

Association of Reactive–Proactive Aggression and Anxiety Sensitivity with Internalizing and Externalizing Symptoms in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract This study evaluates the associations among the symptoms of anxiety, depression, and disruptive behavioral disorders (DBD) in the context of their relationships with reactive–proactive aggression and anxiety sensitivity in children with attention-deficit/hyperactivity disorder (ADHD). The sample consisted of 342 treatment-naive children with ADHD. The severity of ADHD and DBD symptoms were assessed via parent- and teacher-rated inventories. Anxiety sensitivity, reactive–proactive aggression and severity of anxiety and depression symp-

toms of children were evaluated by self-report inventories. According to structural equation modeling, depression and anxiety scores had a relation with the DBD scores through reactive–proactive aggression. Results also showed a negative relation of the total scores of anxiety sensitivity on DBD scores, while conduct disorder scores had a positive relation with anxiety scores. This study suggests that examining the relations of reactive–proactive aggression and anxiety sensitivity with internalizing and externalizing disorders could be useful for understanding the link among these disorders in ADHD.

The association between reactive and proactive aggression, AS, anxiety, depression, and parent-rated ADHD and DBD scores were examined using SEM analytic strategy. The models were significant with the total score from the childhood anxiety sensitivity index (CASI). Subsequent testing with the individual CASI subscales in the models were all not significant and led to poor fit indices.

Keywords ADHD · Disruptive behavioral disorder · Reactive aggression · Proactive aggression · Anxiety sensitivity

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is highly prevalent in children worldwide, affecting approximately 7.2 % of children [1]. ADHD has not only a high prevalence but also high comorbidity rates with both externalizing [e.g., oppositional defiant disorder (ODD) or conduct disorder (CD)] and internalizing disorders (e.g., depression or anxiety disorders) [2–6]. The prevalence of comorbid disorders in community and clinical settings has been reported as 38.9 versus 61.2 % for ODD; 13.2 versus 10.2 % for CD; 24.5 versus 33.5 % for anxiety disorders; and 9.3 versus 22.7 % for depression in children with ADHD [5]. These comorbidities have a significant additive negative influence on ADHD sufferers' academic achievement, family life, social competence, and peer relationships [7, 8]. Thus, the increasing knowledge regarding the comorbid psychiatric disorders in ADHD

appears to be critical to prevent enhanced functional impairments.

Although the underlying substantive reasons of the development of comorbid disorders in ADHD remain uncertain, data related to the interactions among these disorders has increased gradually. Many studies have investigated the connection between coexisting ODD and CD in ADHD [9–11], and they generally have shown that especially the behavioral symptoms of ODD usually precede CD and seem to be a risk factor for the development of CD [9, 11]. Nonetheless, not only is ODD a mild form or precursor of CD, but these disorders also have a distinctive pattern of associations with longer term consequences [10]. The association among anxiety disorders and depression in childhood has been addressed extensively in the general population, so the relationship of these disorders also has been well known [12, 13]. Both disorders frequently co-occur, can trigger each other, and share some common risk factors [12, 13]. However, compared to the association of ODD and CD and the association of depression and anxiety disorders, data regarding how an externalizing disorder affects an internalizing disorder and vice versa has been so far limited in children with ADHD.

Cross-sectional studies generally have shown that coexisting ODD and CD were related to a range of anxiety disorders in ADHD subjects [3, 4]. Some studies have posited that anxiety disorders confer a risk for disruptive behavioral disorders (DBD), and higher anxiety may lower the threshold for the expression of behavioral problems [14, 15]. Others have suggested that children with DBD generate anxiety-provoking situations around themselves and this leads to the development of anxiety disorders [16, 17]. Accordingly, there may be a vicious circle among DBD and anxiety disorders in childhood. However, the data is not universal, and some studies have demonstrated that anxiety may be protective against conduct problems [18–20]. Pliszka [18] compared children with either non-anxious ADHD or anxious ADHD and detected that the combination of ADHD and an anxiety disorder reduced the probability of a comorbid CD. Furthermore, several longitudinal studies have reported a decreased risk for behavioral problems in children who had higher anxiety symptoms [19, 20].

A positive association among the presence of comorbid ODD or CD and depressive disorders also has been reported for ADHD subjects [21–25]. Cross-sectional studies have indicated there are higher depression ratios in ADHD children with comorbid DBD than in those without DBD [21, 22]. Several prospective studies have proposed that elevated depressive symptoms are a risk factor for subsequent behavioral problems [26, 27]. Alternatively, research addressed whether children with conduct problems are at increased risk for depression in the future [25,

28]. A few prospective studies report that the comorbidity of CD or ODD in youth with ADHD increases the risk of developing depression [23–25]. These studies further suggest that the development of depression may be a cumulative result of ADHD- and comorbid DBD-related psychosocial impairments. However, data is not universal, and a follow-up study conducted by Althoff et al. [28] failed to find an association. Therefore, as with anxiety disorders, the links between depression and DBD remain to be elucidated.

Viewing internalizing or externalizing disorders as homogenous entities may well account for inconsistent findings about their relationships, and various authors have posited that it may be beneficial to investigate the subtypes of these disorders independent from those defined by the Diagnostic and Statistical Manual of Mental Disorders [29–31]. For instance, both internalizing and externalizing disorders are related closely to aggression, but aggression is not a unique construct and is divided into two subtypes, reactive and proactive aggression. These subtypes vary according to the differences in function or motivation underlying the behavior [31, 32]. Reactive aggression occurs as a hostile reaction to a real or perceived threat and has a defensive and impulsive character; however, proactive aggression is characterized by deliberate and purposeful acts motivated by an external reward. Studies suggest that ADHD and coexisting disorders are related differentially to reactive and proactive aggression; this may be responsible for the reported discordant results about the link among these disorders in ADHD [31, 33–35].

Primary features of ADHD seem to be related more strongly with reactive aggression than proactive aggression, probably due to impulsivity and regulation problems associated with the disorder [33]. ODD and CD also are associated with reactive aggression, suggesting that reactive aggression may be an important construct for each of the DBD in childhood [34]. On the other hand, proactive aggression, which is related to callous and unemotional traits, primarily co-occurs with CD [35]. Coexisting internalizing disorders such as anxiety and depression also are related with aggression, and similar to externalizing disorders, they appear to be related differentially to various subtypes of aggression. Studies consistently have shown that reactive aggression, but not proactive aggression, is related to the emotional dysregulation and perceptual distortion that occurs in internalizing disorders [36, 37]. In support of the notion of increased vulnerability to internalizing disorders in relation to reactive aggression, previous data also suggest that children who engaged in reactive aggression were more depressive and anxious [14, 38]. Conversely, proactive aggression is characterized by a lack of anxiety [38]. On the other hand, there is some

evidence with regard to higher proactive aggression levels and depressive symptoms in children diagnosed with ADHD [39]. Therefore, aggression appears to be one of the pivotal constructs that play a role in the development of both coexisting internalizing and externalizing disorders in children with ADHD, and taking into account aggression while investigating the association between comorbid internalizing and externalizing symptoms in ADHD may be beneficial.

Distinct aspects of anxiety also may be responsible for inconsistent findings regarding the relationship between internalizing disorders and DBD in ADHD. Kerr et al. [29] took into account this issue and investigated whether behavioral inhibition (BI) and social withdrawal have different relationships with DBD. BI is defined as a tendency to exhibit fearfulness, restraint, reticence, and withdrawal in the presence of novel stimuli and may represent a diathesis for anxiety disorders [40]. Social withdrawal is also a construct related to anxiety and characterized by spending significant time alone, a preference for solitude, social immaturity, and social incompetence [41]. The study of Kerr et al. and a following study have provided evidence that aggressive but behaviorally inhibited children are less aggressive than those with aggressiveness alone, which suggests that BI may lead to decreasing the likelihood of aggressive behavior [29, 42]. However, socially withdrawn but disruptive boys have been shown to be at risk for social problems and depression, and some studies have suggested that positive relationships between externalizing disorders and anxiety disorders may reflect this group of patients [29].

Anxiety sensitivity (AS) is another aspect of anxiety and is characterized by a fear of harmful consequences of anxiety-related arousal sensations. Unlike anxiety symptoms in general, which can fluctuate over time, AS is regarded as a relatively stable personality trait [43]. Indeed, psychometric, clinical, and genetic studies provide converging evidence that AS is a distinct entity beyond anxiety and has a strong hereditary component [44]. Evidence from previous studies suggests that AS can be represented by three structural factors: physical, cognitive, and social subscales [45, 46]; these factors represent the fear of anxiety-related bodily sensations, the fear of cognitive dyscontrol, and the fear of externally observable anxiety symptoms, respectively. Research consistently has demonstrated that a higher AS is associated with the development of internalizing disorders, including a variety of anxiety disorders and major depressive disorders [47, 48]. However, global AS or its certain subdomains may have unique relationships with other psychiatric problems different from anxiety disorders or depression. For instance, studies showed that, although individuals of higher anxiety and depression are at risk for suicidal

behaviors, AS physical concerns had a negative relationship with these behaviors [49]. Similarly, our previous study demonstrated a negative relationship of the AS social subdomain to CD symptoms in children with ADHD, although CD symptoms showed positive relationships with anxiety severity [17]. Thus, AS may be an important factor in the understanding of the development and interaction of internalizing and externalizing disorders in ADHD.

Current Study

There is limited data and uncertainty concerning the links through which the relationships between internalizing and externalizing symptoms emerge in ADHD. The literature reviewed above suggests that several psychiatric constructs, such as reactive–proactive aggression and AS, may help account for the link between internalizing and externalizing symptoms in ADHD subjects. This cross-sectional study has been conducted to investigate the relationships among anxiety, depression, and DBD symptoms in the context of their relationships between reactive and proactive aggression and AS in children with ADHD. To examine the possible direction of the relationships among the variables, the structural equation modeling (SEM) analytic strategy was used. The current study was guided by four overarching hypotheses. First, we expected that anxiety symptoms would be positively related to DBD symptoms through reactive aggression but not proactive aggression. Second, we expected that depression symptoms would be positively related to DBD symptoms through both reactive aggression and proactive aggression. Third, in accord with the idea that development of internalizing disorders may be a cumulative result of DBD-related psychosocial impairments in ADHD [16, 17, 23], it was hypothesized that DBD symptoms would be directly related to anxiety and depression symptoms. Finally, because AS represents a distinct and constitutionally based aspect of anxiety and is suggested to have a role in aversive conditioning [17, 43], AS was expected to have a negative direct relationship with DBD symptoms. Overall, we expected that this study would show that reactive–proactive aggression and AS may be critical constructs for understanding the association between comorbid internalizing and externalizing symptoms in ADHD.

Materials and Methods

Participants

All consecutive referrals for suspected combined subtypes of ADHD to outpatient clinics at six distinct regional

tertiary child and adolescent psychiatry centers in Turkey were enrolled. All participants were Caucasian, age 8–18 years, and typically the first to present at our clinics with suspected ADHD. In order to decrease the effects of potential confounding factors on study variables, patients with the diagnosis of a major physical or neurological illness (e.g., diabetes mellitus, epilepsy, etc.), autism spectrum disorders, schizophrenia, bipolar disorder, and substance abuse or dependence were excluded. Intellectual disability of children and low educational level of parents might impede the fulfillment of questionnaires properly; therefore, patients also were excluded if they had an intelligence quotient (IQ) score below 70 according to the Turkish version of the Wechsler Intelligence Scale for Children Revised (WISC-R) [50, 51], or if their parents had an educational level of less than 5 years. Because psychopharmacologic agents may impact the severity of psychiatric symptoms of subjects, children who had a history of taking psychiatric medications also were excluded. With the implementation of these stringent inclusion and exclusion criteria, a homogeneous group of patients with ADHD was identified; this enabled the examination of natural relationships among internalizing and externalizing symptoms in ADHD patients.

Overall, 377 parents were approached, but 11 of the parents declined to participate and only 366 provided written consent. Twenty-four children were excluded based on the exclusion criteria. The sample, finally, was composed of 342 children who satisfied the DSM-V symptom and impairment criteria of the combined subtype of ADHD. The distribution of the study sample was as follows: Necmettin Erbakan University Meram School of Medicine (study center-1) = 143; Inonu University School of Medicine (study center-2) = 46; Erciyes University School of Medicine (study center-3) = 43; Selcuk University School of Medicine (study center-4) = 36; Izzet Baysal University School of Medicine (study center-5) = 28; and Konya Education and Training Hospital (study center-6) = 28.

Measures/Instrumentation

Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL)

The K-SADS-PL is a semi-structured diagnostic interview tool that inquires about current and past episodes of child and adolescent psychiatric disorders and allows for a diagnosis to be made [52]. The Turkish version of the K-SADS-PL was reported to have a good test–retest and inter-rater reliability [53]. For the current study, the ADHD

module of the K-SADS-PL was used to make the ADHD diagnoses.

Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S)

This scale was developed by Turgay and evaluates ADHD, ODD, and CD based on the DSM-IV diagnostic criteria [54]. The symptoms are scored by assigning a severity estimate for each symptom on a four-point Likert-type scale (namely, 0 = not at all; 1 = just a little; 2 = much; and 3 = very much) composed of 41 items. Ratings of “much” and “very much” for each item were considered positive, as done in other similar investigations. Within this scale, nine items measure severe hyperactivity–impulsivity, nine items measure attention deficit, eight items measure oppositional behavior, and 15 items measure symptoms of CD. The scale was adapted for the Turkish population by Ercan et al. [55]. It had excellent internal consistency, with a Cronbach’s alpha of .95 for the hyperactivity–impulsivity score of .88 for the attention deficit score, .89 for the oppositional behavior score, and .92 for the CD score. In the present study, the scale was completed by parents and teachers.

Children’s Depression Inventory (CDI)

This is a self-reported depression scale for children 6–17 years of age that was developed by Kovacs [56]. It is composed of 27 items, and each item is scored as 0, 1, or 2, according to the severity of the symptoms. These items assess the severity of depression for the previous 2 weeks. The reliability and validity study of this scale for the Turkish population was conducted by Oy [57]. The cutoff point of the CDI was determined as 19, and Cronbach’s alpha of the scale was .77.

Screen for Child Anxiety-Related Emotional Disorders (SCARED)

This 41-item self-report measure screens for DSM-IV anxiety disorders in childhood [58]. Participants rate each factor on a three-point scale. SCARED total scores, derived by summing the responses from the 41 items, range from 0 to 82. The SCARED was translated and adapted for the Turkish population by Karaceylan [59]. Findings suggest that the validity and reliability of SCARED total scores from the Turkish sample were satisfactory for full-scale representation of the population (Cronbach’s alpha = .88). The original version of SCARED included five distinct factors: somatic/panic, generalized anxiety, separation anxiety, social anxiety, and refusal to attend school.

Because we did not aim specifically to investigate the role of anxiety disorders subtypes in ADHD, we only used the SCARED total scores for this study.

Childhood Anxiety Sensitivity Index (CASI)

The CASI is a self-report questionnaire developed by Silverman et al. [60] for assessing AS in children. The CASI assesses fear/catastrophic interpretations of anxiety-related sensations. The CASI includes 18 items and has a three-point Likert-type scale ranging from 1 (not at all) to 3 (very much). The CASI possesses internal consistency and test–retest reliability in clinical and nonclinical samples. It has good concurrent and predictive validity. The CASI also has incremental validity over the anxiety symptoms. Although factor analytic investigations of the CASI have yielded controversial results, studies have provided evidence to suggest that AS can be represented by three factor structures including physical, cognitive, and social subscales; these factors represent fear of anxiety-related bodily sensations, fear of cognitive dyscontrol, and fear of externally observable anxiety symptoms, respectively. The reliability study for the Turkish version was conducted by Yilmaz et al. [61] with a group of Turkish school children. The Cronbach's alpha coefficients of the Turkish version of the CASI total has been reported as .74. The Cronbach's alpha of the CASI physical, cognitive, and social subscales were .73, .43, and .36, respectively.

The Reactive–Proactive Aggression Questionnaire (RPAQ)

The RPAQ is a self-report instrument developed to assess reactive and proactive aggression [36]. It has a total of 23 items and two subscales. In the RPAQ, 11 items measure reactive aggression and 12 items measure proactive aggression. Results have confirmed the two-factor model for the RPAQ in both girls and boys. The items were rated on a three-point scale with the following response options: 0 = never, 1 = sometimes, and 2 = often. For each subscale and the total scale, higher scores indicate higher levels of aggression. The reliability study for Turkish children was conducted by Baş and Yurdabakan [62]. The Cronbach's alpha coefficients have been reported as .77, .79, and .84 for reactive aggression, proactive aggression, and total aggression, respectively.

Wechsler Intelligence Scale for Children-Revised (WISC-R)

The WISC-R was designed to measure the IQ of children ages 6–16 [50]. The standardization of the WISC-R for Turkish children was conducted by Savaşır and Şahin [51]. In the present study, it was used to ensure that participants had an IQ of 70 or higher.

Procedures

This study was approved by the Institutional Review Board of the Necmettin Erbakan University. Parents of children who agreed to participate in the study signed a written informed consent. Verbal assent also was procured from all of the children and their parents. All of the study procedures were in accordance with the Declaration of Helsinki and local laws and regulations. At first, both the target child and a parent were interviewed using the K-SADS-PL by a child and adolescent psychiatrist, and ADHD diagnoses were made according to the DSM-5 criteria. Participants' genders, ages, and parental educational levels were recorded. Children then were administered the CDI, SCARED, CASI, and RPQ. Then, the T-DSM-IV-S was completed by both parents and teachers. A higher score indicated a greater symptomatology in all of the questionnaires. As part of a systematized decision-tree process, when the clinicians deemed it necessary, the WISC-R also was used to rule out any intellectual disability. The tests were administered by an expert psychologist who had specific training and experience regarding the administration.

Statistical Analysis

The analysis of the data was performed using SPSS 20.0-AMOS statistical software (SPSS, Inc., Chicago, IL, USA). In all analyses, raw scores of the questionnaires were used. The Mann–Whitney U test was used to analyze differences in mean ages among genders. The comparison among variables across study centers was performed using the Chi-square test or analysis of variance (ANOVA). Zero-order bivariate Pearson or Spearman correlation coefficients were calculated to examine the relationship between the psychiatric test scores. SEM was conducted further to determine the relationship between psychiatric test scores. To evaluate the goodness of fit of a model, the relative/normed Chi-square (χ^2/df), the root mean square error of approximation (RMSEA) statistic, the comparative fit index (CFI), and Tucker Lewis Indexes (TLI) were used. Although there is no consensus regarding an acceptable ratio for the χ^2/df , various authors typically recommend it to be under 2.0 [63]. For RMSEA, the lower limit is close to 0 while the upper limit should be less than .08 for a well-designed model. For CFI and TLI, a cutoff criterion of $\geq .95$ has been recommended [63, 64]. All of these parameters would be fulfilled for an acceptable model.

Because the scores for symptoms of ADHD and coexisting DBD were measured with both parent- and teacher-rated T-DSM-IV-S scales, the relationship among reactive–proactive aggression, AS, anxiety, depression, and DBD scores were examined with two separate models. Because age and gender may have an impact on the psychiatric

measures, the effects of these variables were controlled in our models. In addition to age and gender, covariant effects among each of the predictor variables also were assessed. When the cases are nested in higher level observations such as institutions, multi-level analysis is a viable option [65]. However, multi-level analysis, as such, is concerned predominantly with linear, Poisson, and logistic regressions, as well as survival analysis [65]. For theoretical evaluation of relationships among latent and observed variables, SEM primarily is used [65]. SEM is a robust technique that also allows specification of the nested data structure within models [66]. Therefore, we added the specific institutions as an observed variable to our models to control the multi-level nature of our data.

Models have been established according to the hypotheses of the study. At the beginning of modeling, all of the covariant components and regression relationships among psychological test scores were taken into account. During the statistical assessment, insignificant relationships were removed step by step from the model. The significance was set at a level of .05 (two-tailed) in this analysis.

Results

The mean age of the children in the sample was 11.1 ± 2.3 years (range = 8–18 years), which consisted of 274 (80.1 %) boys and 68 (19.9 %) girls. No statistical differences were found in terms of the mean ages of the boys (11.1 ± 2.3 years) and girls (11.2 ± 2.5 years; $z = -.31$, $p = .76$). The mean educational levels of the parents were 9.7 ± 4.0 years (range = 5–17 years) and 8.3 ± 3.7 years (range = 5–17 years), respectively. Means, SD, and zero-order correlations for the psychological test scores are given in Table 1. Distributions of study variables according to study centers are shown in Table 2. No significant differences were observed in the factors of age, sex, and parental educational levels in the declined or excluded group compared with the sample group; this implies the low risk for information or selection bias.

The association between reactive and proactive aggression, AS, anxiety, depression, and parent-rated ADHD and DBD scores were examined in Model-1. The model fit the data satisfactorily ($p = .001$, $\chi^2/df = 1.627$, RMSEA = .043, TLI = .953, and CFI = .968). The regression relationships between variables that showed statistical significance and goodness of fit statistics for Model-1 are presented in Fig. 1. This model showed a positive relation of attention deficit scores on ODD scores ($\beta = .23$, $p < .001$) and a positive relation of hyperactivity–impulsivity scores on proactive aggression ($\beta = .12$, $p = .012$), reactive aggression ($\beta = .16$, $p < .001$), and ODD scores

($\beta = .41$, $p < .001$). Depression and anxiety scores were related to the severity of aggression and showed a positive relation of depressive scores on both reactive aggression ($\beta = .37$, $p < .001$) and proactive aggression ($\beta = .38$, $p < .001$), and a positive relation of anxiety scores on reactive aggression ($\beta = .22$, $p < .001$). Depression scores also were related directly to ODD scores ($\beta = .12$, $p < .009$). Regarding the aggression scores, reactive and proactive aggressions were related to ODD ($\beta = .17$, $p < .001$) and CD ($\beta = .25$, $p < .001$) scores, respectively. The model also showed that AS total scores had a negative relation on the CD scores ($\beta = -.11$, $p = .014$), whereas CD scores had a positive relation on anxiety symptoms ($\beta = .10$, $p = .017$).

The association between reactive and proactive aggression, AS, anxiety, depression, and teacher-rated ADHD and DBD scores were examined in Model-2. The goodness of fit also was satisfactory for this model ($p = .001$, $\chi^2/df = 1.600$, RMSEA = .042, TLI = .957, and CFI = .968). The regression relationships between variables that showed statistical significance and the goodness of fit statistics for Model-2 are presented in Fig. 2. Overall, the relationships among psychological test scores were similar to Model-1. Model-2 demonstrated a positive relation of attention deficit scores on ODD scores ($\beta = .20$, $p < .001$) and a positive relation of hyperactivity–impulsivity scores on proactive aggression ($\beta = .12$, $p = .020$), reactive aggression ($\beta = .12$, $p = .012$), and ODD scores ($\beta = .55$, $p < .001$). There were relationships between anxiety scores and reactive aggression ($\beta = .24$, $p < .001$) and among depressive scores and both reactive aggression ($\beta = .34$, $p < .001$) and proactive aggression ($\beta = .37$, $p < .001$). Regarding the aggression scores, the only relationship was among reactive aggression to ODD scores ($\beta = .10$, $p = .012$). Also, in this model, instead of CD scores, AS showed a negative relationship with the ODD scores ($\beta = -.11$, $p = .015$). However, the relationship between CD scores and anxiety symptoms was similar to Model-1 ($\beta = .08$, $p = .049$).

Discussion

The present cross-sectional study evaluated the associations among anxiety, depression, and DBD symptoms in the context of their relationships with reactive–proactive aggression and AS in children with ADHD. In this study, we set out to address four different questions concerning the nature of the link between coexisting internalizing and externalizing symptoms in ADHD.

Our first question was whether anxiety symptoms were positively related to DBD symptoms through reactive aggression in children with ADHD. Consistent with our

Table 1 Intercorrelations among study variables

	Mean ± SD	Range	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Parent T-DSM-IV-S inattention	16.27 ± 5.40	4–27	.43***	.44***	.22***	.27***	.12*	.16**	.12*	.13*	.15**	.20***	.10	.06	.05	.06	.04
2. Parent T-DSM-IV-S hyperactivity	14.25 ± 6.84	4–27	.53***	.31***	.70***	.11*	.41**	.26**	.22**	.18**	.18**	-.04	.14*	.05	.04	.07	-.01
3. Parent T-DSM-IV-S ODD	10.66 ± 5.55	0–24			.70***	.13*	.23***	.38***	.38***	.34***	.33**	.21***	.18***	.08	.07	.05	.02
4. Parent T-DSM-IV-S CD	3.10 ± 3.27	0–16			.02	.14*	.28***	.43***	.43***	.38***	.45***	.20***	.08	.03	.04	-.02	.02
5. Teacher T-DSM-IV-S inattention	14.13 ± 5.72	0–27				.41***	.43***	.29***	.43***	.02	.01	.14**	.03	.02	.01	.08	-.01
6. Teacher T-DSM-IV-S hyperactivity	11.03 ± 7.23	0–27					.65***	.44***	.65***	.13*	.14*	.03	.04	-.03	-.03	-.01	-.02
7. Teacher T-DSM-IV-S ODD	7.98 ± 5.49	0–24						.71***	.71***	.16**	.15**	.11	.01	-.07	-.05	-.07	-.07
8. Teacher T-DSM-IV-S CD	2.69 ± 3.27	0–18							.19***	.17**	.17**	.08	.02	-.07	-.05	-.08	-.07
9. RPAQ reactive	9.52 ± 4.74	0–21							.69***	.69***	.42***	.39***	.32***	.33***	.13*	.10	.10
10. RPAQ proactive	3.28 ± 3.29	0–20								.35***	.35***	.24***	.17**	.18**	.09	.02	.02
11. CDI	14.97 ± 6.65	2–39									.39***	.39***	.23***	.20***	.19***	.13*	.13*
12. SCARED	27.61 ± 12.26	2–66										.62***	.62***	.60***	.41***	.15**	.15**
13. CASI total	30.77 ± 6.42	18–50											.94***	.94***	.62***	.40***	.40***
14. CASI physical	19.94 ± 5.12	12–35												.46***	.46***	.17**	.17**
15. CASI cognitive	4.63 ± 1.49	3–9															
16. CASI social	6.20 ± 1.52	3–9															.12*

N = 342

T-DSM-IV-S turgay DSM-IV-based child and adolescent behavioral disorders screening and rating scale, RPAQ reactive proactive aggression questionnaire, CDI child depression inventory, SCARED screen for child anxiety related emotional disorders, CASI the childhood anxiety sensitivity index, ODD oppositional defiant disorder, CD conduct disorder

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 2 Distributions of variables among study centers

	Study center-1	Study center-2	Study center-3	Study center-4	Study center-5	Study center-6	ANOVA	Post-hoc comparisons ^a
	(n = 161) Mean ± SD	(n = 46) Mean ± SD	(n = 43) Mean ± SD	(n = 36) Mean ± SD	(n = 28) Mean ± SD	(n = 28) Mean ± SD		
Parent T-DSM-IV-S inattention	16.96 ± 5.26	16.89 ± 4.66	16.47 ± 5.7	15.00 ± 5.79	14.68 ± 6.36	14.21 ± 4.63	$F(5, 336) = 2.41$, $p = 0.037$	None significant
Parent T-DSM-IV-S hyperactivity	16.65 ± 5.88	13.86 ± 6.41	13.35 ± 7.09	10.53 ± 6.78	12.14 ± 7.46	9.39 ± 6.31	$F(5, 336) = 11.05$, $p < 0.001$	SC-1 > SC-3, SC-4, SC-5, SC-6; SC-2 > SC-6
Parent T-DSM-IV-S ODD	11.74 ± 5.44	10.48 ± 5.25	9.77 ± 5.95	9.33 ± 5.45	9.36 ± 5.81	9.18 ± 5.14	$F(5, 336) = 2.63$, $p = 0.024$	None significant
Parent T-DSM-IV-S CD	3.71 ± 3.17	2.48 ± 3.30	2.40 ± 2.80	2.78 ± 4.02	2.29 ± 2.92	3.00 ± 3.33	$F(5, 336) = 2.31$, $p = 0.044$	None significant
Teacher T-DSM-IV-S inattention	13.95 ± 5.07	14.04 ± 6.29	15.53 ± 6.61	14.89 ± 7.11	12.80 ± 6.11	13.59 ± 4.16	$F(5, 336) = 1.04$, $p = 0.397$	
Teacher T-DSM-IV-S hyperactivity	12.02 ± 6.87	9.41 ± 7.51	12.49 ± 7.80	12.34 ± 7.63	7.32 ± 7.35	7.83 ± 5.09	$F(5, 336) = 4.43$, $p = 0.001$	SC-1 > SC-5, SC-6; SC-3 > SC-5
Teacher T-DSM-IV-S ODD	8.11 ± 4.73	7.89 ± 6.24	9.51 ± 6.66	8.08 ± 5.18	5.64 ± 5.86	7.21 ± 5.93	$F(5, 336) = 1.84$, $p = 0.104$	
Teacher T-DSM-IV-S CD	2.86 ± 3.08	2.54 ± 3.77	3.07 ± 3.43	2.14 ± 2.27	1.84 ± 3.39	2.97 ± 4.17	$F(5, 336) = .85$, $p = 0.513$	
RPAQ reactive	10.34 ± 4.71	8.17 ± 4.37	8.91 ± 5.16	9.86 ± 4.42	7.96 ± 4.27	9.07 ± 5.05	$F(5, 336) = 2.61$, $p = 0.025$	None significant
RPAQ proactive	3.65 ± 3.32	2.63 ± 3.25	3.00 ± 3.14	3.53 ± 4.09	2.07 ± 2.00	3.57 ± 3.06	$F(5, 336) = 1.67$, $p = 0.140$	
CDI	15.11 ± 6.26	13.83 ± 7.27	14.87 ± 8.60	15.31 ± 6.62	15.46 ± 5.75	15.18 ± 5.54	$F(5, 336) = .34$, $p = 0.891$	
SCARED	28.19 ± 11.61	26.63 ± 13.83	24.09 ± 12.85	29.08 ± 13.09	31.45 ± 11.91	27.18 ± 10.17	$F(5, 336) = 1.70$, $p = 0.135$	
CASI total	30.88 ± 6.37	30.91 ± 6.94	28.88 ± 5.07	31.61 ± 7.02	31.29 ± 5.67	31.29 ± 7.46	$F(5, 336) = .95$, $p = 0.447$	
CASI physical	20.06 ± 5.24	20.07 ± 5.50	18.53 ± 4.07	20.67 ± 5.40	19.93 ± 4.42	20.36 ± 5.59	$F(5, 336) = .85$, $p = 0.516$	
CASI cognitive	4.52 ± 1.53	4.72 ± 1.42	4.51 ± 1.33	4.83 ± 1.56	5.04 ± 1.53	4.61 ± 1.45	$F(5, 336) = .83$, $p = 0.529$	
CASI social	6.30 ± 1.47	6.13 ± 1.56	5.84 ± 1.40	6.11 ± 1.43	6.32 ± 1.70	6.32 ± 1.85	$F(5, 336) = .75$, $p = 0.584$	
Age of patients	10.85 ± 2.46	10.86 ± 1.96	11.56 ± 2.17	11.75 ± 2.83	11.21 ± 1.55	11.48 ± 2.31	$F(5, 336) = 1.519$, $p = 0.183$	
Education levels of mothers (years)	7.94 ± 3.61	8.83 ± 3.70	8.02 ± 3.56	9.24 ± 3.44	8.71 ± 4.32	8.38 ± 3.98	$F(5, 336) = 1.097$, $p = 0.362$	

Table 2 continued

	Study center-1 (n = 161)		Study center-2 (n = 46)		Study center-3 (n = 43)		Study center-4 (n = 36)		Study center-5 (n = 28)		Study center-6 (n = 28)		ANOVA <i>F</i> (5, 336) = 2.128, <i>P</i> = 0.062	Post-hoc comparisons ^a
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n		
Education levels of fathers (years)	9.28 ± 4.02		9.86 ± 3.59		9.33 ± 3.76		10.06 ± 3.76		11.79 ± 3.88		9.74 ± 4.14			
Male/female	126/35		34/12		37/6		32/4		32/4		22/6		23/5	$\chi^2 (5) = 4.26, p = 0.512$

T-DSM-IV-S turgay DSM-IV-based child and adolescent behavioral disorders screening and rating scale, *RPAQ* reactive proactive aggression questionnaire, *CDI* child depression inventory, *SCARED* screen for child anxiety related emotional disorders, *CASI* the childhood anxiety sensitivity index, *ODD* oppositional defiant disorder, *CD* conduct disorder

^a Tukey post-hoc comparisons

expectations, findings of this study showed the positive relationship of anxiety symptoms to reactive aggression and, then, reactive aggression to ODD symptoms. Previous studies have indicated that reactive aggression is related to both anxiety disorders and DBD [34, 67]. The directionality of the associations between reactive aggression and anxiety is not yet clear, but greater evidence is available suggesting a pathway from anxiety to reactive aggression than the reverse [14]. The link among reactive aggression and behavioral problems has been understood better; studies have consistently shown that reactive aggression precedes both ODD and CD [68–70]. In the light of these reports, it has been suggested previously that anxiety symptoms may increase DBD symptoms by triggering reactive aggression among ADHD children [14]. The present study provided evidence for the mediating role of reactive aggression among anxiety and ODD symptoms and supported this hypothesis. However, contrary to our a priori expectation, reactive aggression did not show a direct association with CD symptoms in this study. Given that ODD symptoms were related strongly with CD symptoms in our models, reactive aggression seems to have a relation with CD symptoms through ODD symptoms. Therefore, anxiety symptoms also seem to have an indirect escalating effect on CD symptoms, mediated by reactive aggression and ODD. Further research on these pathways clearly would be of importance.

Our second question concerned whether depression symptoms would positively predict DBD symptoms through reactive and proactive aggression in ADHD. Both of our models demonstrate a positive link from depression to both reactive and proactive aggression. Then, in turn, reactive aggression was related to both parent-rated and teacher-rated ODD symptoms, and proactive aggression was related to parent-rated CD symptoms. Substantial research has shown the association of aggression with both depression and DBD [38, 39, 70, 71]. The relationship between reactive aggression and depression seems to be more robust than with proactive aggression. Fite et al. [71] found that reactive aggression, but not proactive aggression, is linked positively to subsequent depression in adolescents, even when pre-existing levels of depression were controlled. There also is evidence showing the association between reactive aggression and elevated levels of negative emotionality and unhappiness [36]. On the other hand, a study conducted by Connor et al. [39] provides evidence linking depression to proactive aggression by reporting that ADHD subjects with depressive disorders show both higher reactive and proactive aggression scores. The links among reactive aggression and both ODD and CD, and between proactive aggression and CD, are also well known [33–35]. However, the relationship between proactive aggression and ODD is ambiguous, and a recent study

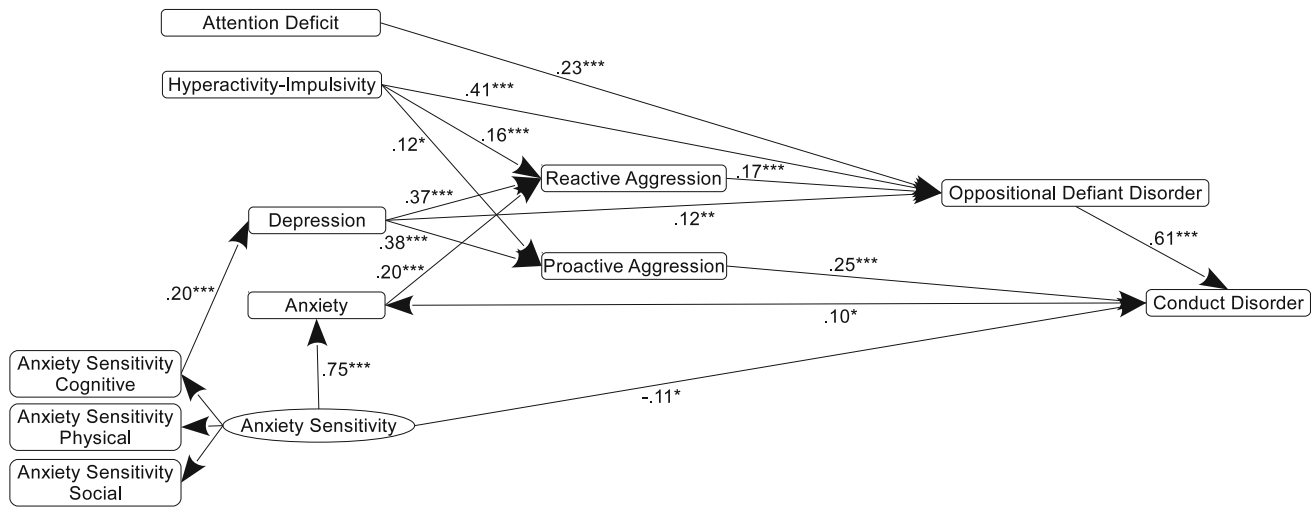


Fig. 1 Structural model for the relationships of anxiety sensitivity, reactive proactive aggression, anxiety, depression, and parent-rated T-DSM-IV-S scores using standardized parameters. Model fit values:

$\chi^2 = 99.23$; $df = 61$; $\chi^2/df = 1.627$; comparative fit index = .968; Tucker–Lewis Index = .953; root mean square error of approximation = .043; $p = 0.001$. * $p < .05$, ** $p < .01$, *** $p < .001$

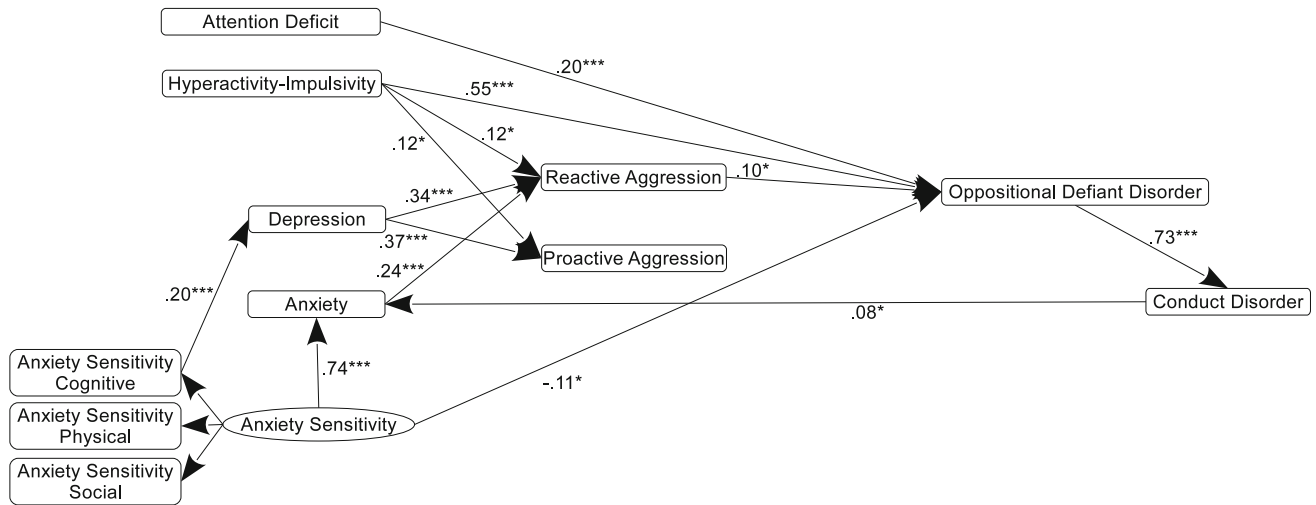


Fig. 2 Structural model for the relationships of anxiety sensitivity, reactive proactive aggression, anxiety, depression, and teacher-rated T-DSM-IV-S scores using standardized parameters. Model fit values:

$\chi^2 = 107.23$; $df = 67$; $\chi^2/df = 1.600$; comparative fit index = .968; Tucker–Lewis Index = .957; root mean square error of approximation = .042; $p = 0.001$. * $p < .05$, ** $p < .01$, *** $p < .001$

suggested that proactive aggression was related to ODD only when certain environmental risk factors, such as inconsistent parental discipline, was also evident [69]. Our findings are consistent with previous reports and firstly showed in the same models that elevated levels of depressive symptoms may have an exacerbating effect on the severity of ODD via their impact on reactive aggression and on CD via their impact on both reactive and proactive aggression.

We expected that depression symptoms affect DBD symptoms only through reactive–proactive aggression. However, our findings demonstrated that depression symptoms also had a direct positive relationship with ODD

symptoms, independent of reactive–proactive aggression. Evidence shows that a subset of symptoms among the criteria for ODD distinguish a dimension of oppositional behavior symptoms from symptoms of anger, touchiness, and spitefulness [72, 73]. This negatively oriented affective dimension of ODD has been shown to have a close relationship with higher symptoms of depression in affected individuals [72, 74]. It has been suggested that depressive symptoms and the dimension of the negatively oriented affect within ODD symptoms may be distinct manifestations of certain dispositional tendencies such as a negativistic cognitive style or negative interpretation of ambiguous stimuli [72, 74]. Theoretically, the link among

depression and ODD symptoms mediated by reactive aggression in our models may reflect such a common underlying tendency related with these disorders. On the other hand, depression may impede relations with prosocial peers and positive relationships with parents and may contribute to interpersonal conflict. Therefore, depression also may cause the development of ODD or reinforce the persistence of ODD with its direct effects on interpersonal relationships. We suggest that this secondary psychosocial effects of depression on ODD may be independent from some third variables such as reactive aggression, and our findings that showed a direct relationship of depression to ODD may reflect this aspect of the link among these disorders.

Our third question concerned the possible impact of DBD-related psychosocial impairments on anxiety and depression symptoms in ADHD. Our models showed a positive link from CD to anxiety symptoms but did not find a relationship among any of the DBD symptoms to depressive symptoms. It has been suggested previously that children with DBD may generate anxiety-provoking situations for themselves by their impulsive and dangerous behavior; this causes the development of anxiety disorders [14, 16]. In line with this point of view, a follow-up study showed that anxiety disorders in young adults were predicted significantly by delinquent and aggressive behavior in childhood and adolescence [75]. Our previous cross-sectional study also showed the positive predictor effect of the severity of CD on anxiety in children with ADHD [17]. Previous studies and our current results suggested that anxiety symptoms may develop as secondary to CD in at least some cases with ADHD. As with anxiety, the majority of studies showed that the comorbidity of CD or ODD in ADHD children increases the risk of depression in later life [23–25, 76, 77]. However, a 14-year follow-up study has failed to find such an association [28]. Our findings showing no relationship from DBD to CD is consistent with this report.

Our final question concerned the role of AS on DBD symptoms in children with ADHD. The present study indicated a negative relationship from global AS to DBD. Little information is available regarding the relationship between AS and externalizing disorders. It has been suggested that individuals with higher AS may show decreased aggressive behaviors in response to provocation to reduce the possibility of intense physiological sensations [78]. Accordingly, people with high AS are thought to avoid stimuli that evoke intense anxiety-related sensations. However, there is no compelling evidence that individuals with elevated AS avoid aggressive behavior. Some studies provided evidence for this hypothesis [78], but some of them did not [79, 80]. Our results appeared to support the idea that elevated AS increases avoidance of aggressive

interactions or behaviors and may be protective for the development of DBD. In our models, the link from AS to DBD has varied according to informant. AS showed a negative relationship with CD based on the parent-rated scale, whereas a negative relationship with ODD symptoms was based on the teacher-rated scale. Cross-informant differences are not uncommon in ADHD, and parent–teacher agreement is low to moderate [81, 82]. Therefore, the discrepancy between models is not incompatible with the literature. We suggest that these findings are perhaps due to the fact that teachers more easily observe ODD symptoms than CD symptom. However, both ODD and CD symptoms are likely to attract the attention of parents; thus, CD symptoms can be rated more reliable by them, and parent-rated data may reflect the link among AS and DBD more precisely.

Our results regarding the association between AS and DBD symptoms may shed some light on the link from anxiety to behavioral problems in ADHD. Previous studies proposed that reasons for the dearth of literature involving co-occurring anxiety and DBD may stem from the multifaceted architecture of anxiety and/or behavioral problems [29–31]. Various authors have suggested that contradictory findings among anxiety and DBD would be disentangled by a more detailed phenotyping of the affected children [14]. In line with this viewpoint, research showed that some constructs, such as BI and social withdrawal, which are closely related to anxiety disorders, may show an opposite relationship with behavioral problems in children [29, 42]. We had hypothesized previously, after accounting for its relationship with anxiety, AS, like BI, may have a negative relationship with behavioral problems [17]. Our past and current findings appeared to be in line with this viewpoint by showing that anxiety symptoms and AS had opposite relationships with behavioral problems exhibited by children with ADHD. Overall, it may be posited that, in the absence of anxiety disorders, having higher AS may play a preventive role in the development of DBD in a child who has ADHD. However, if an anxiety disorder develops, it may increase reactive aggression, and then reactive aggression may induce the development of DBD. Furthermore, because anxiety symptoms are triggered directly by the CD symptoms, a vicious circle among anxiety and DBD symptoms would develop in this child.

Some limitations of this study should be addressed. First, data are cross-sectional in nature, which has the standard limitations on making conclusions regarding the relationships between internalizing and externalizing symptoms of ADHD subjects. Longitudinal research examining these relationships as children develop is necessary to understand further the developmental progression of these psychiatric symptoms. Second, anxiety, AS, depression, and aggression were assessed using child self-reports, and children may

have attempted to respond in a socially desirable manner. Therefore, multiple types of assessment, such as parent and teacher reports, would be beneficial in future studies. Third, a structured interview for the diagnosis of comorbid conditions was not performed, and data related to coexisting disorders were based only on self-reported questionnaires. Fourth, we could not assess the relationships of AS subscales with other study variables in an acceptable model and this may prevent providing further information regarding the effects of AS on DBD. Prior research has shown that AS subfactors may have different relationships with psychiatric problems [49]; so future studies that specifically investigate the relationship among AS subfactors and DBD symptoms in ADHD would increase understanding of the link among these disorders. Additionally, our sample consisted of only subjects with the ADHD combined subtype; therefore, children with the ADHD inattention subtype and those with the hyperactive subtype could not be evaluated. Future research may need to use structured interviews to assess comorbid conditions and may need to examine more comprehensively the various ADHD subtypes and AS concerns.

Taken together, to the best of our knowledge, this is the first report investigating the relationships between reactive and proactive aggression and internalizing and externalizing symptoms within the same models in ADHD subjects. The cross-sectional design of this study precluded making a causal inference; however, our findings posit a possible circular relationship among anxiety and depressive disorders, reactive–proactive aggression, and DBD. Accordingly, the high rate of anxiety and depression may lead to higher levels of antisocial behaviors via their elevated effects on reactive aggression, and antisocial behaviors, which are predicted by reactive aggression, may then lead to anxiety. Higher depressive symptoms also seem to intensify this circular relationship via their increasing effects on reactive and proactive aggression besides its direct effects on ODD. Therefore, if an internalizing disorder or DBD develop in a child who had ADHD, these conditions seem to trigger each other reciprocally. The present study also investigated the relationship between AS and co-occurring DBD symptoms in ADHD subjects. Contrary to anxiety and depression, AS showed a negative relationship with DBD symptoms, which suggests that AS increases avoidance of aggressive interactions or behaviors. Overall, this study posits that to understand the relationships among internalizing and externalizing symptoms, examining certain third factors such as reactive–proactive aggression and AS may be beneficial. It is recommended that future longitudinal studies attempt to resolve the issue of whether reactive–proactive aggression and AS are important constructs for the link between internalizing and externalizing symptoms in ADHD.

Summary

Minimal information is available regarding the relationship between comorbid internalizing and externalizing symptoms in ADHD. This study evaluated the associations between anxiety, depression, and DBD symptoms in the context of their relationships with reactive–proactive aggression and AS in ADHD subjects. The sample consisted of 342 treatment-naïve children with ADHD ages 8–17 years. The severity of ADHD and comorbid DBD symptoms were assessed via parent- and teacher-rated behavioral disorder scales. The severity of anxiety, AS, depression, and reactive–proactive aggression were evaluated by self-report inventories. The association between psychiatric variables was evaluated using two distinct structural modeling equations based on the parent-rated (Model-1) and teacher-rated (Model-2) behavioral disorder scales. According to Model-1, depression symptoms were associated with both reactive aggression and proactive aggression, and anxiety symptoms were associated with reactive aggression. In turn, reactive and proactive aggression were associated with ODD and CD symptoms, respectively. There is a direct relationship from depressive symptoms to ODD symptoms, as well. The models also showed that AS total scores negatively related to CD scores, and CD scores positively related to anxiety scores. In Model-2, there was no relationship among proactive aggression and CD scores, and instead of CD scores, AS total scores had a negative relation with ODD scores. The relationships among other test scores were similar to Model-1. These findings suggest that coexisting depression and anxiety symptoms of ADHD children may escalate DBD symptoms through their increasing effects on reactive–proactive aggression. Results also suggest a decreasing effect of global AS on CD symptoms, while the CD symptoms had an increasing effect on anxiety symptoms.

Compliance with Ethical Standards

Conflict of interest There is no conflict of interest.

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