 < p < 0.01$

Table 3 Sibling correlations for proband and sibling PDD symptoms

	A (n=256)	B (n=246)	C (n=246)	D (n=246)	E (n=246)	F (n=246)
<i>CSBQ-total</i>	0.28*	0.27*	0.30*	0.29*	0.25*	0.27*
Tuned	0.16*	0.15	0.12	0.13	0.08	0.08
Social	0.18*	0.13	0.12	0.13	0.11	0.1
Orientation	0.19*	0.17	0.26*	0.25*	0.19**	0.24*
Understanding	0.15	0.15	0.13	0.1	0.14	0.13
Stereotyped	0.35*	0.36*	0.37*	0.35*	0.35*	0.36*
Change	0.09	0.11	0.09	0.1	0.08	0.09

A = Correlations for CSBQ T-scores; B = correlations for CSBQ T-score residuals, i.e., variance remaining after inclusion of IQ as covariate; C = correlations as under B, but with Conners' DSM-IV total score added to covariates; D = correlation as under C, but with Conners' DSM-IV *inattention* score instead of total score; E = correlation as under C, but with Conners' DSM-IV *hyperactive-impulsive* score instead of total score; F = correlation as under C, but with Conners' *anxious-shy* score added to covariates

CSBQ children's social behavior questionnaire, *DSM-IV* diagnostic and statistical manual of mental disorders, 4th edition, *PDD* pervasive developmental disorder

* $p < 0.001$; ** $.001 < p < 0.01$

(Table 6, columns 2 and 3). For the tuned scale, gender-differences between the correlations for the T-scores, the Conners' parent DSM-IV total corrected residuals, and the residuals corrected for the Conners' parent anxious-shy scale reached statistical significance ($z=2.21, p=0.03$; $z=2.51, p=0.01$, and $z=2.40, p=0.02$, respectively), with female probands showing stronger sibling correlations than male probands.

Results for the age-matched sibling pairs can be found in the right two columns of Table 6. Younger sibling pairs showed weaker correlations on the social scale than did elder pairs, with significant differences for the T-scores and the IQ corrected data ($z=-2.21, p=0.03$ and $z=-2.29, p=0.02$, respectively). Differences in sibling correlations between younger and elder pairs for the other subscales were not significant. For elder sibling papers, correlations appeared to decrease in strength when the Conners' DSM-IV total score was included as a covariate, especially for the tuned scale. This suggests that the relation between the familiarity of ADHD and PDD symptoms may be age dependent, with possibly more shared familiarity between ADHD and PDD symptoms for elder sibling pairs.

Discussion

The current study confirms the high levels of PDD symptoms in children with ADHD (Clark et al. 1999, Luteijn et al. 2000, Reiersen et al. 2007, Santosh and Mijovic 2004). Our study sample consisted of children with ADHD combined type, a subtype that has previously been reported to have the highest levels of PDD symptoms compared to other ADHD subtypes (Reiersen et al. 2007). Indeed, subtle PDD traits covered by the CSBQ were elevated in the children with ADHD compared to their siblings, with sibling scores still well above those of healthy control children. The elevations in PDD symptoms were not restricted to a specific subset or subscale of PDD symptoms, but covered the whole PDD spectrum, again in line with previous findings (Clark et al. 1999, Reiersen et al. 2007, Santosh and Mijovic 2004).

A positive relation was found between ADHD and PDD symptoms. This endorses the association between ADHD and PDD. However, ADHD-PDD correlations were of modest strength, indicating that PDD symptoms as measured in this study should not be considered a mere proxy for ADHD

Table 4 Cross-correlations between proband PDD symptoms and sibling ADHD symptoms

	Proband (n=256)						
	<i>CSBQ-total</i>	Tuned	Social	orientation	understanding	stereotyped	change
Sibling (n=256)							
<i>Conners' DSM-IV total</i>	0.06	0.10	0.06	0.01	0.04	0.02	0.03
DSM-IV inattentive	0.06	0.08	0.03	0.03	0.06	0.01	0.02
DSM-IV hyperactive-impulsive	0.06	0.09	0.07	-0.01	0.01	0.04	0.03

ADHD attention-deficit/hyperactivity disorder, *DSM-IV* diagnostic and statistical manual of mental disorders, 4th edition, *PDD* pervasive developmental disorders, *CSBQ* child social behavior questionnaire

Table 5 Characteristics for proband subgroups

Characteristic	Boys (<i>n</i> =219)			Girls (<i>n</i> =37)			Younger probands (<i>n</i> =88)			Elder probands (<i>n</i> =65)			
	Mean (sd)	ANOVA	η^2	Mean (sd)	ANOVA	η^2	Mean (sd)	ANOVA	η^2	Mean (sd)	ANOVA	η^2	<i>p</i>
Age	11.3 (2.7)			10.8 (2.6)			9.0 (1.3)			13.8 (1.9)		n.s.	
IQ	98.3 (12.5)			98.7 (12.8)			98.9 (13.4)			97.1 (11.3)		n.s.	
ADHD-symptom-scores													
Conners' DSM-IV total	75.1 (8.2)		0.14	84.5 (7.1)	$F(1,254)=48.9$		76.1 (8.3)			79.0 (9.3)		n.s.	
DSM-IV inattentive	69.3 (7.6)		0.16	78.9 (8.0)	$F(1,254)=49.1$		71.8 (8.7)			71.2 (8.3)		n.s.	
DSM-IV hyperactive-impulsive	77.8 (9.0)		0.07	84.5 (7.9)	$F(1,254)=18.1$		77.3 (8.7)			81.7 (9.0)		$F(1,151)=10.0$	<0.01
PDD-symptoms													
CSBQ-total	71.9 (12.3)		0.04	79.7 (15.8)	$F(1,254)=11.7$		73.3 (12.7)			74.6 (14.4)		n.s.	
Tuned	72.6 (12.4)		n.s.	73.9 (14.2)			71.3 (11.3)			75.9 (15.3)		$F(1,151)=4.5$	<0.05
Social	61.1 (14.6)		0.02	68.0 (19.0)	$F(1,254)=6.33$		64.6 (15.8)			58.9 (13.0)		$F(1,151)=5.7$	<0.05
Orientation	71.9 (14.9)		0.05	81.9 (16.0)	$F(1,254)=14.0$		72.4 (12.5)			77.5 (18.5)		$F(1,151)=3.9$	<0.05
Understanding	68.2 (13.2)		0.04	76.0 (14.5)	$F(1,254)=10.6$		71.8 (12.8)			68.4 (15.9)		n.s.	
Stereotyped	67.1 (17.7)		0.03	75.9 (23.7)	$F(1,254)=7.0$		66.5 (17.7)			62.3 (20.0)		n.s.	
Change	60.4 (15.1)		0.04	69.4 (19.5)	$F(1,254)=10.4$		62.1 (14.8)			64.4 (17.4)		X^2 -test	
Gender													
Boy							N (%)			N (%)			
Girl							71 (80.9)			58 (89.2)		n.s.	
							17 (19.1)			7 (10.8)			

ADHD attention-deficit/hyperactivity disorder, ANOVA analysis of variance, DSM-IV diagnostic and statistical manual of mental disorders, 4th edition, n.s. not significant, PDD pervasive developmental disorders, CSBQ child social behavior questionnaire

severity, but point to a different set of problems. As expected beforehand, correlations were the weakest for the most typical PDD subscales, but even the subscales that are conceptually related to ADHD correlated only moderately with the Conners' scores. For most CSBQ subscales, there was no indication that either symptoms of attention deficit or of hyperactivity-impulsivity alone could explain the association. The most outspoken exception was found for the CSBQ social subscale, which showed a weak and non-significant correlation with hyperactive-impulsive symptoms in contrast to symptoms of attention deficits. This suggests that children with combined type ADHD who have mainly inattention problems may show more withdrawn behavior than primarily hyperactive-impulsive children.

Our findings furthermore suggest that PDD symptoms in the context of ADHD are familial, and that this familiarity is largely independent from that of ADHD. This finding is strengthened by the fact that IQ and comorbid anxiety were found to be unlikely factors confounding the familiarity of PDD symptoms. These results speak against substantial common genetic factors for ADHD and PDD.

This finding is somewhat surprising given that two studies that have previously addressed the familiarity of PDD symptoms point to a shared etiology between ADHD and PDD (Constantino et al. 2003, Ronald et al. 2008). It should be noted, however, that both studies involved general population twin samples rather than clinical samples. Interestingly, in a previous study involving the IMAGE sample, but measuring more stringent autism symptoms, the familiarity of PDD and ADHD also appeared to be largely independent, as indicated by rather weak PDD-ADHD correlations between siblings (Mulligan et al. 2008). Our IMAGE findings clearly need independent replication, however.

It should be noted that our sibling-pair design allows us to report on familiarity rather than heritability. However, previous twin studies suggest PDD is highly heritable (Muhle et al. 2004) and that genetic effects rather than shared environmental factors are largely responsible for sibling similarity in PDD symptomatology. Thus, familiarity estimates as identified in the present study are likely to be mostly resulting from genetic factors.

It has been reported that different PDD dimensions may be genetically independent (Georgiades et al. 2007, Kolevzon et al. 2004, Ronald et al. 2005, 2006a, 2006b). In line with this, we found different sibling correlations for the different CSBQ subscales. The CSBQ subscale 'stereotyped behavior' appeared to show the strongest correspondence between siblings. It contains items referring to repetitive movements and sensory stereotypies. The potential dissimilarity in heritability of different PDD dimensions in children with ADHD is a new finding, and needs to be considered in future research.

Table 6 Sibling correlations for subgroups

Correlations for CSBQ, T-scores				
	Male probands (n=219)	Female probands (n=37)	Younger sibpairs (n=88)	Elder sibling pairs (n=65)
Correlations for CSBQ T-score residuals (variance remaining after inclusion IQ as covariate)				
<i>CSBQ-total</i>	0.23**	0.44**	0.35**	0.33**
Tuned	0.09	0.46**	0.28**	0.26*
Social	0.13	0.33*	0.03	0.38**
Orientation	0.15	0.24	0.18	0.31*
understanding	0.13	0.24	0.13	0.12
stereotyped	0.33**	0.48**	0.32**	0.37**
change	0.03	0.31	0.21	-0.04
Correlations for CSBQ T-score residuals, Conners' DSM-IV total score added to covariates				
<i>CSBQ-total</i>	0.24**	0.35*	0.37**	0.37*
tuned	0.09	0.39*	0.29**	0.25
social	0.07	0.24	0.03	0.39**
orientation	0.16*	0.09	0.23*	0.33*
understanding	0.15*	0.09	0.18	0.17
stereotyped	0.31**	0.52**	0.43**	0.39**
change	0.05	0.29	0.22*	0.06
Correlations for residuals, Conners' anxious-shy score added to covariates				
<i>CSBQ-total</i>	0.25**	0.53**	0.40**	0.20
tuned	0.06	0.48**	0.26*	0.05
social	0.08	0.22	0.03	0.30*
orientation	0.24**	0.36*	0.27*	0.26
understanding	0.12	0.24	0.12	0.07
stereotyped	0.30**	0.60**	0.42**	0.33*
change	0.05	0.25	0.23*	-0.07
Correlations for CSBQ T-score residuals, Conners' DSM-IV total score added to covariates				
<i>CSBQ-total</i>	0.22**	0.46**	0.31**	0.21
tuned	0.03	0.44*	0.17	0.03
social	0.07	0.15	-0.04	0.29*
orientation	0.23**	0.31	0.24*	0.26
understanding	0.11	0.28	0.07	0.11
stereotyped	0.30**	0.55**	0.38**	0.32*
change	0.08	0.13	0.15	0.06

CSBQ children's social behavior questionnaire, *DSM-IV* diagnostic and statistical manual of mental disorders, 4th edition

**sibling correlation $p < 0.01$; *sibling correlation $p < 0.05$

In line with the study by Reiersen et al. (2007), we found elevated levels of subtle PDD symptoms in both boys and girls with ADHD. In fact, girls with ADHD had even higher gender and age specific CSBQ scores than boys, also similar to what Reiersen et al. (2007) found. Therefore, despite the fact that boys are overrepresented in PDD in general, in children affected with combined type ADHD girls are at least as affected with PDD symptoms as are boys. Furthermore, our results suggest that PDD symptoms are more familial when girls are affected, although this

needs to be confirmed in a twin sample. This is inconsistent with previous studies indicating that the familial loading is similar in families of boys and girls with PDD, and that that the genes that influence autistic traits are the same for both genders (Constantino and Todd 2003, Goin-Kochel et al. 2007). It should be noted, however, that these studies pertain to PDD while our study focused on subtle PDD symptoms within ADHD.

We observed some differences in familiarity for subtle PDD traits in younger versus elder sibling pairs, especially with regard to the social subscale. As far as we know, no data have been published about heritability changes depending on age for PDD symptoms. Nevertheless, it has been found that prosocial behavior shows declining shared environmental and increasing genetic influences with increasing age (Knafo and Plomin 2006, Scourfield et al. 2004). This corresponds with our findings of higher familiarity of the social scale, which is negatively correlated with prosocial behavior, in elder sibling pairs.

One of the limitations of this study is that it involved clinically referred children with combined type ADHD. Our findings in this highly selected sample therefore cannot be translated directly to ADHD in the general population. Furthermore, despite a diagnosis of autism being one of the exclusion criteria of the IMAGE study, a few children with comorbid PDD may still have been included in our sample. We think that as such our sample is representative of current clinical practice, where sometimes PDD may go unnoticed when ADHD symptoms dominate the clinical picture. Another issue is that, perhaps besides a rare exception, the majority of children in our sample had PDD traits below the autism cut-off. We do not know whether the underlying genetic factors for these subtle PDD features are the same for full blown autistic symptoms. However, findings from a study using the social responsiveness scale, an instrument similar to the CSBQ, do suggest so (Constantino et al. 2006). Although representative of clinically relevant ADHD, our sample was predominantly male. We found interesting gender differences with regard to the familiarity of PDD symptoms, but these findings need replication in samples with more females represented. Also, the cross-sectional nature of our study limits the interpretation of the age effects, which clearly deserve further study in a longitudinal design. Finally, we used parent reports only whereas, ideally, a detailed developmental history and observational data should be collected to assess autistic symptomatology.

In conclusion, this study demonstrates that both boys and girls with combined type ADHD have increased levels of PDD symptoms. Although the major classification systems (*DSM-IV* and *ICD-10*) discourage diagnosing a combination of ADHD and PDD, our results as well as others' speak against this strict segregation. Furthermore,

we found the familiarity of PDD symptoms to be largely independent of the familiarity of ADHD. Of all PDD dimensions, stereotyped behavior showed the strongest familiarity. Our results suggest that PDD familiarity may be higher in ADHD affected girls than in boys, but our female sample was of limited size. PDD familiarity appeared age dependent, which stresses the importance of taking age into account when interpreting genetic study results and comparing between such studies. Future research may try to elucidate the genetic loci involved in PDD symptoms in the context of ADHD in comparisons with genetic findings in PDD as such. The implications of the presence of PDD symptoms for the prognosis and treatment of children with ADHD need attention.

Acknowledgements The IMAGE-study was supported by National Institute of Health grant 1 R01 MH62873-01A1 to S.V. Faraone.

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