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Co-transmission of conduct problems with attention-deficit/hyperactivity disorder: familial evidence for a distinct disorder

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Summary. Common disorders of childhood and adolescence are attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD). For one to two cases in three diagnosed with ADHD the disorders may be comorbid. However, whether comorbid conduct problems (CP) represents a separate disorder or a severe form of ADHD remains controversial. We investigated familial recurrence patterns of the pure or comorbid condition in families with at least two children and one definite case of DSM-IV ADHDct (combined-type) as part of the International Multicentre ADHD Genetics Study (IMAGE). Using case diagnoses (PACS, parental account) and symptom ratings (Parent/Teacher Strengths and Difficulties [SDQ], and Conners Questionnaires [CPTRS]) we studied 1009 cases (241 with ADHDonly and 768 with ADHD + CP), and their 1591 siblings. CP was defined as ≥ 4 on the SDQ conduct-subscale, and $T \geq 65$, on Conners' oppositional-score. Multinomial logistic regression was used to ascertain recurrence risks of the pure and comorbid conditions in the siblings as predicted by the status of the cases. There was a higher relative risk to develop ADHD + CP for siblings of cases with ADHD + CP

(RRR = 4.9; 95%CI: 2.59–9.41); $p < 0.001$) than with ADHDonly. Rates of ADHDonly in siblings of cases with ADHD + CP were lower but significant (RRR = 2.9; 95%CI: 1.6–5.3, $p < 0.001$). Children with ADHD + CP scored higher on the Conners ADHDct symptom-scales than those with ADHDonly. Our finding that ADHD + CP can represent a familial distinct subtype possibly with a distinct genetic etiology is consistent with a high risk for cosegregation. Further, ADHD + CP can be a more severe disorder than ADHDonly with symptoms stable from childhood through adolescence. The findings provide partial support for the ICD-10 distinction between hyperkinetic disorder (F90.0) and hyperkinetic conduct disorder (F90.1).

Keywords: ADHD; conduct problems; conduct disorder; comorbidity; diagnosis; oppositional defiant disorder; relative risk

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ADHDct	ADHD-combined type
CD	Conduct disorder
CP	Conduct problems
CP/TRS	Conners Parent/Teacher Rating Scale
DSM-IV	Diagnostic and statistical Manual of the American Psychiatric Association, 4th version

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<i>ICD-10</i>	International Classification of Diseases, 10th version
<i>IMAGE</i>	International Multicentre ADHD Genetics Study
<i>ODD</i>	Oppositional defiant disorder
<i>PACS</i>	Parental account of children's symptoms
<i>SDQ</i>	Strengths and Difficulties Questionnaire

Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by the symptom clusters of hyperactivity, inattention, and impulsivity, develops in early childhood and frequently leads to social, academic, and occupational impairments. ADHD, conduct disorder (CD) and oppositional defiant disorder (ODD) are three common behavioral disorders in childhood. The syndromes occur separately but can be comorbid. Both genetic and environmental factors contribute to the expression of the single diagnosis and their aggregation in families with attention deficit (Thapar et al. 2001; Nadder et al. 2002) and antisocial disorders (Faraone et al. 1995; Burt et al. 2005). Yet it remains controversial, whether the co-occurrence of the disorders in individuals (e.g., ADHD + CD) aggregates in families, and represents a separate heritable entity.

Taylor and colleagues (1991) proposed that comorbid ADHD + CD may be a separate condition arising mainly out of poor impulse control, and exacerbated by high parental expressed emotion. More recently Drabick et al. (2006) also reported hostile, inconsistent, and detached parenting to be associated with CD symptoms in ADHD children. Consistent with this Hurtig et al. (2007) reported that adolescents with comorbid CD exhibited more severe symptoms of ADHD than those without CD, and were more likely to come from nonintact families with disaffected mothers. On the other hand the clinical findings of Schachar and Wachsmuth (1990) indicated that forms of ADHD with and without aggression were separate and distinct. Halperin (1991) supported this viewpoint with a description of separate neuropsychological correlates for the two forms. The purely hyperactive type was more inattentive and the mixed hyperactive/aggressive type was more impulsive. Taylor (1998) however accommodated these findings by suggesting that they represent alternative trajectories leading to aggressive ADHD children or children with combined type ADHD.

ADHD is a highly heritable behavioral condition for which recent estimates suggest a 4–8 fold increase in risk for the condition in first-degree relatives of ADHD cases compared to those in the general population (Faraone et al. 2000a; Willcutt et al. 2000). Numerous studies of parent- and teacher-rated symptoms in twins demonstrate the predominant role of genetic factors on the familial prevalence

for ADHD symptoms with heritability estimates of 60–90% (Thapar et al. 1999; Faraone et al. 2005b).

ODD, like ADHD, typically has an onset in early childhood, but is characterized by temper tantrums, irritability, spiteful attitudes, frequent arguments, anger, defiance of adults' authority, and excessive blaming and intentional annoyance of others (Dick et al. 2005). ODD cases differ from those with comorbid CD in their social impairment and the prevalence of mood disorders (Greene et al. 2002). CD usually develops later than ODD, and is characterized by antisocial behaviors covering the symptoms of four domains (e.g., theft, lying, truancy, threatening and aggressive behavior towards people and animals, fire setting, and destruction of property (Nock et al. 2006)). ODD often precedes CD as children reach adolescence, but not all those with CD have a history of ODD (Lahey et al. 2000). Prevalence rates for CD (7–12% in males) approximate those for ADHD (Kratzer and Hodgins 1997; Faraone et al. 2003; Nock et al. 2006), but heritability estimates (about 40%) are more modest than for ADHD (Ehringer et al. 2006).

Previous studies of whether there are separate or overlapping etiologies for the disorder of ADHD with oppositionality (ODD and/or CD) from ADHD only have used familial aggregation, longitudinal, and genetic designs to clarify the patterns of comorbidity found in clinical data. We outline briefly the most relevant findings.

Family studies suggest that ADHD + CD represents a specific subtype of disorder with familial risk factors independent of ADHD alone (Stewart et al. 1980; Lahey et al. 1988; Frick et al. 1991; Faraone et al. 1991, 2000b; Szatmari et al. 1993; Faraone and Biederman 1997). August and Stewart (1983) found that, among hyperactive children, a family history of antisocial behavior predicted more CD symptoms in the child and a greater risk of CD to siblings. In contrast those without a family history of antisocial problems showed attentional difficulties, but not symptoms of CD and did not have siblings with CD symptoms. August et al. (1983) also found in a four-year follow-up that baseline childhood CD symptoms predicted the degree of CD shown in early adolescent hyperactive boys. Thus longitudinal data support the predictive validity of the classification of a distinct subtype.

Lahey et al. (1988) also reported higher rates of antisocial disorders, depression and substance abuse among relatives of ADHD + CD cases compared to cases of ADHD only. In another study, the mothers of ADHD + CD children were found to have higher rates of psychopathology than the mothers of children with ADHD only (Lahey et al. 1989). Similarly Frick et al. (1991) noted that

parents of ADHD + CD children had higher rates of childhood hyperactivity, CD and substance abuse than parents of children with ADHD only. Faraone et al. (1991) compared families with Attention Deficit Disorder (ADD) cases with those of normal controls. They found an increased risk for antisocial disorders among the relatives of DSM-III ADD cases with CD and ODD, but not among the relatives of those with only ADD. In the families of ADD + CD cases, ADD and CD co-segregated. These results suggested ADD + CD might be distinct from ADD without CD.

Twin studies

Early twin studies of juvenile delinquency found a low heritability with substantial but similar concordance rates for identical and fraternal twins, that were only marginally higher for the monozygotic twin (McGuffin and Gottesman 1985). More recent twin studies suggest that the comorbidity of CD/ODD with ADHD is not only extensive (Simonoff et al. 1997), but it defines a more severe form of ADHD in terms of genetic loading (Silberg et al. 1996; Thapar et al. 2001; Dick et al. 2005).

The Virginia twin study (Silberg et al. 1996) found that the genes influencing variation in scores of hyperactivity were also responsible for the variation in conduct problems (CP), accounting for 76–88% of the correlation between scores (confirmed by Nadder et al. 2002). Thapar et al. (2001) examined categories of ADHD and CP based on parental ratings of symptoms in the DSM-III-R, ICD-10 and Rutter-A scales in 2082 twin-pairs. On the basis of a heritability estimate for CP of 47% and a shared environmental contribution of 36% they concluded that ADHD + CP represents a more extreme variant of ADHD in terms of genetic loading and clinical severity. The report from Vierikko et al. (2004) supports this position. They performed bivariate analyses on hyperactivity and aggression traits in a Finnish twin sample, and found that, in addition to significant genetic and environmental influences specific to each behavior, aggression and hyperactivity-impulsivity shared a common genetic and environmental etiology. Both studies imply that comorbidity represents a more severe form of ADHD.

The Minnesota study of 1782 11 year-old twins (Burt et al. 2005), though in partial agreement, went even further. On the basis of bivariate analyses of hyperactivity and aggression traits, they reported a substantial shared environmental factor with only marginal genetic contributions to the etiology. However, this result varied significantly with the source of the information analyzed (i.e., children's self-ratings vs. ratings by the mother). These twin studies pro-

vide some support for the proposal that ADHD + CP is a distinct subtype, but vary quite widely on the heritable or environmental contribution.

The CP distinction

Several studies suggested that apart from a positive family history, the *severity* of antisocial behavior plays a major role in correlations of ADHD with comorbid externalizing behavior. For example, chronic CP was differentiated from persistent low CP by risk factors in child, parenting, and family domains (Shaw et al. 2005). This affects whether ADHD + CP is accepted as a more severe variant of ADHD than ADHD only, as widely advocated (Jensen et al. 1997; Kuhne et al. 1997; Banaschewski et al. 2003; Levy et al. 2006).

The validity of the CP dimension in the present study depends in part on it being a modest reflection of the category of CD. There is in fact evidence that the degree of CD is under separate environmental and familial influences. Levy et al. (2006) differentiated CD into the expression of symptoms to a mild (like ODD), moderate (modest CD: e.g., lying) or extreme degree (severe CD: e.g., fire-setting). They studied ADHD + CD in the Australian twin study and found a best fit for the 3-level model of CD in terms of additive genetic, shared and non-shared environmental factors (ACE-model). Extreme CD was found to have a very high common environment factor, and a negligible effect of heredity. This indicates that growing-up in the same family has a strong influence on the development of extreme CD, but not so much on the appearance of ADHD or milder forms of CD. Also, the extreme form of CD (as compared to mild or moderate CD) was much less correlated with the expression of inattention and hyperactivity/impulsivity. Indeed, in a nontwin study based on 68 subjects with CD or ADHD + CD diagnoses, the canonical correlation analysis of Mathias et al. (2007) describes an association for the less-than-extreme expression of CP with inattention and hyperactivity. Together these results imply that extreme CD is a disorder distinct from mild and moderate CD. Importantly, milder conduct problems (CP) are more likely to be comorbid with ADHD and have a common biological etiology.

The present study

To test these competing hypotheses, a large sample of ADHD combined-type cases and their siblings from the IMAGE study were investigated. The combined type of ADHD is more prevalent than the inattentive or hyperac-

Table 1. Hypotheses on the familial association between ADHD and CP

Hypothesis	Case diagnosis	Siblings recurrence risks				Co-segregation
		No disorder	ADHD only	ADHD + CP	CP only	
1. ADHD + CP etiologically independent, i.e. chance co-occurrence	ADHDonly	-	++	-	-	no
	ADHD + CP	-	+	+	+	
2. ADHD + CP as a distinct condition from ADHD only, i.e., "cosegregated" pattern	ADHDonly	-	+++	-	-	yes
	ADHD + CP	-	+	+++	-	
3. ADHD + CP as an extreme severe variant of ADHD i.e., common genetic etiology	ADHDonly	-	+	-	-	no
	ADHD + CP	-	++	+++	-	
4. ADHD + CP share common environmental risk factors	ADHDonly	-	++	-	-	no
	ADHD + CP	-	+	++	++	

"++"/"+" = high/intermediate risk for disorder, and "-" = no increased risk for disorder, vs. controls.

ADHD Attention-deficit/hyperactivity disorder, ADHD + CP = ADHD with CP conduct problems; ADHDonly = ADHD without CP.

tive-impulsive forms, and manifests comorbidity with CP more frequently than the other forms (Eiraldi et al. 1997). The sample consisting only of combined-type ADHD therefore minimizes the effects of confounding factors present in a sample of mixed ADHD subtypes. It is therefore particularly suitable to test these competing hypotheses. Our aim was to test whether cases of ADHD + CP should be regarded as an etiologically and heritably separate condition, as endorsed by the ICD-10 classification.

Different hypotheses could account for the co-occurrence of ADHD and ODD/CD (see Table 1: evidence for each proposal is discussed in Schachar and Tannock 1995; Faraone et al. 1997; Greene et al. 2002). However, diagnostic interviews (PACS) were not available for all siblings. As a category referring to CP was required for the whole sample of cases and siblings, we first validated the questionnaire ratings (e.g., Conners, Strengths and Difficulties) that were available for all subjects for representing an adequate measure of the behavioral problems related to CD/ODD across the sample. Here the term CP is thus a broad category that allows for the occurrence of CD and ODD. Having operationally defined and validated CP (see results), we sought to resolve predictions arising from the four principle proposals (Table 1) with a study of a large population of families with cases of ADHD and unaffected siblings recruited by the IMAGE genetics consortium (Asherson and the Image Consortium 2004).

We would predict *Proposal 2*. This suggests that comorbid CP and ADHD, represented by ADHD + CP, is a distinct disorder: cases with ADHDonly will tend to have siblings with ADHDonly, while cases with ADHD + CP will likely have siblings with ADHD + CP. But if ADHD + CP is merely an extreme variant of ADHD (*Proposal 3*), then cases with comorbid ADHD + CP will have many siblings with ADHDonly, but also many siblings with ADHD + CP. However, one can conceive ADHD and CP

to be separate entities. If they share environmental risk factors (*Proposal 4*) then ADHDonly cases should have many siblings with ADHDonly, many ADHD + CP cases will have siblings with ADHD + CP, and there should also be a high number of siblings with only CP. If however, ADHD and CP are etiologically independent with only a chance concordance (*Proposal 1*), then the distribution of the disturbances of siblings of cases with ADHD + CP will be lower and evenly distributed across the subgroups compared to a more marked likelihood of ADHDonly cases having siblings with ADHDonly. The outcome of the analysis has nosological implications. The American Psychiatric Association maintains these disorders as separate entities (DSM-IV, 1994: ADHD 314.x, CD 312.8, ODD 313.8), while the World Health Organization recognizes a distinct subtype of "hyperkinetic conduct disorder" (ICD10, 1991: F90.1) separate from "simple attention-deficit/hyperactivity disorder" (F90.0) and CD (F91.x).

In summary, to support the concept of ADHD + CP as a distinct condition, we predict finding (i) a specific pattern of ADHD + CP recurrence in siblings related to cases with ADHD + CP (*Proposal 2*, reflecting cosegregation); (ii) there is no support for a shared environmental effect, as shown by the absence of an increased rate of CPonly in siblings of ADHD + CP cases (*Proposal 4*); and (iii) there is no evidence of increased ADHD loadings in siblings, as indicated by the absence of an increased rate of ADHDonly in the siblings of ADHD + CP cases (*Proposal 3*).

Methods and materials

Participants

This study is based on 3229 offspring from 1187 fathers and 1341 mothers. Entry criteria for the cases included a diagnosis of DSM-IV "combined subtype" of ADHD (ADHDct) and having one or more full siblings available for the ascertainment of clinical information and without a diagnosis of ADHD. This restricted the analysis to 1401 cases with diagnostic informa-

Table 2. Characteristics of the sample (percentages and standard deviations in parentheses)

Group	Subgroup	N	Age (years)	IQ	Gender (males)	Socio-Economic Scale (SES)
ADHD N = 1401 [#]	ADHDonly	241 (17.2%)	10.8 (2.7)	101.5 (15.3)	204 (84.6%)*	3.8 (1.0)
	ADHD + ODD	202 (14.4%)	10.8 (2.4)	102.5 (16.4)	175* (86.6%)	3.9 (1.0)
	ADHD + CD	11 (0.8%)	13.0 (3.2)	103.8 (17.1)	11* (100%)	4.2 (0.7)
	ADHD + ODD + CD	44 (3.1%)	10.2 (2.8)	99.0 (16.4)	40* (90.9%)	3.7 (1.1)
	ADHD + CP	768 (54.8%)	11.0 (2.8)	98.6 (15.5)	671* (87.3%)	3.7 (1.1)
Siblings N = 1828 [#]	no disorder	1123 (61.4%)	10.8 (3.4)	102.8 (13.7)	522 (46.4%)	3.5 (1.3)
	ADHDonly	252 (13.8%)	10.7 (3.1)	101.1 (15.0)	136 (53.9%)	3.9 (1.0)
	ADHD + CP	233 (12.7%)	10.6 (3.2)	96.7 (15.3)	142* (60.9%)	3.4 (1.0)
	CPonly	49 (2.7%)	10.6 (3.0)	103.6 (13.8)	36* (73.4%)	data missing on 48 subjects

There were no group differences except for gender* where there were predominantly more males (MANOVA: $p < 0.0001$). [#] From the original sample data were missing for 135 cases (9.6%) and 171 siblings (9.4%).

tion. Symptom ratings were available for these cases and 1828 siblings. The families constitute a subsample of those who were recruited for the International Multi-Center ADHD Genetics Study (IMAGE: Faraone et al. 2005a) from 12 specialist clinics in Belgium, Germany, Holland, Ireland, Israel, Spain, Switzerland and United Kingdom. At all 12 centers an agreed study protocol in accord with the criteria of the Declaration of Helsinki was reviewed and approved by the local institutional review board. Verbal and written information was prepared for the children and the parents who provided written consent.

All children were aged from 5 to 17 years (cases: mean 10.9 years, SD 2.8; siblings: mean 10.9 years, SD 3.4), and were of European Caucasian descent. They had an IQ of >70 (cases: mean 100.1, SD 15.7; siblings: mean 101.8, SD 14.3) on the short version of the WISC (information, picture arrangement, similarities and block-design: Sattler 1992). Among the cases 86.5% and among the siblings 50.2% were male. Exclusion criteria for both cases and siblings included autism, epilepsy, general learning difficulties, brain disorders and any genetic or medical disorder associated with externalizing behavior that mimics ADHD. Table 2 shows the characteristics of the sample (gender, age, IQ, and socio-economic status).

Clinical measures

Diagnoses were based on a standardized, semi-structured interview with the parents (Parental Account of Childhood Symptoms, [PACS]; Taylor et al. 1991; Chen and Taylor 2006). Interviewers, who had received formal training in London, obtained detailed descriptions of the child's typical behavior in a range of specified situations defined by the context (e.g., play) or the behavior shown (e.g., crying). Items that had occurred in the previous week and in the previous year were rated on a 4-point scale for frequency and severity. PACS includes 4 subscales: hyperactivity (attention span, fidgetiness and restlessness), defiance (e.g., tantrums, disobedience and destructiveness), emotionality (e.g., misery, worries, fears) and comorbid disorders (autistic spectrum, attachment, mania, substance-abuse, psychotic symptoms, obsessive-compulsive symptoms, and other specific developmental and neurological conditions). An age adjustment for symptom thresholds is built into the PACS algorithm for diagnosis. Situational pervasiveness is captured by the different situations investigated within the PACS interview as well as the presence of at least one symptom in each domain reported by teachers using the Conners CTRS ADHD sub-scales (see below).

Inter-rater reliability was high with product-moment correlations for pairs of interviewers ranging from 0.79 to 0.96. A mean kappa coefficient across all the sites of 0.88 (range 0.71–1.00) and an average agreement percentage of 96.6% (range 78.6–100) were obtained. Concurrent validity of PACS diagnosis was confirmed by the biserial correlation between PACS diagnosis of ADHDct with Conners Teacher N-scale (18 DSM-items) scores at 0.68 and with Conners' Parent N-scale scores at 0.78.

ADHD symptoms in both cases and siblings were rated with the long version of Conners' parent and teacher rating scales (CPRS-R:L; CTRS-R:L; Conners 2002), and the parent and teacher versions of the Strengths and Difficulties Questionnaires (SDQ; Goodman 1997; Woerner et al. 2004). The SDQ has 25 items on 5 scales relating to emotionality, conduct, hyperactivity/inattention, peer-problems, and pro-social behavior. The N-scale of the CPRS and CTRS combines 18 items, compatible with the DSM-IV checklist, from 9 inattentive (subscale L) and 9 hyperactive-impulsive items (subscale M). Missing subscale data were prorated if 7 or more from 9 items were present. T-scores (standardized for age and gender) for the CPRS and CTRS were based on published data (Conners 2002), and for the SDQ a comparable procedure was based on tables from R. Goodman (personal communication).

As PACS information was not available for all siblings, the CP/TRS and SDQ ratings were used to define the "presence" of ADHD and CP symptoms in these children who otherwise had no diagnosis. ADHD was recorded as present for a T-score of ≥ 65 (1.5 standard deviations over the mean) on the CPRS and CTRS 18 item DSM-IV scales. Concurrent validity for Conners and clinical assessments have been reported (Conners et al. 1998a, b; Kuntsi and Stevenson 2001). The ADHD criterion was shown by 485 siblings. CP was recorded as present on the basis of conduct items from CPRS and CTRS oppositional subscales and the SDQ conduct scale in all children. The SDQ items (rated 0–2) concern temper tantrums, obedience, arguing a lot, lying and stealing, and the CP/TRS items (rated 0–3) include anger-resentment, fighting or arguing with adults, loss of temper, irritability, defiant or not compliant with adult requests, easily annoyed, blaming others for own misbehavior, intentional annoyance of others and spiteful-vindictive behavior.

To exclude autism spectrum disorders that might confound the analysis of ADHD, both cases and siblings were screened using the Social Communication Questionnaire (≥ 15) in conjunction with the pro-social scale from the SDQ (≤ 4). Those falling outside these thresholds were further evaluated with the autism spectrum disorder section of the PACS interview.

Statistical analyses

All raw data were stored on a database at the London site with the ratings controlled for consistency by entry and re-entry of the data at two time points. Data reduction and analyses were carried out using the statistical package STATA version 9 and SPSS 14.0.

As PACS data were not available for all siblings we evaluated initially the concurrent validity of the CP/TRS and SDQ oppositional scales against the PACS diagnosis of CD/ODD found in the cases to reduce the likelihood of misclassification. First, point-serial correlations (after Pearson) were computed between the ODD/CD PACS status and the CP/TRS and SDQ scales. Second, linear discriminant analyses were used to assess which scales (or

combination of scales) provided the best prediction of ODD/CD cases. The sensitivity and specificity of the composite construct of conduct problems (CP) against the PACS diagnoses was calculated. Lastly receiver operating characteristics (ROC) were plotted to show the rate of the true positive rate against the false positive one for the chosen scales.

In the second stage of the main analysis, a multinomial logistic regression to ascertain the pattern of recurrence risks of ADHD and comorbid conditions amongst siblings was used. More specifically, we tested whether there was a specific pattern in the siblings' recurrence risks as predicted by the status of the cases as ADHDonly or ADHD + CP consistent with cosegregation. Thus all cases were used as predictors (independent variables) and all siblings as criterion (dependent variables). As the predictions above are based on related groups (the cases and their siblings are statistically not independent), we applied Huber's bootstrap corrections, as implemented in STATA to correct for correlated family data (see Faraone et al. 2000b).

In a last step, MANOVAS were calculated to assess the severity of symptoms for the different subgroups (i.e., ADHDonly, ADHD + CP, and for siblings additionally CPonly, and no disorder). CPRS and CTRS ratings of the DSM-IV based ADHDct were entered into the MANOVA as measures of symptom severity. Analyses were repeated for both cases and siblings younger and older than 11 years, in order to see if the prevalence of the comorbid condition increased with age or remained stable. The choice of 11 years reflects the median onset age of 11.6y reported by Nock et al. (2006), who also described an age-dependent increase of CD prevalence.

Results

Psychometric validity of rating scales

Correlation coefficients were calculated to show the degree of concordance between different informants (teacher, parent) on the CPRS-R: L, CTRS-R: L, SDQ (and their oppositional or CP subscales), and PACS ratings for ODD and CD for cases only (Table 3).

There were strong correlations for both sets of parental ratings with the diagnostic assessments of ODD and CD from the PACS. The correlations for teacher ratings were weaker yet remained highly significant. Importantly, the

Table 3. Correlations for Conners and SDQ Parent and Teacher Rating-Scales with PACS assessments of ADHD, with/without ODD and CD

ADHD groups	Conners parent oppositional	Conners teacher oppositional	SDQ parent conduct problems	SDQ teacher conduct problems
ADHD only ($n = 1009^*$)	-0.454	-0.117	-0.420	-0.183
+ODD ($n = 202$)	+0.448	+0.117	+0.407	+0.182
+CD ($n = 11$)	+0.331	+0.115	+0.424	+0.171
+ODD + CD ($n = 44$)	+0.345	+0.114	+0.418	+0.161

All positive and negative correlations were significant (Point serial correlations after Pearson, two-way $p < 0.0001$). * Cases were defined from PACS assessments).

ODD and CD diagnoses derived from PACS diagnoses of cases correlated positively with parent and teacher ratings on the Conners and SDQ oppositional scales, whereas the group of cases with ADHDonly defined by PACS showed negative correlations with the CP. Thus, concurrent validity for CP items is apparent.

To examine further potential informant effects, parent and teacher ratings of oppositional behavior or putative CP, as measured by the Conners and SDQ scales, were entered into a stepwise linear discriminant analysis (LDA). Parents' ratings of CP items on the CPRS and SDQ oppositional scales yielded the best discrimination of ADHDonly, CD, ODD groups defined by PACS. They correctly classified 70.4% of all cases; 69.6% of cases with ADHDonly (specificity) and 73.2% of cases with ADHD + ODD + CD (sensitivity).

Lastly, ROC-curves for the parental ratings on both the Conners and SDQ oppositional subscales and for the com-

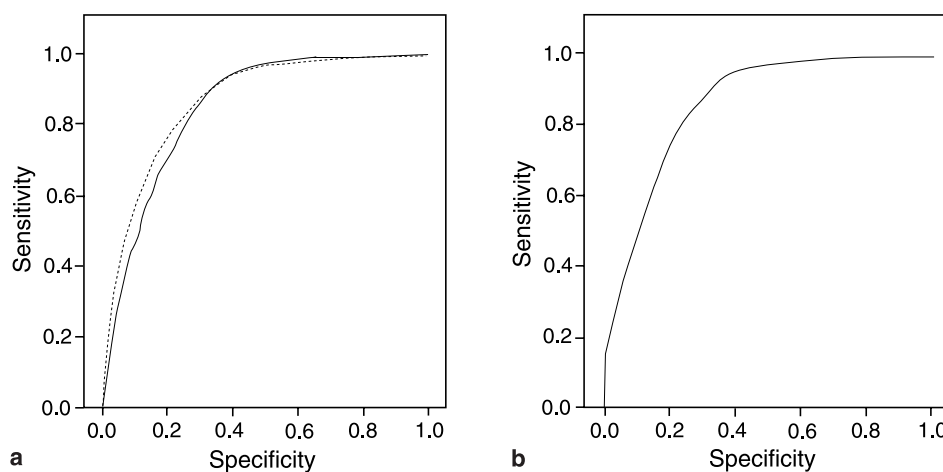


Fig. 1a. Receiver operating characteristic (ROC) – curves and areas under the curve for parental ratings of oppositional behavior based on Conners and SDQ scales: The area under the curve for the CPRS oppositional scale is .847 and for the parent SDQ is 0.865. (b) The ROC curve for the combined parental (CP) ratings of oppositional behavior: the area under the curve is 0.860

bined CP scale were plotted (Fig. 1). The closer the curve follows the left-hand border and the larger the area under the curve, the better is the prediction. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate is the prediction. Each ROC-curve in Fig. 1a and b followed the left-hand and then the top border, and thus showed a high accuracy for the scales. The areas under both curves (SDQ and CPRS ratings) indicated a high degree of correspondence between the CP construct and DSM-IV CD diagnosis (0.84 and 0.86, respectively) as did the combined CP-Scale (0.86). Thus, the findings confirmed with three different analyses that the composite of parent SDQ conduct and Conners' oppositional items is a sensitive and specific measure for differentiating between individuals with and without CP.

To reduce the potential for misclassification of siblings further, the ROC-curve was used to identify the best cut-off point for identifying CP. The findings show CP was best defined by a composite of the CPRS and SDQ subscales scoring $T=65$ and more on the CPRS (1.5 standard deviations above a mean of 50) and scoring ≥ 4 on the SDQ Parent conduct scale. This corresponds to a cut-off above the 85th percentile in both rating scales. This analysis was based on data derived from 498 cases with available PACS and rating scale data. Thus all further analyses of CP in ADHD cases and siblings relied on this combination of measures for identifying CP and resulted in the identification of 768 cases and 282 siblings with CP.

Patterns of familial co-transmission

A multinomial logistic regression (MLR) was conducted to test the hypotheses in Table 1 by ascertaining the siblings recurrence risks for "no disorder", "ADHDonly", "CP-

only" and "ADHD + CP" subgroups (Table 4). This prediction of the pattern of symptoms recorded in the siblings was based on using cases with ADHDonly and ADHD + CP as independent variables, and subgroup membership for the siblings as the dependent variable. (The regression was confined to this comparison as the IMAGE sample did not include an unrelated control group without diagnoses of ADHD or ratings of CP. To control for the relationship between groups, Huber's correction was applied.)

Table 4 illustrates the pattern of co-transmission of "ADHD + CP". Based on 267 siblings of 241 cases with ADHDonly, 4.9% of the siblings were rated as showing ADHD + CP symptoms. This proportion increased by 11.4% on examination of 1324 siblings of 768 cases with ADHD + CP. Comparing these ratios, the relative risk for concordance was 4.5, and rose to 4.9 after taking socioeconomic status and gender into consideration (see Table 1, Proposal 2). However, the relative risk for a discordant status in siblings (ADHDonly) of cases with ADHD + CP also rose significantly, albeit to a lesser extent (6.2%: see Proposal 3). The prevalence of CPonly in siblings of cases with ADHD + CP also rose significantly (by 1.9%), but is less firmly based on the relatively few subjects in the analysis (see Proposal 4).

Severity of symptoms

We examined whether cases and siblings show more ADHD symptoms when CP is also present, to see if ADHD + CP may be considered as a more severe disorder than ADHDonly. Differences in ADHD severity across diagnostic subgroups were calculated from the means of the 18 DSM-IV ADHDct symptom scores in the CP/TRS. They were entered into a MANOVA comparing all cases

Table 4. Results of the multinomial linear regression predicting presence/absence of ADHD, ADHD + CP or CP status in siblings from the status of combined-type ADHD cases with or without CP

Case status	Sibling status				Total
	No disorder	ADHDonly	ADHD + CP	CPonly	
ADHDonly (241*)	230 (86.1%)	20 (7.5%)	13 (4.9%)	4 (1.5%)	267
ADHD + CP (768)	848 (64.1%)	216 (16.3%)	215 (16.2%)	45 (3.4%)	1324
Relative risk ratio ¹ (95% CI)		2.93, $p < 0.001$ (1.7–5.0)	4.49, $p < 0.001$ (2.6–7.8)	3.05, $p < 0.034$ (1.1–8.5)	
Adjusted relative risk ratio ² (95% CI)		2.92, $p < 0.001$ (1.6–5.3)	4.93, $p < 0.001$ (2.6–9.4)	5.67, $p = 0.019$ (1.3–24.2)	
Total	1078 (67.8%)	236 (14.8%)	228 (14.3%)	49 (3.1%)	1591 (100%)
Pearson's Wald χ^2 (9) = 49.55, $Pr < 0.001$					

¹ RRR Relative risk ratio is computed as the ratio of risk in siblings of ADHDonly cases (as the comparison group) to those of ADHD + CP cases.

² Data adjusted for gender and parental SES Socio-Economic Status.

* Sample numbers are based on PACS diagnosis of ADHD with (ADHDonly) and without (ADHD + CP) CP scores based on CPRS and SDQ ratings.

Table 5. MANOVA comparing ratings of severity (T-scores) on the Conners' scales in subgroups of cases and siblings (means and standard deviations)

DSM-IV Combined type (Conners' ratings)	Cases			Siblings		
	ADHDonly	ADHD + CP	No disorder	ADHDonly	ADHD + CP	CPonly
Parent						
Mean	72.1	79.8	46.8	69.0	77.0	54.9
SD	11.0	8.9	6.8	9.8	9.2	5.5
Teacher						
Mean	68.9	70.0	52.0	61.4	65.0	56.2
SD	10.5	12.2	11.9	12.8	14.3	11.5
Multivariate Wilks lambda						
F	19.6			496.6		
df	33.0			10.0		
P	0.0001			0.0001		
η^2	0.114			0.454		

T-scores of >70 are 2 SD above the mean of 50.

(ADHDonly, ADHD + CP) and all siblings (no disorder, ADHDonly, ADHD + CP, CPonly: see Table 5).

The ADHD + CP subgroup showed the more severe symptom scores in both parent and teacher ratings, for both cases and siblings. The siblings with no disorder or CPonly were the least disturbed. Multivariate tests were highly significant between groups (cases: ADHDonly vs. ADHD + CP; siblings: no disorder, ADHDonly, ADHD + CP, CPonly) with effect sizes accounting for 11% and 45% of the differences, respectively.

Age comparisons

Analyses were repeated for cases and siblings 11 years and younger and those over 11 years, in order to examine whether the distinct comorbid ADHD + CP subtype is stable across the age span studied, or if an increasing prevalence is a feature of increasing age. There were overall fewer children older than 11 years for cases and siblings.

As above, parent and teacher ratings for the Conners DSM-IV ADHDct scale were entered into a MANOVA (cases with ADHDonly, or ADHD + CP, and siblings with no disorder, ADHDonly, ADHD + CP, or CPonly). The ADHD + CP cases showed more symptoms overall across the age span (except for teacher ratings of younger ADHDonly cases), and the older cases showed more symptoms than the younger ones (Table 6a). Both main effects (for age and CP) were significant, but accounted for only 2 and 5% of the variance, respectively. The interaction between age and CP was also significant, but accounted for only 0.5% of the variance.

A similar pattern emerged for the siblings (Table 6b). Siblings with ADHD + CP showed more symptoms in both parent and teacher ratings than the other conditions, regardless of age. Further, the symptom ratings were more severe

Table 6. (a) MANOVA comparing Conners' severity ratings (T-scores: DSM-IV ADHD combined type) for younger (≤ 11 y) and older subjects (> 11 y) in ADHDonly and ADHD + CP cases; (b) MANOVA comparing Conners' severity ratings (T-scores: DSM-IV ADHD combined type) for younger (≤ 11 y) and older subjects (> 11 y) in 4 groups of siblings (No disorder, ADHDonly, ADHD + CP, CPonly)

(a) Cases	Younger (≤ 11 y)		Older (> 11 y)	
	Conners (parent)	Conners (teacher)	Conners (parent)	Conners (teacher)
ADHDonly				
Mean	72.1	68.5	72.2	69.4
SD	9.4	9.2	13.3	12.4
ADHD + CP				
Mean	78.2	67.2	82.0	72.9
SD	8.5	11.0	9.1	12.8
Main effects	F	df	p	η^2
Age	14.2	2.0	0.0001	0.021
\pm CP	37.8	4.0	0.0001	0.054
Interaction	3.5	4.0	0.008	0.005
(b) Siblings	Younger (≤ 11 y)		Older (> 11 y)	
	Conners (parent)	Conners (teacher)	Conners (parent)	Conners (teacher)
No disorder				
Mean	47.4	51.0	45.9	53.4
SD	5.8	9.6	7.9	14.4
ADHDonly				
Mean	67.5	59.9	71.2	63.6
SD	9.7	10.8	9.5	15.1
ADHD + CP				
Mean	76.3	62.8	78.1	68.4
SD	8.9	13.8	9.6	14.4
CPonly				
Mean	55.5	54.6	54.1	58.2
SD	5.3	11.4	5.7	11.7
Main effects	F	df	p	η^2
Age	9.4	2.0	0.0001	0.011
Disorder	321.1	8.0	0.0001	0.438
Interaction	4.4	8.0	0.0001	0.011

for children older than 11 years. Both main effects (age and disorder) were significant, accounting for 1 and 43% of the variance, respectively. The interaction (age \times disorder) was small (1% explained variance), but significant.

Discussion

There are two key findings in this study. First, in a family with a case of ADHD with conduct problems (ADHD + CP) there was a nearly 5-fold increased risk of the sibling showing ADHD + CP over the likelihood of this status if the case was diagnosed with ADHD only. The recurrence of the risk for ADHD + CP in siblings suggests that ADHD + CP often has a prevalence consistent with co-segregation and may thus often constitute a distinct familial disorder (Proposal 2, Table 1). However, the evidence also suggests that this is not always so. The second finding shows that, if cases have CP along with a diagnosis of ADHD, then there is a nearly 3-fold increased likelihood that the ADHD part of their disturbance will also be shown by their siblings. This supports the widely reported high heritability for ADHD, and perhaps a genetic contribution to the etiology of ADHD (Proposal 3). The implication is that the ADHD + CP condition represents a more severe disturbance than ADHD alone.

Indeed, this ADHD + CP subtype manifested more severe symptoms of ADHD than those classified as having ADHD only or CP only. This characteristic is detected in both younger and older subjects, with a tendency towards a more marked expression in adolescents than in children. In other words, this feature of severity supports the distinction of ADHD + CP from other subtypes in both the younger and the older individuals. Thus, there is familial, and a certain degree of predictive validity for ADHD + CP as a distinct subtype.

The strength of these results is emphasized by the demonstration of the validity of the definition of CP based on parent and teacher ratings on two symptom assessment scales (Conners' scales and the SDQ) against the diagnosis of comorbid ODD and CD in ADHD cases resulting from the PACS.

However, there was a third less robust finding. There were comparatively few siblings of ADHD + CP cases who showed CP only. Nonetheless there was an increased risk of siblings showing CP only if the cases had ADHD + CP rather than ADHD only. The increased perception of CP in these siblings tentatively points to shared common risk factors that were likely to be of an environmental nature (Proposal 4). But, two features may be considered as potentially influencing this and the main result above. First,

the parent's perception and ratings of CP in the siblings may be "sensitized" by the severity of the ADHD + CP status of the case in the family. Second, this feature could be compounded by the number of families in which there were several siblings of the ADHD + CP case.

Psychometric validity

The CP construct used here has been validated against CD and ODD diagnostic categories based on PACS, a research diagnostic instrument. Biserial correlations confirmed strong associations between PACS ratings of ODD/CD and the oppositional rating scales used. Correlations also showed the expected concurrent and discriminant validity, as indicated by positive correlations for cases with ODD/CD and negative ones for cases with ADHD only. Discriminant analyses identified parental oppositional ratings for SDQ and CPRS as the best predictors of cases with and without ODD/CD according to PACS. Teacher ratings showed lower correlations and did not contribute as much to the discrimination of groups as the parent ratings. ROC-curves confirmed the high accuracy for both parental measures. Thus the psychometric properties of the CP construct defined here have been robustly tested and validated.

Support for the proposals and consistency with other findings

The findings help to reconcile in part the previously divergent research findings reported by family studies (Faraone et al. 1991; Faraone and Biederman 1997; Faraone et al. 2000a) and twin studies (Thapar et al. 2001; Vierikko et al. 2004). Both directions receive some support. Findings from family studies (Faraone et al. 1991; Faraone and Biederman 1997; Faraone et al. 2000) largely support the co-segregation of ADHD + CP amongst relatives, and that this subtype is a distinct familial condition (Proposal 2). Twin studies (Thapar et al. 2001; Vierikko et al. 2004) on the other hand support the model that ADHD and CP share common underlying genetic and environmental influences; and that the ADHD + CP subtype merely represents a severe variant of a continuous ADHD trait with a corresponding genetic loading (Proposal 3). It is therefore not a distinct disorder. We show an increased risk for both etiologies, although the relative risk for the former is much higher.

Certainly, "ADHD + CP" is often a distinct familial disorder characterized by severe symptoms that maintain the differentiation from other groups across the 5–17 year age-span studied. There is familial, concurrent and predictive

validity in the postulate of “ADHD + CP” being a distinct condition. The findings therefore combine and reconcile Proposals 2 and 3 in so far as: ADHD + CP can be a distinct familial subtype, and is then characterized by more severe ADHD symptoms. Similarly in a recent study of 457 adolescents with and without ADHD, Hurtig et al. (2007) reported that those with comorbid CD and ODD showed more ADHD symptoms than others with ADHDonly. Our finding milder and more severe variants of ADHDct cases concurs with others from Latent Class Analyses, which have consistently identified distinctive “moderate-ADHDct” and “severe-ADHDct” subtypes across twin samples in the USA, (Todd et al. 2002), Brazil (Rohde et al. 2001) and Australia (Rasmussen et al. 2002). However, Latent Class Analysis has not so far identified severe-ADHDct associated with ODD or CD (Volk et al. 2006), although the canonical correlation analysis by Mathias et al. (2007) described an association of impulsive-conduct problems with inattentive and hyperactive components of ADHD and that impulsivity was the common construct underlying ADHD and CD.

Overall, cases and siblings with ADHD + CP showed more severe hyperactivity, impulsivity, and inattention on the Conners DSM-IV ADHDct scale (both parent and teacher ratings) compared to those with ADHDonly, CPonly, or no disorder. The severity of these symptoms increased in cases and siblings older than 11 years of age compared to the younger participants. These results are in accord with Nock et al. (2006) who also reported more severe symptoms for children with ADHD and CD who were older than 11 years. These findings thus also agree with studies proposing that ADHD + CP is a more severe disorder, distinct from ADHDonly (Faraone et al. 1991, 1997, 2000a; Thapar et al. 2001). Recently this could also be shown for adults with ADHD with and without ODD (Gadow et al. 2007).

Against our predictions, our findings offer some support for the DSM-IV nosological paradigm that ADHD + CP represents an over-lap of two independent conditions for ADHD and CP. But this overlap would be more embodied in Proposal 4, which emphasizes shared environmental risk factors, than in Proposal 1 that suggests co-occurrence by chance. But the findings are based on too few subjects to test reliably the shared “toxic environment” hypothesis (exemplified by Proposal 4: Taylor et al. 1991; Drabick et al. 2006). However, the implication is that a shared exposure to the same pathogenic features of the environment could be a contributor in some instances, for there were increased rates of all 3 disturbances assessed in the siblings of cases with ADHD + CP.

Levy et al. (2006) identified heterogeneity of CD in their Australian twin study. Their analysis decomposed CD into three categories: that is, those expressing mild, moderate and severe symptoms (see introduction). On their ACE analysis severe CD had a very high common environment factor, and a negligible effect of heritability: (i.e. growing-up in the same family has a strong influence on the development of extreme CD, but far less on the appearance of ADHD or milder forms of CD). Further, extreme CD (compared to mild or moderate CD) was much less correlated with the expression of the main domains of ADHD and seemed distinct from mild and moderate CD. Importantly, they reported that milder conduct problems (CP) are more likely to be comorbid with ADHD (and have a common biological etiology). This scheme is broadly compatible with the present results. The construct of ADHD + CP bears resemblance to the milder form of CD defined by Levy et al. and is here more closely associated with ADHD. However, the present data do not allow a meaningful analysis of variants of CP stratified by severity.

Molecular genetic studies have started to identify contributions to a potential genetic etiology of ADHD + CP as implicated by specific risk alleles associated with the comorbid variant. Kirley et al. (2004) observed significant association between DRD4 7-repeat allele transmission and ADHD children with comorbid ODD. The DRD4 7-repeat allele was also significantly associated with positive family history of ADHD. Rowe et al. (1998) found that paternal DRD4 7-repeat risk allele was closely associated with the ADHD and conduct symptoms, while the maternal DAT1 10/10 repeat risk allele associated with inattention symptoms (Rowe et al. 1998; Kirley et al. 2004). Further genetic analyses of this nature are in progress with the IMAGE sample and will help elucidate the molecular basis for the risk of transmission.

Limitations to the study

There are several limitations to this study. First, no independent healthy controls were recruited. Therefore statements of risk for ADHD and CP symptoms among siblings relate not to the population at large, but are relative between cases of ADHD with and without CP. Secondly, PACS data were not available for the all siblings. Original recruitment instructions required a sibling without a diagnosis of ADHD, and therefore PACS was ascertained only for persons where there were clinical reasons to doubt the absence of the condition. Thus, the classification of sibling groups could only be based on information derived from questionnaire data. However, validity and psychometric

properties of the scales used have been well validated (e.g., Goodman 1997; Conners et al. 1998a; Kunsti and Stevenson 2001; Woerner et al. 2004). Thus misclassification due to false information is unlikely to provide a substantial bias to the results. It could be argued that the significant difference in size between the correlations for parent and teacher ratings with PACS assessments (Table 3) undermines the reliability of the CP designation. However, we note first that correlations from both information sources were highly significant ($p < 0.0001$), and second that correlations for parent Conners and SDQ ratings with PACS scores would likely be higher as parents were also the information source for the PACS assessments. Thirdly, this does not represent a meaningful bias as the correlations were highly significant between both the parent and teacher ratings of Conners' oppositional ($r = 0.21$, $p < 0.01$, 2-tail) and those for SDQ oppositional features ($r = 0.33$, $p < 0.01$).

The number of siblings in the logistic regression varied considerably and the procedure would have benefited from data from independent controls. However, as there were large numbers for the groups central to the analysis, the multivariate procedures used were adequate. Nevertheless, future studies should confirm our findings in larger and more balanced samples. In the current sample, male cases with ADHD outnumbered females, whereas the gender ratio was almost equal for siblings of cases. Since ADHD and ADHD + CP affect more boys than girls, the results on ADHD + CP could also reflect a general gender bias. However, this seems unlikely for an increased representation of female siblings would not favor the high proportion of ADHD + CP siblings recorded.

A developmental question arises over the predictive validity of ADHD + CP as a distinct subtype. CD itself does not necessarily persist in older cohorts. Longitudinal data will be needed to demonstrate conclusively if there is a similar pattern for ADHD + CP, and whether ADHD and CP are distinct components or multiple explanations are required for the developmental course of separate and combined phenocopies. Further, this issue overlaps with an increasing awareness of pleiotropic effects. We have already noted above that there may be a common genetic influence on hyperactivity and CP in a twin study (Silberg et al. 1996). Recently, Jain et al. (2007) provided evidence in a linkage analysis for a common inheritance pattern for the cosegregation of ADHD with disruptive behaviors. While such evidence for pleiotropy supports evidence presented here for a distinct ADHD + CP subtype the role of maturation in the expression of a gene or of several genes will only be resolved with longitudinal data.

Lastly we should mention that a potential limit of the current study lies with the possibility for bias in the ascertainment of cases. The research protocol of the IMAGE project was strict and complex. The informed consent procedures required parents reading extensive written information. This may have incurred lower participation rates by families with social disadvantage and a higher problem burden, such as having children with ADHD and CP. Related to this, the requirement for the availability of the biological parents in the IMAGE study may also have reduced the proportion of families participating from disadvantaged backgrounds.

Thus future work should focus on ADHD and CD/ODD as defined by DSM-IV and ICD-10 with regard to the nature of recruitment and referral (Smith and Taylor 2006), the environment in which the children are raised (e.g., rural vs. urban: Goodman and Stevenson 1989), take account of the apparent gender differences that will also influence outcome (Kratzer and Hodgins 1997) and relate the results to an independent age-matched control or comparison group.

Conclusions

The results support the frequent occurrence of ADHD + CP as a distinct disorder, based on the nearly 5-fold increased risk of recurrence in siblings of the same "comorbid" disturbance compared to the appearance of ADHD + CP symptoms in siblings of cases with ADHD only. However, a 2- to 3-fold increased relative risk for the ADHD or CP components to appear separately in siblings of ADHD + CP cases suggests both that ADHD + CP can also be a more severe variant of the ADHD diagnosis and that the environment can exert an influence on the development of the condition. These conclusions are supported by ratings of the increased severity of symptoms expressed in youngsters with ADHD + CP compared to ADHD only, and the relative stability of this expression, with symptoms becoming moderately more severe with age.

Nonetheless the evidence that for some families there is an increased risk of prevalence for ADHD in siblings of cases with ADHD + CP supports the DSM-IV view of the disturbances representing variants of a single disorder. In contrast, for other families the familial nature and predictive validity of ADHD + CP support the maintenance of this entity in the ICD-10 category of hyperkinetic conduct disorder (F90.1). But, this ICD-10 category explicitly refers to CD, a more severe form of CP and not ODD. In our and other studies ADHD + CP resembles a slightly different category with the milder symptoms of CP more closely related to ODD. As neither DSM-IV nor ICD-10 recog-

nizes this nosological entity, the placement of this category along the dimension of oppositional behavior remains a topic for further study.

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