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Impulsive Aggression in Attention-Deficit/Hyperactivity Disorder: Symptom Severity, Co-Morbidity, and Attention-Deficit/Hyperactivity Disorder Subtype

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Abstract

Objective: The aim of this study was to characterize aggression and its relationship to psychiatric co-morbidity, attention-deficit/hyperactivity disorder (ADHD) subtype, and ADHD symptom severity in clinically referred ADHD youngsters. We also wanted to ascertain whether reactive and impulsive aggression is more prevalent than proactive aggression in an ADHD sample.

Method: Consecutively referred ADHD children and adolescents ($n = 268$) and community controls ($n = 100$) were assessed systematically regarding demographics, psychiatric diagnosis, overt aggression severity, proactive and reactive aggression severity, and ADHD symptom severity using correlational analysis and analysis of covariance (ANCOVA).

Results: Across all aggression measures, ADHD children were more aggressive than community controls. ADHD children with nonanxiety co-morbid disorders were more aggressive than ADHD children without such co-morbidity. The number of co-morbid psychiatric diagnoses and ADHD symptom severity were significantly associated with aggression. ADHD youngsters demonstrated significantly more reactive than proactive forms of aggression across all co-morbid diagnoses.

Conclusions: Aggression is common in clinically referred ADHD youngsters and should be identified as a legitimate target for psychopharmacological treatment in children and adolescents with moderate to severe ADHD and nonanxiety co-morbid diagnostic disorders.

Introduction

Recent expert consensus supports the study of aggression separately from conduct disorder (CD) in well-defined patient groups within well-established psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) (Jensen et al. 2007). Aggression is common and important but not well studied in clinical samples of ADHD youngsters (Pliszka 2009). For example, in the Multimodal Treatment Study of Children with ADHD (MTA Cooperative Group 1999), 267 of the original sample of 579 children (46%) exhibited clinically significant aggression and 44% of these 267 children remained aggressive despite treatment (Jensen et al. 2007). Although not a criterion for the diagnosis of ADHD, aggression is an important variable in determining psychopharmacological treatment of ADHD youngsters. For example, in seeking ADHD treatment, child aggression may drive treatment referral (Connor and Doerfler 2008) and/or influence the decision to initiate or increase medication dose in children receiving medications (Jensen et al. 2007; Connor and Doerfler 2008). Severe aggression in the context of ADHD increases the likelihood that more than one medication may be combined concurrently in treatment, including mood stabilizers, alpha agonists, and/or atypical antipsychotics (Connor et al. 1998; Pliszka et al. 2006). Given the influence of aggression in ADHD treatment, a better understanding of the characteristics of aggression in ADHD children is important.

An emerging literature in the psychopharmacology of aggression distinguishes between reactive aggression (impulsive, defensive, high affective valence), also called impulsive aggression (IA), and proactive aggression, also called instrumental aggression (low arousal, planned, premeditated) (Connor 2002). Although these forms of aggression remain nascent in their specific meanings and correlates, a clinical consensus is emerging that reactive (IA) aggression may be most responsive to psychopharmacological interventions (Vitiello and Stoff 1997; Steiner et al. 2003; Connor et al. 2004; Pappadopulos et al. 2006; Jensen et al. 2007). As such, it is important to understand better the type of aggression most highly associated with specific disorders such as ADHD (Jensen et al. 2007).

Additional variables to better understand aggression in ADHD are important to consider. For example, given the high rates of psychiatric co-morbidity in clinically referred ADHD children, it is important to investigate the relationship between psychiatric co-morbidity and the total number of psychiatric diagnoses and aggression in ADHD samples. Additionally, questions remain about the relationship between the different subtypes of ADHD (e.g.,

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combined, inattentive, hyperactive) and about the relationship in psychiatrically referred children with impairing symptoms of inattention, hyperactivity, and/or impulsivity that do not meet full criteria for the diagnosis of ADHD, which are referred to here as the inattentive or hyperactive-impulsive (IHI) problems group), and different aspects of aggressive behavior in clinical ADHD samples. For example, studies report an association between aggression and the specific ADHD symptom domain of hyperactive-impulsivity (Taylor et al. 1996). Other studies support a relationship between ADHD total symptom severity and aggression and conduct problems (Connor and Doerfler 2008) Thus, it is important to investigate ADHD symptoms and subtypes and relationships with aggression in clinical samples.

Given the importance of aggression in ADHD psychopharmacological treatment planning, we sought to understand aggression better in a clinically referred ADHD sample. We investigated how diagnostic co-morbidity, ADHD subtype, and ADHD symptom severity influence risk for aggression in a clinically referred ADHD sample of children and adolescents. Specific aims of our study were to: (1) Assess the relationship between the number of co-morbid diagnoses and aggression in a clinically referred sample of ADHD children and adolescents; (2) assess the association between specific types of co-morbid disorders, including CD, oppositional defiant disorder (ODD), bipolar disorder (BD), depression, and anxiety disorders with aggression in a clinically referred sample of ADHD children and adolescents; (3) assess the relationship between the different subtypes of ADHD, and aggression in a clinically referred sample of ADHD children and adolescents compared with community controls; (4) assess the relationship between overall ADHD symptom severity and aggression in the sample; and (5) ascertain the type of aggression (reactive or IA versus proactive aggression) most prevalent in our ADHD sample.

Methods

Participants

ADHD children and adolescents ($n = 268$) were consecutively referred to the outpatient child and adolescent psychiatry clinic at a teaching hospital. All participants met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) diagnostic criteria for ADHD at evaluation. ADHD subtypes included combined, inattentive, and hyperactive-impulsive. An IHI Problems group was included because ADHD symptoms in children not meeting full ADHD criteria are associated with meaningful impairment, including high rates of stimulant use (Leslie et al. 2005), and association with serious psychopathology, including juvenile bipolar spectrum disorders (Leibenluft et al. 2003; Galanter and Leibenluft 2008). The inclusion of the IHI problems group increases the ecological validity of the sample as many referred youngsters with non-ADHD diagnoses may have IHI problems and symptoms that cause significant impairment (Barkley 1997). To assess whether aggression scores were elevated across psychiatric diagnoses in referred children, we compared proactive, reactive, and overt scores with scores obtained from 100 nonreferred children and adolescents from the community. Control children were recruited by advertisement and word of mouth and paid a $100 stipend for participation. Children with major sensorimotor handicaps (i.e., blindness, deafness, paralysis), mental retardation, schizophrenia, and unstable medical or neurological conditions were excluded from the study.

The institutional review boards at the University of Massachusetts Medical School and the University of Connecticut Medical School approved this study. Informed consent for evaluation and participation was obtained from the participant's parent/guardian and assent from all children less than 14 years old. Older adolescents gave informed consent.

Procedures

Children and adolescents were systematically evaluated at clinical intake. Parents were interviewed by child and adolescent psychiatrists using a reliable and valid semistructured diagnostic interview. A master's degree-level nurse clinician with a specialty degree in child mental health clinically interviewed all children. Children and caregivers completed diagnostic interviews and rating scale measures about the child. All data on each child were reviewed in a team meeting. Diagnoses were assigned using a best estimate procedure (Leckman et al. 1982) and met DSM-IV diagnostic criteria.

Assessment and measures

DSM-IV diagnoses were based on the following assessments: (1) A structured diagnostic interview obtained through caregiver report using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–epidemiologic version 5 (K-SADS) (Orvaschel 1995), (2) a semistructured clinical assessment of the child, and (3) parent-completed rating scales. Previous research has demonstrated that caregiver report of childhood psychopathology shows excellent accuracy, specificity, reliability, and validity for ADHD, ODD, CD, depression, BD, and anxiety disorders (Faraone et al. 1995). Diagnoses were only considered positive if full DSM-IV symptom criteria were met and associated with clinically meaningful impairment in the child's daily functioning. Five board-certified or board-eligible child and adolescent psychiatrists completed all interviews. Interviewers were blind to study aims and hypotheses. Interrater reliability for diagnosis was assessed by the kappa (κ) statistic (Cohen 1960) in a subsample of 53 children by two child psychiatrists. Interrater reliability was as follows: ADHD ($\kappa = 0.85$), CD ($\kappa = 1.0$), ODD ($\kappa = 1.0$), separation anxiety disorder (SAD) ($\kappa = 0.92$), panic ($\kappa = 0.89$), social phobia ($\kappa = 0.85$), generalized anxiety disorder (GAD) ($\kappa = 0.88$), depression ($\kappa = 0.84$), and BD ($\kappa = 0.79$). The interrater reliability for all diagnoses was $\kappa = 0.87$. We followed the DSM-IV exclusion rules stating that in the presence of conduct disorder, ODD is not diagnosed. Because the anxiety disorders encompass many different syndromes and to increase statistical power, we used the designation of multiple anxiety disorders consisting of two or more anxiety disorders to define a severe anxiety syndrome (Greene et al. 2002).

Two rating scales assessed overt aggression. We used T-scores from the parent completed Child Behavior Checklist (CBCL) aggression subscale (Achenbach 1991), and total scores from the parent completed Modified Overt Aggression Scale (MOAS) (Kay et al. 1988). The items in the CBCL aggressive behavior scale include argues, brags, cruelty to others, demands a lot of attention, destroys own and others property, disobedient at home and at school, jealous, gets in many fights, physically attacks people, screams, shows off, stubborn, sudden changes in mood, talks too much, teases a lot, temper tantrums, threatens people, and is unusually loud. The MOAS assesses the frequency and intensity of verbal threats, explosive property destruction, self-injurious behavior, and physical assault over the week previous to evaluation. A total MOAS score was calculated (maximum score = 240).

Aggression motivation, assessed as either proactive or reactive (IA) aggression, was assessed using the proactive/reactive

aggression rating scale (Dodge and Coie 1987; Dodge 1991), which was completed by parents. Although proactive and reactive aggression are correlated, confirmatory factor analysis has shown that a two-factor model better fits the data than a single-factor model (Polman et al. 2007), suggesting overlapping yet distinct constructs. Studies have shown differential correlates of reactive and proactive aggression in elementary school children (Dodge and Coie 1987), in adolescent boys (Raine et al. 2006), and in seriously emotionally disturbed youngsters (Connor et al. 2004), supporting their distinctiveness. The proactive/reactive rating scale consists of three questions assessing reactive aggression and three questions assessing proactive aggression. The respondent can use a 1- to 5-point scale, ranging from never to almost always to indicate how frequently a question applies to an individual child. The proactive/reactive aggression scale demonstrates adequate reliability and validity in children and adolescents (Coie et al. 1991; Collett et al. 2003).

ADHD symptom severity was assessed using the ADHD Rating Scale IV (ADHD-RS-IV) (DuPaul et al. 1998). The ADHD-RS-IV is reliable and valid and lists the 18 ADHD symptoms from DSM-IV, is scored on a 0 to 3 scale (total possible score = 54), and was completed by parents.

Socioeconomic status was assessed by self-reported parent income. Average yearly family income was categorically coded as: (1) <$10,000, (2) between $10,000 and $19,999, (3) between $20,000 and $29,999, (4) between $30,000 and $39,999, (5) between $40,000 and $49,999, (6) between $50,000 and $75,000, and (7) >$75,000. Child age and gender were assessed by clinical interview.

Data analysis

Statistical analyses were conducted using SPSS version 15.0 (SPSS Inc., Chicago IL). Descriptive statistics, including demographics and psychiatric diagnoses, were generated for the study sample. One-way analysis of variance (ANOVA) tests assessed ADHD subtype and control group differences for continuous variables, whereas chi-squared tests were used for discrete variables. The Brown–Forsythe statistic was reported for those continuous variables violating the homogeneity of variance assumption. The probability value of $p < 0.05$ was used to determine statistical significance.

Analyses using only ADHD children and adolescents ($n = 268$) were conducted to determine the relationship of co-morbid psychiatric disorders with ADHD to the four aggression measures. The Pearson correlation (r) evaluated associations between the number of co-morbid diagnoses for each ADHD child and proactive, reactive, and overt aggression scores. The relationship of specific co-morbid diagnoses (i.e., CD, ODD, BD, depressive disorder, and anxiety disorder) to aggression in the ADHD sample was also assessed. Independent t-tests compared individuals with ADHD and a co-morbid diagnosis to ADHD subjects without the co-morbid disorder on aggression measures. The false discovery rate (FDR) procedure evaluated statistical significance for each t-test, controlling the Type I error rate for the multiple tests performed (Benjamini and Hochberg 1995).

Statistical tests were conducted to evaluate differences in aggression between control participants and ADHD subjects by ADHD subtype (combined, inattentive, hyperactive/impulsive, and IHI problems group). One-way analysis of covariance (ANCOVA) tested the effect of control and ADHD subtype group membership on overt, proactive, and reactive aggression measures. A series of models for each measure of aggression was tested. Age and household income were entered as covariates in all models tested; differences across the five groups were identified in preliminary tests. Gender was not controlled for in these analyses because no differences in gender were found across the five groups (see Table 1). CD, ODD, BD, depressive disorder, and anxiety disorder with ADHD were controlled for individually in each model. That is, all models tested control and ADHD subtype group differences in aggression after adjustment for covariates (i.e., age, household income, and one co-morbid psychiatric disorder). *Post hoc* comparisons were conducted by the Sidak t-test, comparing all possible group pairs on the adjusted means of aggression. The FDR was again used to control for Type I error inflation in testing statistical significance.

Additional analyses with ADHD subjects ($n = 268$) evaluated the relationship of ADHD severity to aggression, as well as compared proactive and reactive measures of aggression. Pearson correlations (r) associated ADHD symptom severity with overt, proactive, and reactive aggression measures. The paired t-test was used to examine mean differences between proactive and reactive aggression scores.

Results

This study includes 268 clinically referred ADHD youngsters and 100 community controls. Table 1 provides descriptive characteristics and psychiatric diagnoses for control and ADHD children. A total of 155 children were diagnosed with ADHD combined subtype (120 male, M age = 9.61, standard deviation [SD] = 2.87 years), 65 with ADHD inattentive subtype (41 male, M age = 11.94, SD = 2.89 years), 18 with ADHD hyperactive/impulsive subtype (16 male, M age 7.83, SD = 3.82 years), and 30 with IHI ADHD problems (20 male, M age 12.10, SD = 3.57 years). Nine community control subjects (9%) met criteria for ADHD. The IHI problems group was heterogeneous, consisting of children with ADHD symptoms not meeting full diagnostic criteria, subsyndromal ADHD and subsyndromal BD not otherwise specified (NOS) ($n = 4$), and those who fulfilled all ADHD criteria except age-of-onset criteria. ADHD subtype and control groups differed on age and household income at $p < 0.05$. The control and IHI ADHD problems groups were older, whereas the hyperactive impulsive group was younger. The ADHD inattentive group had the highest median household income and contained more females.

ADHD, co-morbidity, and aggression

Of 268 ADHD participants, 255 (95%) also met diagnostic criteria for at least one other psychiatric disorder in addition to ADHD, including CD ($n = 59$), ODD ($n = 161$), BD ($n = 22$), depression ($n = 123$), and anxiety ($n = 202$). Most ADHD participants were diagnosed with more than one co-morbid disorder; therefore, the frequency of co-morbid disorders exceeds 100%. For example, 23.9% of participants carried one co-morbid diagnosis, 33.2% participants carried two co-morbid diagnoses, and 38.0% carried three or more co-morbid diagnoses. Rates of psychiatric co-morbidity were higher in all ADHD groups compared to community controls ($p < 0.05$; see Table 1).

Pearson correlations were used to correlate the number of co-morbid psychiatric diagnoses for each subject and our four aggression measures. For ADHD participants ($n = 268$), the total number of co-morbid disorders carried by each subject showed positive correlations ($p < 0.001$) with aggression, including CBCL

Table 1. Descriptive Characteristics and Psychiatric Diagnoses by ADHD and Control Groups ($N = 368$)

Variable	*ADHD Combined* (n = *155*)	*ADHD Inattentive* (n = *65*)	*ADHD Hyperactive* (n = *18*)	*IHI Problems* (n = *30*)	*Control*[a] (n = *100*)	*Statistic (df)*	p *value*
Gender (% male)	77.3	63.1	88.9	66.7	78.0	$\chi 2(4) = 8.69$	0.069
Ethnicity (% Caucasian)	90.3	90.8	100.0	96.7	93.9	$\chi^2(16) = 17.18$	0.374
Age (years)	9.61 (2.87)	11.94 (2.89)	7.83 (3.82)	12.10 (3.57)	12.27 (3.26)	$F(4,362) = 18.96$	<0.001
Median household income	$50,000–75,000	>$75,000	$50,000–75,000	$50,000–75,000	$50,000–75,000	$F(4,360) = 4.14$	0.004
CD	34.2	4.6	5.6	6.7	1.0	$\chi^2(4) = 63.59$	<0.001
ODD	60.6	63.1	66.7	46.7	10.0	$\chi^2(4) = 76.15$	<0.001
Bipolar disorder	9.0	4.6	5.6	13.3	0.0	$\chi^2(4) = 12.04$	0.017
Depressive disorder	45.8	50.8	22.2	50.0	9.0	$\chi^2(4) = 17.18$	<0.001
Anxiety disorder	73.5	84.6	66.7	70.0	21.0	$\chi^2(4) = 93.65$	<0.001

Values denote means (standard deviations) unless otherwise indicated. The Brown–Forsythe statistic was reported for median household income. Psychiatric diagnoses are reported as the proportion (%) of subjects with a positive diagnosis.

[a]9% of community controls met criteria for ADHD.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; df = degrees of freedom; CD = conduct disorder; ODD = oppositional defiant disorder.

overt aggression ($r = 0.42$), MOAS overt aggression ($r = 0.31$), proactive aggression ($r = 0.35$), and reactive aggression ($r = 0.40$).

Separate ANCOVAs were conducted to compare ADHD subjects with a specific diagnostic co-morbid condition (CD, ODD, BD, depression, or anxiety disorder) with ADHD subjects who did not have that specific co-morbid disorder, while controlling for age and family income. The FDR procedure was used to control for Type 1 error inflation in testing statistical significance. These results are presented in Table 2 (for externalizing disorders) and Table 3 (for internalizing disorders). For example, Table 2 shows that in the sample there were 209 ADHD children without co-morbid CD and 59 ADHD children with co-morbid CD. Results show significant differences on all four aggression measures comparing these two groups of ADHD children. Results are presented in similar fashion for ADHD children with/without ODD, BD, depression, and anxiety disorder (see Tables 2 and 3). Results show that ADHD subjects diagnosed with CD and BD showed significantly higher mean scores compared to ADHD subjects without these diagnoses on all four aggression measures ($p < 0.05$; Table 2). Other co-morbidities in combination with ADHD varied in their relationship with aggression. ADHD subjects with ODD showed higher mean scores only on CBCL overt aggression and reactive aggression ($p < 0.05$), whereas ADHD subjects with depressive disorder showed higher means on CBCL overt, proactive, and reactive aggression ($p < 0.05$). Conversely, ADHD subjects with anxiety disorder showed no mean differences on aggression compared with ADHD subjects without co-morbid anxiety (Table 3).

ADHD subtype and aggression

ANCOVA compared ADHD subtype and control subjects on the four measures of aggression, while controlling for co-morbidity, age and family income (Table 4). Statistically significant differ-

Table 2. Externalizing Disorder Co-Morbidity and Aggression among ADHD Children and Adolescents ($N = 268$)

Variable	ADHD, no co-morbid condition	*ADHD + co-morbid condition*	t-*test (df)*	p
	ADHD, no CD (n = *209*)	*ADHD + CD* (n = *59*)		
Overt aggression (CBCL)	64.29 (10.16)	77.05 (10.88)	$t(258) = -8.35$	<0.001
Overt aggression (MOAS)[a]	27.62 (27.25)	61.06 (40.76)	$t(66) = -5.63$	<0.001
Proactive aggression[a]	1.38 (0.60)	2.40 (1.08)	$t(62) = -6.62$	<0.001
Reactive aggression[a]	2.83 (1.18)	3.86 (0.82)	$t(120) = -7.25$	<0.001
	ADHD, no ODD (n = *107*)	*ADHD + ODD* (n = *161*)		
Overt aggression (CBCL)[a]	65.13 (13.34)	68.54 (10.15)	$t(178) = -2.33$	0.029
Overt aggression (MOAS)	30.84 (36.07)	37.71 (31.90)	$t(237) = -1.54$	0.125
Proactive aggression	1.57 (0.95)	1.62 (0.78)	$t(237) = -0.50$	0.620
Reactive aggression	2.84 (1.25)	3.20 (1.13)	$t(237) = -2.27$	0.024

Values denote means (standard deviations). The false discovery rate (FDR) procedure was used to control for Type 1 error inflation in testing statistical significance.

[a]*t*-test calculated assuming unequal variability between groups.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; CD = conduct disorder; CBCL = Child Behavior Checklist; MOAS = Modified Overt Aggression Scale; ODD = oppositional defiant disorder.

Table 3. Internalizing Disorder Co-Morbidity and Aggression among ADHD Children and Adolescents ($N = 268$)

Variable	*ADHD, no co-morbid condition*	*ADHD + co-morbid condition*	t-*test (df)*[a]	p
	ADHD, no BD (n = *246)*	*ADHD + BD* (n = *22)*		
Overt aggression (CBCL)	66.50 (11.32)	74.59 (12.45)	$t(258) = -3.18$	0.002
Overt aggression (MOAS)	33.58 (33.12)	50.90 (36.42)	$t(237) = -2.22$	0.027
Proactive aggression	1.56 (0.82)	2.05 (1.07)	$t(237) = -2.47$	0.014
Reactive aggression	2.99 (1.18)	3.80 (1.06)	$t(237) = -2.94$	0.004
	ADHD, no Dep *(n = 145)*	ADHD + Dep (*n* = 123)		
Overt aggression (CBCL)	65.32 (11.62)	69.39 (11.27)	$t(258) = -2.86$	0.005
Overt aggression (MOAS)	32.46 (33.75)	37.85 (33.51)	$t(237) = -1.34$	0.217
Proactive aggression	1.48 (0.77)	1.74 (0.91)	$t(237) = -2.39$	0.018
Reactive aggression	2.79 (1.15)	3.35 (1.17)	$t(237) = -3.74$	<0.001
	ADHD, no anxiety disorder (n = *66)*	*ADHD + anxiety disorder* (n = *202)*		
Overt aggression (CBCL)	66.13 (12.85)	67.53 (11.20)	$t(258) = -0.84$	.402
Overt aggression (MOAS)	32.77 (28.61)	35.82 (35.32)	$t(237) = -0.61$	.540
Proactive aggression	1.55 (0.87)	1.62 (0.84)	$t(237) = -0.57$	.568
Reactive aggression	2.95 (1.10)	3.10 (1.22)	$t(237) = -0.88$	.378

Values denote means (standard deviations). The false discovery rate (FDR) procedure was used to control for Type 1 error inflation in testing statistical significance.

[a]*t*-test calculated assuming unequal variability between groups.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; df = degrees of freedom; BD = bipolar disorder; CBCL = Child Behavior Checklist; MOAS = Modified Overt Aggression Scale; Dep = depression.

ences (all $p < 0.05$) between ADHD subtypes and community controls were identified for all measures of aggression. For overt aggression measured by the CBCL, adjusted mean aggression scores were significantly higher ($p < 0.05$) for all ADHD subtypes compared to controls, with the combined subtype showing the highest adjusted mean scores across ADHD and control groups. The effect sizes of ADHD subtypes on measures of overt aggression as assessed by the parent report CBCL were small to moderate (Table 4). The combined subtype also displayed higher adjusted mean scores than other groups for proactive and reactive

Table 4. Analysis of Covariance for Aggression Measures by ADHD and Control Groups

Variable	*Co-morbidity covariate*	*ADHD Combined* (n = *154)*	*ADHD Inattentive* (n = *65)*	*ADHD Hyperactive* (n = *18)*	*IHI problems* (*n* = *30)*	*Control* (n = *100)*	*F test (df)*[a]	*p*	*Effect size*
CBCL aggression	CD	68.85 (0.80)[a]	63.71 (1.15)[a]	64.79 (2.26)[a]	61.61 (1.75)[a]	53.95 (0.95)	F(4,349) = 32.61	<0.001	0.272
	ODD	70.15 (0.81)[a]	61.80 (1.22)[a]	63.40 (2.39)[a]	60.13 (1.83)[a]	53.82 (1.06)	F(4,349) = 34.19	<0.001	0.282
	BD	70.51 (0.80)[a]	62.63 (1.20)[a]	64.00 (2.39)[a]	59.69 (1.84)[a]	52.77 (0.98)	F(4,349) = 46.12	<0.001	0.346
	DD	70.28 (0.81)[a]	62.06 (1.21)[a]	64.26 (2.39)[a]	59.98 (1.84)[a]	53.35 (1.03)	F(4,349) = 37.89	<0.001	0.303
	AD	70.58 (0.82)[a]	62.18 (1.26)[a]	64.13 (2.42)[a]	60.03 (1.86)[a]	52.83 (1.09)	F(4,349) = 38.57	<0.001	0.307
MOAS aggression	CD	34.97 (2.35)[a]	28.71 (3.44)[a]	44.56 (6.66)[a]	19.20 (5.51)	12.77 (2.70)	F(4,328) = 10.75	<0.001	0.116
	ODD	38.95 (2.44)[a]	24.75 (3.67)[a]	41.11 (7.12)[a]	14.35 (5.82)	10.95 (3.05)	F(4,328) = 12.68	<0.001	0.134
	BD	39.57 (2.38)[a]	25.87 (3.63)[a]	42.41 (7.07)[a]	14.42 (5.81)	9.21 (2.81)	F(4,328) = 17.32	<0.001	0.174
	DD	39.25 (2.40)[a]	24.60 (3.67)[a]	42.99 (7.07)[a]	13.45 (5.83)	10.53 (2.96)	F(4,328) = 14.95	<0.001	0.154
	AD	39.87 (2.42)[a]	25.06 (3.79)[a]	42.76 (7.11)[a]	14.32 (5.86)	9.23 (3.08)	F(4,328) = 15.56	<0.001	0.159
Proactive aggression	CD	1.60 (0.06)[a]	1.51 (0.09)	1.46 (0.17)	1.34 (0.14)	1.30 (0.07)	F(4,328) = 2.69	0.031	0.032
	ODD	1.75 (0.06)[a]	1.41 (0.10)	1.39 (0.19)	1.20 (0.15)	1.19 (0.08)	F(4,328) = 7.64	<0.001	0.085
	BD	1.75 (0.06)[a]	1.42 (0.09)	1.40 (0.19)	1.20 (0.15)	1.18 (0.07)	F(4,328) = 8.75	<0.001	0.096
	DD	1.73 (0.06)[a]	1.38 (0.10)	1.42 (0.18)	1.17 (0.15)	1.24 (0.08)	F(4,328) = 7.16	<0.001	0.080
	AD	1.76 (0.06)[a]	1.42 (0.10)	1.14 (0.19)	1.20 (0.15)	1.17 (0.08)	F(4,328) = 8.50	<0.001	0.094
Reactive aggression	CD	3.10 (0.10)[a]	2.94 (0.14)[a]	2.88 (0.27)	2.52 (0.22)	2.19 (0.11)	F(4,328) = 9.79	<0.001	0.107
	ODD	3.17 (0.10)[a]	2.79 (0.14)[a]	2.72 (0.28)	2.37 (0.23)	2.24 (0.12)	F(4,328) = 8.95	<0.001	0.098
	BD	3.22 (0.09)[a]	2.86 (0.14)[a]	2.81 (0.28)	2.38 (0.23)	2.11 (0.11)	F(4,328) = 14.73	<0.001	0.152
	DD	3.17 (0.09)[a]	2.75 (0.14)	2.85 (0.27)	2.29 (0.22)	2.26 (0.11)	F(4,328) = 9.95	<0.001	0.108
	AD	3.23 (0.10)[a]	2.82 (0.15)[a]	2.83 (0.28)	2.37 (0.23)	2.12 (0.12)	F(4,328) = 12.24	<0.001	0.130

Values denote estimated marginalized means (standard errors).

[a]All analyses control for age, household income, and one co-morbidity (i.e., CD = conduct disorder; ODD = oppositional defiant disorder; BD = bipolar disorder; DD = depressive disorder; AD = anxiety disorder). Sidak adjustment applied for multiple comparisons.

[b]The mean difference with the control group is significant at the $p < 0.05$ level.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; IHI = inattentive or hyperactive-impulsive; CBCL = Child Behavior Checklist; MOAS = Modified Overt Aggression Scale.

aggression. Only the combined subtype differed significantly from control subjects on proactive aggression, and both the combined and inattentive subtypes differed from the controls on reactive aggression. For MOAS overt aggression, the highest adjusted means were displayed by the ADHD hyperactive-impulsive subtype. Apart from the ADHD problems group, ADHD subtypes were significantly different from control subjects on MOAS overt aggression.

Two of the covariates in the ANCOVA analyses, CD ($p < 0.001$) and depressive disorder ($p < 0.05$), were significantly associated with all measures of aggression after adjusting for other covariates (i.e., age and family income). In contrast, an anxiety disorder diagnosis did not vary significantly with aggression, and the relationships of ODD and BD to aggression differed dependent on the type of aggression measured. The diagnosis of ODD was significantly associated with CBCL overt and reactive aggression ($p < 0.001$), but not MOAS overt and proactive aggression; BD was related to aggression (i.e., overt and reactive aggressions, $p < 0.05$) with the exception of proactive aggression. The covariate of family income was significantly associated with aggression in the ANCOVA analyses. As expected, reduced family income predicted increased aggression of all types ($p < 0.05$), excluding overt aggression when adjusting for the covariates of age and CD. The covariate age showed little relationship with aggression after controlling for family income and co-morbidities with ADHD.

ADHD symptom severity and aggression characteristics

ADHD symptom severity as rated by the ADHD-RS-IV was significantly correlated ($p < 0.001$) with aggression in ADHD subjects ($n = 268$). Greater ADHD symptom severity was associated with increased aggression, including CBCL overt aggression ($r = 0.37$), MOAS overt aggression ($r = 0.39$), proactive aggression ($r = 0.37$), and reactive aggression ($r = 0.36$). Furthermore, ADHD subjects showed significantly higher reactive (IA) aggression scores ($M = 3.06$, SD = 1.19) compared to proactive aggression scores ($M = 1.60$, SD = 0.85; $t(238) = 22.86$, $p < 0.001$) across the entire ADHD sample. This mean difference between proactive and reactive aggression was replicated in ADHD subjects with co-morbid CD (reactive, $M = 3.86$, SD = 0.82; proactive, $M = 2.40$, SD = 1.08), ODD (reactive, $M = 3.20$, SD = 1.13; proactive, $M = 1.62$, SD = 0.78), BD (reactive, $M = 3.80$, SD = 1.06; proactive, $M = 2.05$, SD = 1.07), depressive disorder (reactive, $M = 3.35$, SD = 1.17; proactive, $M = 1.74$, SD = 0.91), and anxiety disorder (reactive, $M = 3.10$, SD = 1.22; proactive, $M = 1.62$, SD = 0.84).

Discussion

We conducted a single-site study seeking to further understand relationships between aggression and ADHD in a clinically referred sample. Results suggest high rates of overt, proactive, and reactive aggression in referred ADHD children and adolescents in our sample compared with community controls. Results further suggest that diagnostic co-morbidity, ADHD subtype, and ADHD symptom severity all contribute to aggression in referred ADHD youngsters. Reactive forms of aggression appear to be significantly more frequent than proactive forms of aggression in our ADHD sample.

The number of co-morbid psychiatric disorders was significantly related to overt aggression as measured by parental report CBCL aggression T-score or the MOAS, and was also significantly related to both proactive and reactive aggression. As the number of co-morbid disorders increased, so did aggression scores in these ADHD youngsters. This is consistent with a cumulative disease model in which aggression symptom severity increases in more vulnerable ADHD individuals with higher rates of psychiatric co-morbidity. Results are also consistent with aggression as a generalized marker for illness severity in ADHD, as previously reported across many psychiatric disorders in referred pediatric patients (Connor and McLaughlin 2006). Indeed, aggressive behavior in ADHD patients may function like pain or fever in medicine and surgery, as a generalized marker for illness severity (Jensen et al. 2007).

We found a high rate of parent-reported anxiety disorders in our clinical sample (67–85% across ADHD subtypes vs. 21% in community controls). The MTA study also reported that about one-third of ADHD children had parent-reported anxiety disorders (MTA 1999). However, very little overlap is reported between parent- and child-identified anxiety syndromes (Jensen et al. 1999). Parent-identified anxiety disorders acquired via structured clinical interviews may be not be the same as child-identified anxiety syndromes. Our high rates of parent-reported anxiety syndromes may be inflated either because anxious parents are over-reporting anxiety symptoms in their children (Pfiffner et al. 1999), or parents misidentify behavioral or affective dysregulation symptoms in their ADHD offspring as anxiety (Jensen et al. 2001), thereby spuriously increasing co-morbidity rates.

In our analysis, anxiety disorders were found to be unrelated to measures of aggression, suggesting that co-morbid anxiety may confer a protective effect on aggression in ADHD youth. These findings are similar to ADHD co-morbidity findings from the MTA study wherein anxiety appeared to confer a benefit on ADHD children exerting an ameliorating effect on concurrent conduct and ODD (Jensen et al. 2001).

Consistent with previous research (Taylor et al. 1996), ADHD subtypes that contained hyperactive-impulsive behaviors (combined and hyperactive subtypes) were associated with higher aggression scores compared to the inattentive and mixed IHI ADHD problem group, and more particularly community controls. Our results support the hypothesis that central nervous system (CNS) regulatory dyscontrol over motor inhibition leading to hyperactivity and dysregulation of impulse control are a significant "driver" of aggressive behavior in referred ADHD youngsters (Babinski et al. 1999).

Significant correlations occurred between ADHD symptom severity scores on all four of our aggression variables. This suggests that as ADHD symptom severity increases in referred ADHD youngsters, overt aggression, proactive aggression, and reactive aggression scores also increase. Our study is consistent with previous research that finds an association between ADHD symptom severity and severity of oppositional, delinquent, and CD problems (Kuhne et al. 1997), and extends this relationship to include overt, proactive, and reactive aggression. Scores for reactive aggression were significantly higher than ratings for proactive aggression comparing the ADHD group with controls, in the ADHD alone group, and in each of the five ADHD + co-morbid groups (CD, ODD, BD, depression, and anxiety), suggesting that reactive, impulsive, affectively charged, and defensive aggressive behaviors (impulsive aggression as opposed to instrumentally aggressive behaviors) are important in these ADHD youngsters.

A consensus report on IA as a symptom across diagnostic categories in child psychiatry concluded that IA is a substantial

public health and clinical concern. It can be measured with sufficient precision across different psychiatric diagnoses such that pharmacological studies are warranted, and IA constitutes a key therapeutic target across multiple disorders such as ADHD, autism, and childhood BD (Jensen et al. 2007). The authors noted that IA was best investigated when clinical trials focused on IA in a single underlying well-defined DSM disorder. The report concluded that an increased understanding of the differences between IA and proactive aggression within well-defined diagnostic disorders independently of the diagnostic categories of CD and ODD and the application of these distinctions in future research and clinical trials development would have a major impact on treatment planning, public policy, and prevention programs (Jensen et al. 2007). Our results are largely in support of the panel's conclusions within the diagnosis of ADHD. We found that although proactive aggression was higher in combined ADHD relative to community controls, reactive aggression (IA) was very prevalent in both the combined and inattentive ADHD subtypes. Our findings suggest that the trait of impulsivity and overall ADHD symptom severity are important correlates of reactive aggression (IA) in our ADHD sample. Given a growing consensus that reactive types of aggression may be more responsive to psychopharmacological intervention than proactive forms (Vitiello and Stoff 1997) and given high rates of aggressive behaviors in clinically referred ADHD youngsters (MTA Cooperative Group 1999), investigations of medication efficacy in reactive (IA) types of aggression in ADHD are important.

Limitations to our study should be noted. Ours was a single-site clinical sample referred for treatment and largely Caucasian from intact middle class families, so results might not generalize to other populations of youths with ADHD. Our methodology was cross sectional in design, so causality cannot be inferred from our findings. Our classification of the IHI ADHD problems group was heterogeneous, comprising many different types of subsyndromal ADHD children. Although this may have confounded results, we chose to include an IHI ADHD problems group as many referred children have significant impairment but do not meet full ADHD criteria. The cell containing hyperactive-impulsive ADHD children was relatively small. Despite these limitations, we are able to demonstrate a robust association between aggression and ADHD in our clinical sample.

Conclusion

These results suggest that although reactive (IA) aggression is not a criterion for diagnosis in ADHD, it is common in clinically referred ADHD youngsters and should be identified as a new treatment target for psychopharmacological therapeutics in children and adolescents with moderate to severe ADHD and nonanxiety comorbid diagnostic disorders. A testable hypothesis for further clinical research is whether therapeutics that downregulate overall ADHD symptom severity and/or hyperactive-impulsive ADHD behaviors are associated with improved reactive (IA) aggression scores in aggressive ADHD children compared with controls.

Disclosures

In the past 3 years, Dr. Connor has served as an ADHD consultant and speaker for Shire Pharmaceuticals, Inc. and as a consultant for Abbott Pharmaceuticals. He received research support from Shire Pharmaceuticals, Inc. He received additional support from the National Institute of Mental Health (NIMH) and the State of Connecticut. Drs. Chartier, Preen, and Kaplan have no conflicts of interest or financial ties to disclose.

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