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Callous-Unemotional Traits, Proactive Aggression, and Treatment Outcomes of Aggressive Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective—Stimulant treatment improves impulse control among children with attention-deficit/hyperactivity disorder (ADHD). Decreased aggression often accompanies stimulant pharmacotherapy, suggesting that impulsiveness is integral to their aggressive behavior. However, children with high callous-unemotional (CU) traits and proactive aggression may benefit less from ADHD pharmacotherapy because their aggressive behavior seems more purposeful and deliberate. This study's objective was to determine if pretreatment CU traits and proactive aggression affect treatment outcomes among aggressive children with ADHD receiving stimulant monotherapy.

Method—We implemented a stimulant optimization protocol with 160 6- to 13-year-olds (mean [SD] age of 9.31 [2.02] years; 78.75% males) with ADHD, oppositional defiant or conduct disorder, and significant aggressive behavior. Family-focused behavioral intervention was provided concurrently. Primary outcome was the Retrospective Modified Overt Aggression Scale. The Antisocial Process Screening Device and the Aggression Scale, also completed by parents, measured CU traits and proactive aggression, respectively. Analyses examined moderating effects of CU traits and proactive aggression on outcomes.

Results—82 children (51%) experienced remission of aggressive behavior. Neither CU traits nor proactive aggression predicted remission (CU traits: odds ratio=0.94, 95% CI=0.80–1.11;

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proactive aggression, odds ratio=1.05, 95% CI=0.86–1.29). Children whose overall aggression remitted showed decreases in CU traits (effect size=–0.379, 95% CI=–0.60 to –0.16) and proactive aggression (effect size=–0.463, 95% CI=–0.69 to –0.23).

Conclusions—Findings suggest that pretreatment CU traits and proactive aggression do not forecast worse outcomes for aggressive children with ADHD receiving optimized stimulant pharmacotherapy. With such treatment, CU traits and proactive aggression may decline alongside other behavioral improvements.

Keywords

aggression; attention-deficit/hyperactivity disorder (ADHD); CNS stimulants; oppositional defiant disorder; psychopathy

Introduction

Chronic aggressive behavior usually first develops during childhood^{1–3} and is among the foremost impairments for which children obtain mental health care.⁴ Different types of aggression, though, are thought to have distinct determinants and may therefore require different treatments.^{5–7} The leading approach to subtyping aggressive behaviors distinguishes incidents by the aggressor's motivation.^{7–11} This framework differentiates aggressive behaviors with mainly defensive aims (reactive) from aggressive behaviors whose goals seem chiefly acquisitive (proactive).

Reactive aggression arises when frustration, annoyance, or perceived threat provokes hostile behaviors to repel them. Observers judge these reactions as aggressive when they are abnormally intense, dyscontrolled, or forceful and seem unwarranted because they follow commonplace triggers that age-mates endure with composure. Reactive aggression is a frequent complication of psychiatric disorders that raise susceptibility to negative affect, especially irritability, that impair impulse control, or that distort one's detection and appraisal of threat.^{12–19}

Proactive aggression describes harmful volitional behavior that extracts objects of desire (e.g., material goods, social dominance, sexual contact) through unjustified violation of someone else's rights or well-being. Characteristics that facilitate proactive aggression include impulsiveness and inflated belief in one's entitlement to satisfaction regardless of its consequences.^{20–22} Environmental factors that foster proactive aggression include association with milieus that reward and valorize coercive behavior, or that condone aggressive conduct because they regard its victims as adversaries or outsiders.^{23–25}

An important individual factor that contributes to proactive aggression is flattened emotional response to others' suffering, and, in particular, indifference to the hardship one's behaviors cause.²⁶ The leading descriptor of these features as callous-unemotional (CU) traits²⁷ evokes well the diminished empathy, lack of remorse, and insincerity they engender. These characteristics are central to most definitions of psychopathy.^{28–30}

While a proactive–reactive dichotomy offers a useful framework for aggressive behaviors, its value as a classification method for individuals is less clear. Many individuals display

aggressive behaviors of both types.^{31,32} Quantitative measures of these behaviors show strong correlations.^{33–36} Among children, persistent proactive aggression most frequently develops among those with significant reactive aggressive behavior as well.³² The most common behavioral phenotypes involve either reactive aggressive behavior alone or reactive-plus-proactive aggressive behaviors.³⁷

Elevated impulsivity in childhood seems to be a common substrate for both proactive and reactive aggressive behavior, which further reinforces their linkage.³⁵ Psychometric and diagnostic data likewise show that impulsivity's correlation with CU traits is substantial.^{2,31,38,39} More broadly, trait impulsivity heightens one's risk for the "externalizing" disorders (oppositional defiant disorder [ODD], conduct disorder [CD], substance use, etc.) that share weak inhibitory behavioral control.⁴⁰

Effective pharmacotherapy for the impulsivity, inattention, and hyperactivity associated with attention-deficit/hyperactivity disorder is well-established. Optimized stimulant treatment also often culminates in reduced aggressive behavior among youngsters with attention-deficit/hyperactivity disorder (ADHD), consistent with impulse control problems having an elemental role in childhood aggression.⁴¹ However, a common view is that proactive aggression, with roots not only in impulsivity but also in unfavorable socialization, will be less responsive to pharmacotherapy. *e.g.*,⁴² High proactive aggression might also signify greater severity and so predict weaker treatment effects for all conduct problems. Similarly, because aggression related to interpersonal callousness seems largely volitional, high CU traits may reduce the likelihood that conduct problems will diminish with pharmacotherapy for ADHD. Indeed, there is concern that improved self-control might contribute to more skillful deceit and coercive behavior.⁴³

This study examined whether baseline CU traits and proactive aggression attenuate favorable changes in aggression and other behavioral outcomes following optimized stimulant pharmacotherapy among 6- to 13-year-old children with ADHD. Changes in CU traits and proactive aggression were also evaluated.

Method

Study Design

This report's data come from the initial open stimulant titration phase of two clinical trials for children with ADHD, oppositional defiant or conduct disorder, and persistent aggressive behavior. One trial was conducted at Stony Brook University Medical Center (Stony Brook, New York) and at Long Island Jewish Medical Center (New Hyde Park, New York). The University of Texas Health Science Center at San Antonio joined these sites in a second trial.

Both trials implemented the same stimulant titration and monitoring protocol, whose objective was to identify each child's most effective and best-tolerated stimulant monotherapy regimen. This protocol served as a lead-in phase to determine eligibility for randomized, double-blinded controlled trials of treatments added to stimulant medication for children whose aggressive behavior proved refractory to stimulant monotherapy.^{41,44}

Participants

Participant eligibility criteria for both trials differed only by the required age at enrollment, which was 6-to 13-years-old in the first trial and 6–12 in the second. Boys and girls were eligible who met the following additional inclusion criteria.

Diagnosis: Participants fulfilled *DSM-IV-TR* criteria for (a) attention-deficit/hyperactivity disorder (any subtype), and (b) either oppositional defiant disorder (ODD) or conduct disorder (CD).

Severity of ADHD and Aggression: Parent ratings yielded scores at least 1.5 standard deviations above the normative mean for the child's age and gender on both the Restless/Inattentive subscale of the Conners Global Index^{45,46} (ConnGI-P) and the Aggressive Behavior subscale of the Child Behavior Checklist⁴⁷ (CBCL). Aggressive behavior during the preceding week had to be clinically significant, gauged by a total score more than 24 on the parent-completed Retrospective Modified Overt Aggression Scale (R-MOAS), as described in an earlier publication.⁴⁴

Prior Pharmacotherapy: Children needed to have had prior treatment with psychostimulant medication for one month on at least 30 mg per day of methylphenidate or equivalent (e.g., 15 mg of an amphetamine-based compound, 15 mg of dexamethylphenidate).^{48,49} Requiring this threshold for prior treatment in addition to current symptom severity aimed to increase the likelihood that participants would have incomplete response to stimulant monotherapy and be eligible for the controlled trial of adjunctive medication.

Other: Eligibility required the child to live with a caregiver legally empowered to permit study enrollment and able to complete study assessments.

We excluded from participation children with major depressive disorder, bipolar I disorder, Tourette's disorder, psychotic disorders, autistic disorder, and IQs below 70. An anxiety disorder was disqualifying if aggressive behavior was mainly a complication of it (e.g., a child with separation anxiety who became aggressive only in the context of separation situations). Health-related exclusion criteria were seizure disorders, pregnancy, and medical contraindications to treatment with stimulants, risperidone, or divalproex sodium.

After complete description of the study, parents or legal guardians provided written informed permission and children over 8 years old gave written assent. Each site's Institutional Review approved procedures prior to trial commencement and conducted annual reviews for reapproval.

Recruitment and Evaluation Procedures

Parents interested in their child's participation completed a screening interview, usually by telephone. Thereafter, eligible families attended an evaluation appointment that included the following components.

Diagnostic assessment comprised interviews with both parent and child utilizing the Schedule of Affective Disorders and Schizophrenia for School-Age Children⁵⁰ (K[iddie]-

SADS) by a clinical child psychologist (J.C.B.) or a child and adolescent psychiatrist (S.R.P., W.B.D., T.M.). Parents and children met for a separate clinical diagnostic evaluation with a child and adolescent psychiatrist (C.A.F., V.K., S.R.P., T.M., W.B.D., J.S., D.M.) or an advanced-practice nurse practitioner in child and adolescent psychiatry (C.S.) who also obtained medical history. The K-SADS interviewer and the clinical assessor conferred to arrive at consensus diagnoses.

Behavioral Outcomes

The primary outcome was the child's posttreatment RMOAS total aggressive behavior score. Other endpoints were ADHD symptom status (per the ConnGI-P's Restless/Inattentive subscale) and the CBCL's Aggressive Behavior factor.

Measures of Proactive-Reactive Aggression and Callous-Unemotional Traits

Parents' completed ratings on Vitiello and Stoff's³³ 16-item Aggression Questionnaire (VAQ). This measure provides scores reflecting how much of the child's aggressive behavior seems proactive (e.g., items pertaining to control, planning, concealment, care not to injure self) and reactive (e.g., items pertaining to dyscontrol, spontaneity, remorse, self-defeating or self-harmful acts during episodes). The scale emphasizes these elements of conduct disturbances, rather than the frequency of specific types of problem behaviors, making it a more specific assessment of willful/controlled vs. reactive/dyscontrolled aggressive behavior.

Parents also completed the Antisocial Process Screening Device⁵¹ (APSD). We used this scale's 6-item Callous/Unemotional traits (CU) factor, which emphasizes unconcern for others, remorselessness, shallow emotionality, and manipulativeness. Parents completed the full scale, which also yields Narcissism and Impulsivity factors scores. This instrument has been widely used in research on CU traits among youth.

Parents completed these measures at the baseline assessment and at the end of the stimulant monotherapy protocol.

Stimulant Titration and Treatment Protocol

This section summarizes the stimulant monotherapy titration and treatment procedures used in both trials, which prior publications have detailed.^{41,44}

Upon enrollment, children discontinued all nonstimulant psychotropic medications with tapering and duration appropriate to the compound's elimination time course. Initial stimulant titration in most instances used a triphasic, osmotically-releasing methylphenidate preparation given once daily (MPH-TRI). Children who experienced problems attributable to MPH-TRI's long duration of action (e.g., insomnia), could switch to a biphasic, bead-released MPH preparation (MPH-BI). Children who gained insufficient benefit for ADHD symptoms with MPH could switch to extended-release mixed amphetamine salts, administered once-daily as a biphasic-release, beaded preparation (MAS-XR).

Adjustments to stimulant agent and dosage concluded when (a) ADHD symptoms resolved, (b) unacceptable or unmanageable adverse effects contraindicated dose escalation, or (c) the

agent's daily ceiling was attained (MPH-TRI: 90 mg/d; MPH-BI: 50 mg/d; MAS-XR: 35 mg/d). Clinicians reviewed data from preceding weeks to identify the best tolerated regimen associated with greatest symptomatic improvement. That regimen was continued or reinstated for a "replication" week, followed by the endpoint assessment. Because the number of agents and dosages undertaken to identify each child's optimal regimen differed between children, the length of this stimulant monotherapy optimization period varied. In some instances, children who completed this titration protocol during summer school breaks with good response had the final assessment of their regimen's adequacy deferred, when clinically indicated, until school had resumed. The mean (SD) interval from baseline to stimulant endpoint assessments was 70.22 (37.48) days.

Concurrent Psychosocial Treatment

Families had behaviorally-oriented psychosocial treatment throughout the trial. Treatment content was the COPE program,⁵² adapted for trials involving children with ADHD.⁵³ Clinical psychologists or advanced graduate students provided this treatment.

Classification of Remitted vs. Refractory Aggressive Behavior

At the endpoint assessment, children with R-MOAS scores 15 and higher were classified as stimulant refractory. Those with lower scores were classified as having remission of their aggressive behavior, based on prior work indicating this range was associated with no or negligible aggressive behavior.^{41,44}

Data Analysis

Linear and logistic regression, using SAS[®] PROC GLIMMIX,⁵⁴ evaluated demographic variables and study site for their associations with baseline proactive aggression subtype, CU traits and behavioral outcomes so that subsequent analyses could adjust for potential confounds.

Logistic regression tested the influence of baseline proactive aggression and CU trait ratings on the odds that aggression remitted at the end of the stimulant monotherapy protocol.

Analyses of change in the continuous-scale behavioral outcomes used SAS[®] PROC GLIMMIX,⁵⁴ treating subjects as random effects, time as a fixed effect, and their interaction as the index of change. The interaction of baseline CU traits with time and of baseline proactive aggression with time tested moderation effects. Further analyses used severity groupings of these covariates as discrete, rather than continuous, predictors.

Results

Participant Sample Derivation and Characteristics

Between January 2004 and September 2012, 780 children were screened for the two trials. Figure 1 contains the CONSORT diagram of this cohort's progress through the trial's selection and treatment stages. Table 1 presents demographic and clinical characteristics of the 160 children who furnished data for this report.

Age showed a significant association with overall aggression ratings. Older children had lower R-MOAS parent ratings averaged over time ($B_{\text{Age/Yrs}} = -1.99$, $t[147] = -2.17$, $p = .032$), but reduction from baseline to endpoint was unrelated to age ($B_{\text{Age/Yrs} \times \text{Time}} = 1.29$, $t[147] = 1.18$, $p = .24$). Children at one site obtained lower aggression ratings than the other two ($B_{\text{Site}} = -10.77$, $t[147] = -2.23$, $p = .027$). Subsequent analyses included age, the random effects of site, and their interactions with time as covariates.

Behavioral Outcomes

Table 2 summarizes behavioral rating scales data obtained at baseline and at the conclusion of the stimulant optimization trial. The table also contains standardized mean differences (SMD) from baseline to endpoint assessment⁵⁵ and their 95% CI.

Just over half (82 of 160; 51%) experienced remission of their aggressive behavior. Children whose aggression remitted showed statistically reliable reductions from baseline on all measures (i.e., confidence intervals for the SMDs exclude zero), including proactive aggression and callous-unemotional traits.

Children whose overall aggressive behavior did not remit showed no statistically reliable changes from baseline (i.e., CIs included zero) on proactive aggression, reactive aggression, and callous-unemotional ratings. Their other behavioral outcomes reflected improvements, but SMDs were only 34% to 53% the magnitude found for the remitter group.

Effects of Baseline Proactive Aggression and CU Traits Scores on Behavioral Outcomes

Neither baseline proactive aggression nor CU traits affected the likelihood that a child would remit (Table 3). Likewise, interactions of baseline proactive aggression and CU traits with time were not statistically significant for any continuous-scale behavioral outcome, indicating that neither variable affected changes on these outcomes.

Baseline proactive aggression was associated with greater severity on several measures averaged over assessments. There were significant main effects on overt aggression, restless/inattentive symptoms, CBCL Externalizing Behavior, and CU traits. Baseline CU traits showed main effects for restless/inattentive symptoms, CBCL Externalizing Behavior, and proactive aggression ratings, signifying in a similar manner their association with severity.

We tested the joint effects of proactive aggression and CU traits by including both of these covariates and their interaction. There were no significant interactions of proactive aggression and CU traits on any outcome.

We tested whether CU traits predict less improvement in proactive aggression specifically. The bottom row of Table 3 shows a meager CU traits by Time interaction on proactive aggression ($p = .08$). However, this effect is toward larger reductions in proactive aggression as a function of baseline CU traits.

Effects of Severity Groupings for Baseline Proactive Aggression and CU Traits

Scores of 0 or 1 on the VAQ's proactive subscale captured the lower 30.3%; of 2 or 3 were the middle 42.3%; and 4 through 7 were the upper 27.4%. Scores of 0 through 4 on the

APSD's CU subscale captured the lower 32.8%, 5 or 6 were the middle 42.2%, and 7 or above the upper 27.1%.

Figure 2's histograms and analyses show overall higher behavioral symptoms as a function of baseline proactive aggression and CU traits severity grouping. However, a child's severity group was unrelated to the magnitude of improvement on behavioral outcomes. The only significant interaction between baseline proactive aggression group and time was for proactive aggression itself (2a); those in the high group showed larger reductions after treatment. Baseline CU traits showed a similar pattern (4b).

Effects of Categorical Callous-Unemotional CD Subtype Criteria

A new specifier for the diagnosis of CD, "With Significant Callous-Unemotional Traits", designates individuals who manifest at least two of four CU cardinal features.⁵⁶ Using baseline APSD CU ratings to apply these criteria,⁵⁷ we identified 26 children (16.25%) as specifier-positive (diagnosis of conduct disorder, however, was not required). At the endpoint assessment, eleven (42.2%) met aggression-remission criteria, compared with 71 of 126 (53%) of the other participants. This difference is not statistically significant (OR [95% CI], 0.8 [0.52 – 1.26]). Most (17 [62.4%]) children who fulfilled specifier-positive criteria at baseline did not at the endpoint assessment. Ten who were specifier-negative at baseline (7.46%) became specifier-positive at the endpoint.

Discussion

We examined whether elevated baseline CU traits or proactive aggression would diminish the effectiveness of stimulant monotherapy in reducing aggressive behavior among children with ADHD. These findings indicate that they do not. The possibility that CU traits selectively keep proactive aggression elevated was not supported.

Baseline ratings of proactive aggression and CU traits correlated with severity of behavioral disturbance. However, children who experienced remission of overt aggressive behavior also showed substantial reductions in post-treatment ratings of both CU traits and proactive aggression.

The assumption that successful coercive control over others perpetuates proactive aggression has implied that pharmacotherapy would be unhelpful in ameliorating it. Proactive aggression might also signify a more pernicious pattern of overall conduct problems that would prove refractory to treatment. Our results, in contrast, show that optimized treatment for ADHD warrants strong consideration as first-line intervention for children who present with significant aggression whether or not informants perceive that such behaviors are often volitional. This inference might not apply to children with ADHD whose aggressive behaviors are exclusively proactive, but preadolescents with this presentation in clinical settings are uncommon.

Mechanisms through which improved impulse control may lead to reduced proactive aggression warrant examination. Possible mechanisms may include improved capacity to delay gratification and, relatedly, to redirect one's behavior away from high-intensity, high-

reward situations that have unfavorable consequences.^{58,59} While pharmacotherapy may affect one or more “substrates” of childhood aggression (e.g., impulsiveness), environmental factors are probably important to changes in behavior. To delay gratification is not to forgo it entirely. Accordingly, devising alternative pathways to reward is a core element of behavioral interventions, including the one used in this trial. Peer group facilitation and reinforcement of antisocial behavior is a common feature of adolescent misconduct.^{60,61} Pharmacotherapy for underlying vulnerabilities, such as impulsivity, may be ineffective in reducing adolescent conduct disturbances unless disengagement from problematic peers also occurs.⁶²

Earlier studies of CU traits and treatment response in this age group reported mixed results. Among 4- to 8-year-old children with ODD, but not ADHD, CU ratings predicted less benefit from behavioral management training for parents.⁶³ In a full-day treatment program for 7- to 12-year-olds with ADHD and ODD/CD, those with higher CU ratings appeared to require stimulant treatment to ameliorate their conduct problems; children with lower CU ratings had consistently low daily conduct problems with or without stimulant treatment.⁶⁴ In contrast, outpatient treatment for ODD or CD showed no influence of CU traits on outcomes adjusted for baseline severity, although teachers provided CU rating while parents supplied outcome data.⁶⁵

The present report resolves some of these ambiguities. High CU ratings correlated with overall severity, but, in this cohort with significant persistent aggression, they did not work against treatment response to stimulant pharmacotherapy and behavioral intervention. Moreover, CU traits themselves improved along with reduced overt aggressive behavior.

Consistent with their conceptualization as traits, CU ratings display moderate consistency over time.^{66–69} Treatment studies that evaluated changes in children’s CU traits reported decreases, as we have.^{70, p. 138} These sets of findings are not incompatible. Although they decline when aggressive behavior improves, CU ratings among aggression remitters still corresponded to the 75th–95th percentiles of the normative sample.^{51, p. 36} Although it is encouraging that high CU trait ratings did not militate against treatment, the longer-term impact of persistently high CU traits is uncertain.

Still, our finding that CU ratings decline alongside other symptoms after stimulant monotherapy is not an obvious corollary of prevailing ideas about interpersonal callousness. This topic’s literature emphasizes the separability of CU traits from other factors that influence aggressive and antisocial behavior.⁷¹ But CU’s distinctiveness does not exclude a role for other factors in generating the behaviors associated with it. Some studies support a distinction between “primary” and “secondary” psychopathic traits^{72,73}. Primary psychopathy designates callous and harmful individuals who nevertheless show high social adeptness, confidence, and few psychiatric symptoms. In the secondary variant, psychopathic features result from psychopathology or adverse experiences, and so may be more responsive to treatment. Emotional instability and abuse have drawn attention in the genesis of secondary psychopathy.⁷² Likewise, the impulse control deficits that epitomize ADHD may identify those whose apparent callousness develops as a complication of long-

term interpersonal conflict. CU features might then recede when timely treatment curbs the impulsive behavior that instigates these clashes.

An important limitation of this study is that measurement of proactive aggression and CU traits involves parents' attributions and inferences concerning child motives. This method is susceptible to biases relating to parent-child relationships and parents' explanatory frameworks for their children's difficulties. Misspecification of aggression proactivity and CU traits is therefore possible. Relatedly, reductions in one salient characteristic such as aggression may evoke in raters a tendency to overestimate other positive changes, such as in CU traits. Such "halo effects," however, seem tempered by findings that the effects sizes for CU traits are smaller than for overt aggression and ADHD symptoms.⁷⁴

Clinical trials, like other treatment encounters, provide participants information about diagnosis and treatment. This trial also included behavioral therapy intended to improve parent-child interactions. These psychoeducational and behavioral interventions may have led parents to attach less blame to the child as a willful protagonist of upsetting behavior.⁷⁵ One might then expect that ratings of proactivity and CU traits would show meaningful reductions even if behavioral symptoms remained high. However, such reductions were not apparent among children whose aggression did not improve. Another limitation, common among short-term trials for chronic disturbances, is that their significance for long-term outcomes is uncertain.

Numerous studies have explored the psychophysiological, cognitive, neurofunctional, and neuroanatomical, correlates of aggression and CU traits, e.g.,⁷⁶⁻⁷⁹ with several focusing on youth.⁸⁰ Stimulant treatment is likely to affect several of the brain systems implicated. This study suggests that the association between treatment-related neural changes and behavioral response may be a useful avenue to advance research on the emergence, differentiation, and curtailment of severe conduct problems among youth.

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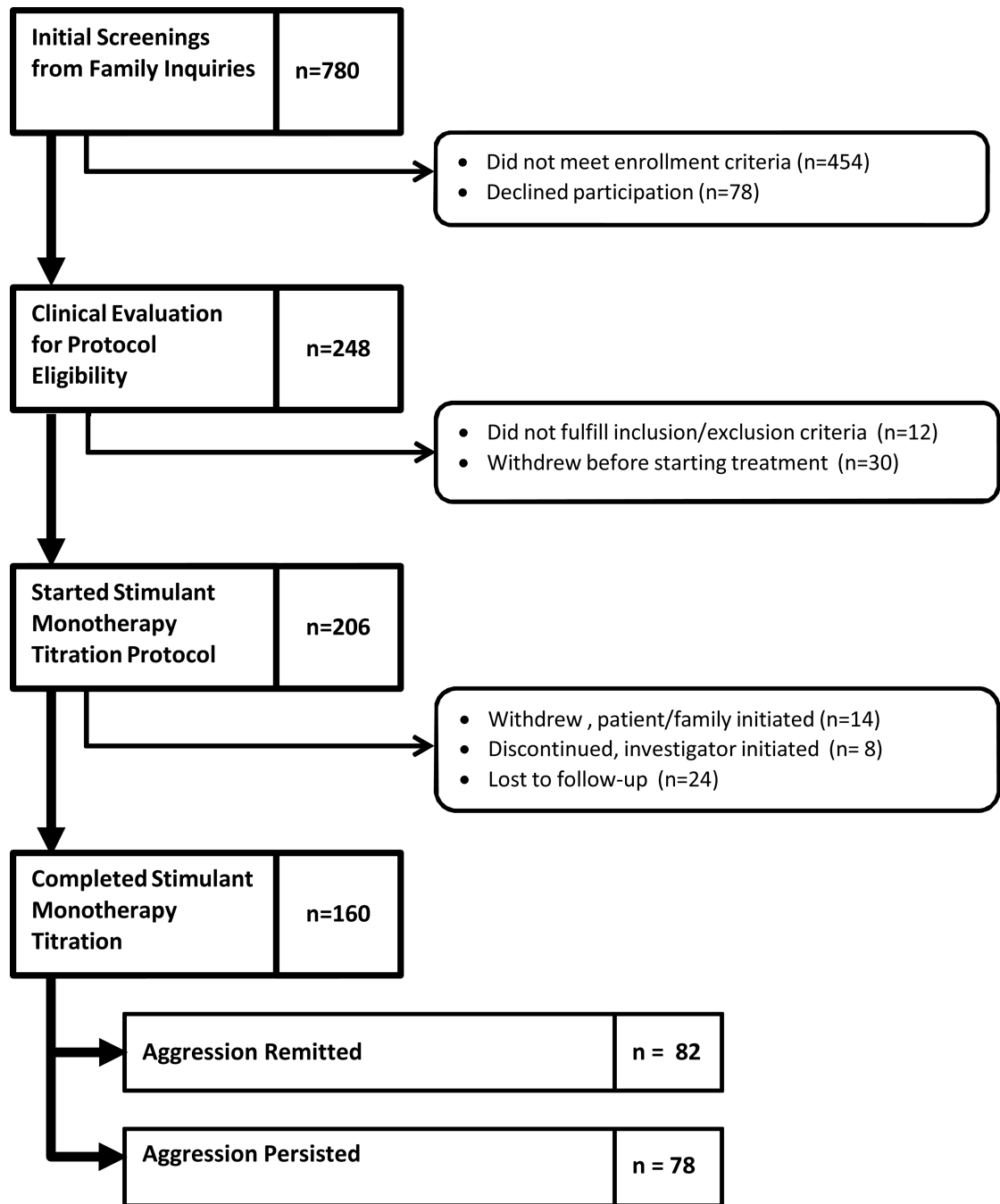
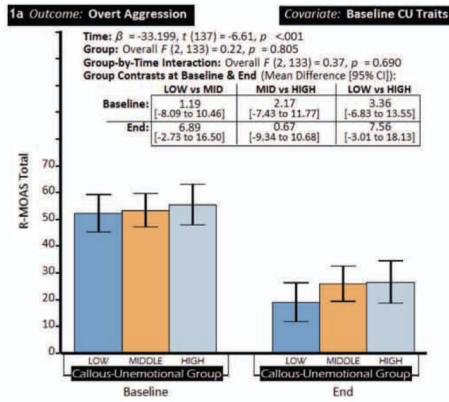
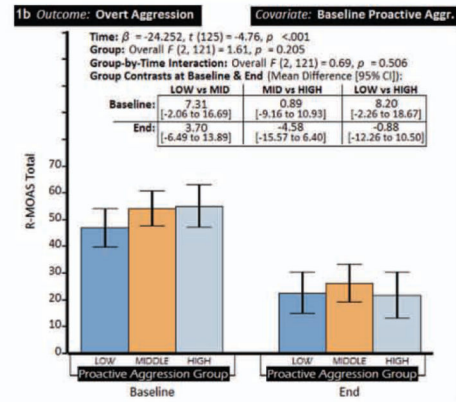


Figure 1.
Consolidated Standards of Reporting Trials (CONSORT) Diagram.

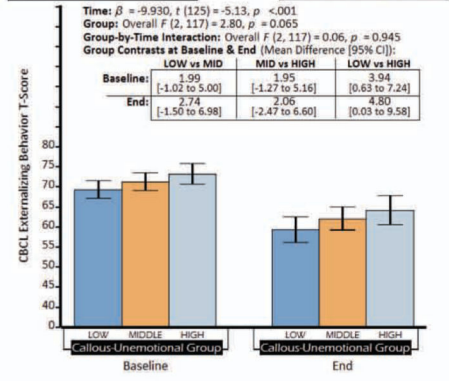
CU Traits Baseline Severity Groups



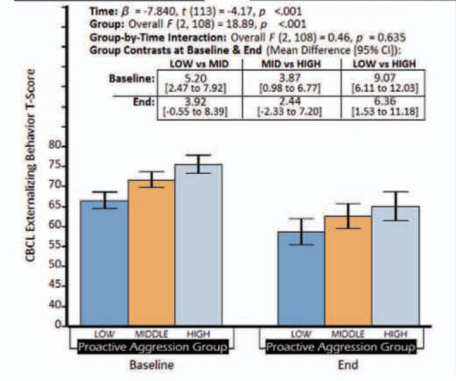
Proactive Aggression Baseline Severity Groups



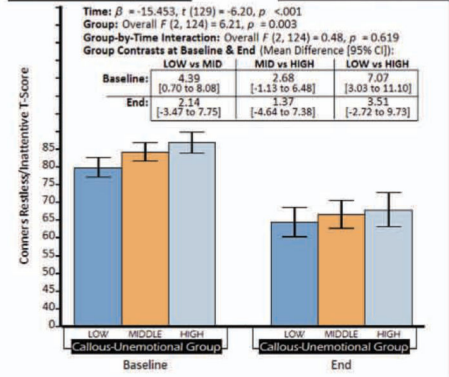
2a Outcome: Externalizing Beh. **Covariate: Baseline CU Traits**



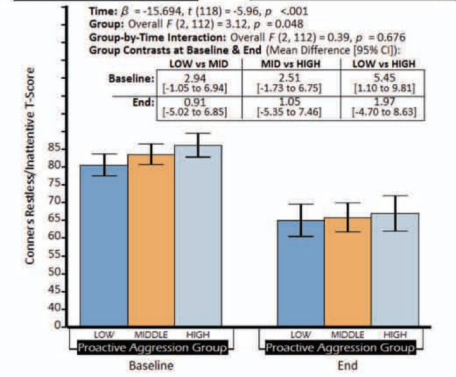
2b Outcome: Externalizing Beh. **Covariate: Baseline Proactive Aggr.**



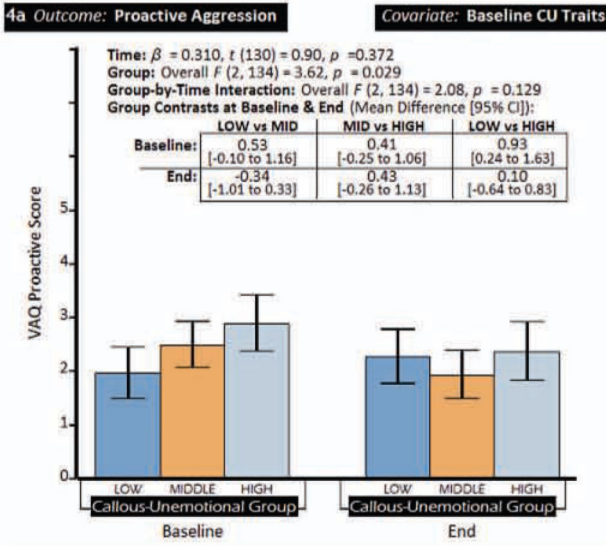
3a Outcome: ADHD Symptoms **Covariate: Baseline CU Traits**



3b Outcome: ADHD Symptoms **Covariate: Baseline Proactive Aggr.**



CU Traits Baseline Severity Groups



Proactive Aggression Baseline Severity Groups

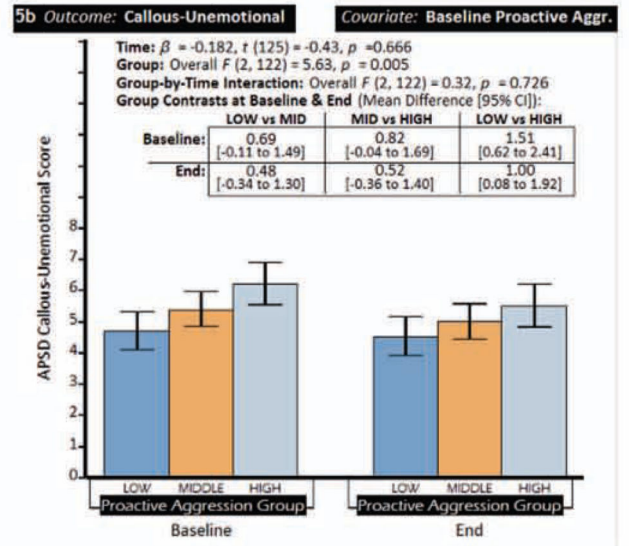
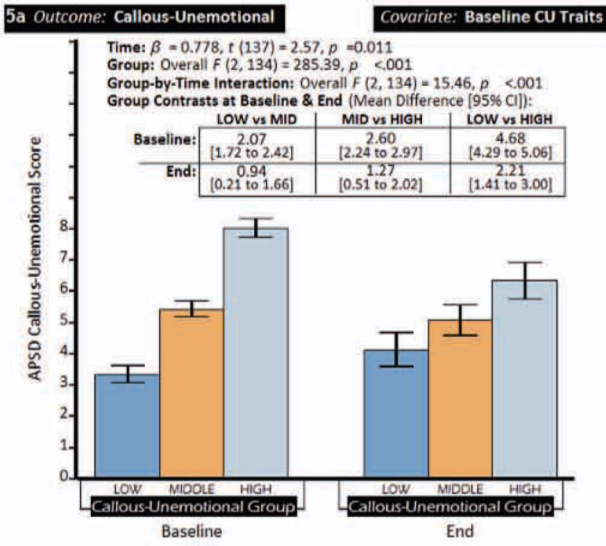
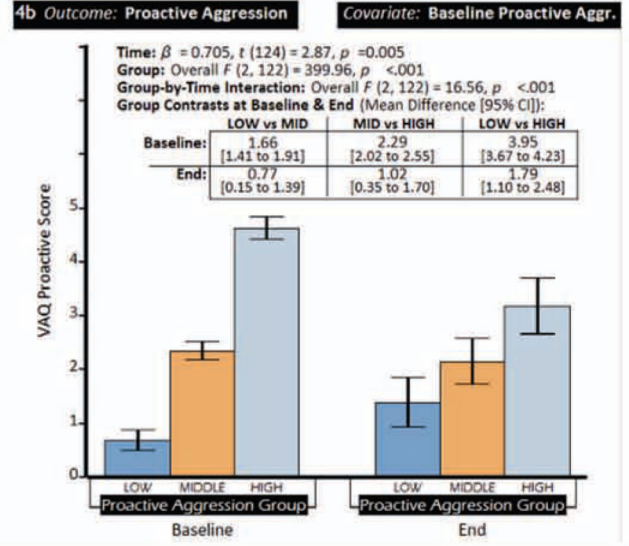


Figure 2.

Behavioral outcomes for groups with low, middle, and high scores at baseline on proactive aggression and callous-unemotional traits. Note: Each row shows associations between one behavioral outcome and baseline severity groups (low, middle, high) of proactive aggression and callous-unemotional traits. Panels on the left show behavioral outcomes with participants stratified by proactive aggression group. Panels on the right show callous-unemotional traits groups. The table within each chart shows the contrasts between the 3 severity groups (the differences in least-squares means and the 95% CI for that difference) at baseline and at the end of the stimulant monotherapy protocol. APSD C-U = Antisocial Process Screening Device Callous-Unemotional scale; CBCL = Child Behavior Checklist; ConnGI-P =

Conners Global Index (Parent Version); R-MOAS = Retrospective-Modified Overt Aggression Scale; VAQ = Vitiello Aggression Scale.

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Table 1

Participants' Demographic and Clinical Characteristics (N=160)

Age, m (SD)		
Years	9.31	(2.20)
Gender, n (%)		
Male	126	(78.75)
Female	34	(21.25)
Race or Ethnic Group, n (%)		
White	94	(58.75)
African-American	25	(15.63)
Hispanic	31	(19.38)
Other or mixed heritage	10	(6.25)
Diagnoses Comorbid with ADHD, n (%)		
Oppositional defiant disorder	143	89.38
Conduct disorder	17	10.63
Anxiety disorder	39	24.53
Mood disorder	18	11.32
Optimized Stimulant Monotherapy Regimen, n (%)		
Stimulant Preparation		
Methylphenidate, triphasic release	100	62.50
Methylphenidate, biphasic release	16	10.00
Mixed amphetamine salts, extended release	38	23.75
Other	6	3.75
Total daily dose in MPH equivalent, m (SD)		
Complete sample	43.07	15.63
Aggression-remitted group	42.02	16.06
Aggression-refractory group	44.61	16.58
Days from baseline assessment to final stimulant monotherapy endpoint assessment, m (SD)		
Complete sample	70.22	37.47
Aggression-remitted group	67.90	35.73

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Aggression-refractory group	72.66	39.30
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Note: ADHD = attention-deficit/hyperactivity disorder; MPH = methylphenidate

Table 2

Behavioral Ratings and Standardized Mean Differences from Baseline to Endpoint

	Full Sample (N = 160)			Stimulant Monotherapy Outcome Groups					
	BASELINE ₁ M (SD)	STIM END ₁ M (SD)		BASELINE ₂ M (SD)	STIM END ₂ M (SD)	DIFFERENCE Standardized (95% CI)	BASELINE ₃ M (SD)	STIM END ₃ M (SD)	DIFFERENCE Standardized (95% CI)
Overt Aggression Total (RMOAS)	52.65 (23.72)	22.74 (24.14)		47.30 (21.88)	5.07 (5.32)	-1.769 (-2.58 to -0.96)	58.28 (24.46)	41.32 (22.17)	-0.711 (-1.73 to 0.311)
Proactive Aggression (VAQ)	2.46 (1.58)	2.16 (1.57)		2.51 (1.60)	1.77 (1.30)	-0.460 (-1.33 to 0.41)	2.41 (1.57)	2.58 (1.74)	0.106 (-0.83 to 1.04)
Reactive Aggression (VAQ)	3.86 (1.54)	2.97 (1.99)		3.73 (1.56)	2.04 (1.76)	-1.065 (-2.24 to 0.11)	3.99 (1.55)	3.95 (1.77)	-0.029 (-0.88 to 0.82)
Callous-Unemotional (APSD)	5.48 (2.01)	5.10 (2.02)		5.36 (1.95)	4.64 (1.87)	-0.358 (-1.20 to 0.48)	5.60 (2.05)	5.59 (2.06)	-0.007 (-0.76 to 0.75)
Narcissism (APSD)	6.45 (3.07)	4.59 (2.77)		6.79 (3.25)	3.93 (2.59)	-0.916 (-1.73 to -0.10)	6.10 (2.83)	5.27 (2.80)	-0.263 (-0.95 to 0.43)
Impulsivity (APSD)	7.14 (1.72)	5.53 (2.20)		7.07 (1.63)	4.74 (2.14)	-1.340 (-2.45 to -0.23)	7.22 (1.81)	6.37 (1.94)	-0.486 (-1.25 to 0.28)
Restless/Inattentive, T (ConnGI)	82.72 (9.15)	64.68 (13.59)		82.87 (9.65)	59.61 (12.88)	-2.499 (-3.62 to -1.37)	82.56 (8.63)	70.01 (12.21)	-1.348 (-2.58 to -0.12)
Emotional Lability, T (ConnGI)	79.48 (9.57)	63.65 (15.10)		78.95 (10.04)	55.70 (12.88)	-2.412 (-3.58 to -1.24)	80.03 (9.10)	72.01 (12.50)	-0.832 (-2.00 to 0.34)
Externalizing Behavior, T (CBCL)	71.50 (6.84)	61.55 (10.17)		70.82 (7.00)	56.98 (9.84)	-1.922 (-3.02 to -0.83)	72.20 (6.81)	66.35 (8.08)	-0.812 (-1.76 to 0.14)

Note: APSD = Antisocial Process Screening Device; CBCL = Child Behavior Checklist; ConnGI-P = Connors Global Index (Parent Version); R-MOAS = Retrospective-Modified Overt Aggression Scale; Stim = stimulant; VAQ = Vitello Aggression Scale.

Effects of Baseline Measures of Proactive Aggression and Callous-Unemotional Traits on Trial Outcomes

Table 3

OUTCOMES	EFFECTS									
		Time	Proactive Aggression		Baseline Aggression INTERACTION WITH TIME	Callous-Unemotional Traits		Baseline Unemotional Traits INTERACTION WITH TIME		
			MAIN EFFECT	INTERACTION WITH TIME		MAIN EFFECT	INTERACTION WITH TIME			
Remission of Aggressive Behavior	OR		1.042				0.941			
	95% CI		0.904-1.20				0.840-1.054			
	<i>t</i>		0.564				-1.049			
Overt Aggression Total	B	-37.987	2.454	-2.315			0.994	1.376		
	<i>t</i>	-5.616***	2.060*	-1.664			1.019	1.202		
	B	-15.318	1.237	-0.711			1.182	-0.490		
Restless/Inattentive, <i>T</i>	<i>t</i>	-4.630***	2.641**	-0.994			3.282***	-0.863		
	B	-13.029	0.756	-0.694			0.480	-0.506		
	<i>t</i>	-3.646***	1.596	-0.916			1.270	-0.828		
Externalizing Behavior, <i>T</i>	B	-11.780	2.066	-0.438			0.918	0.338		
	<i>t</i>	-5.171***	6.329***	-0.869			3.170**	0.860		
	B	-0.201	0.332	-0.076						
Callous-Unemotional Traits	<i>t</i>	-0.721	3.400***	-0.789						
	B	0.385					0.218	-0.124		
	<i>t</i>	0.935					3.435***	-1.741		

Note: OR = odds ratio.

* *p* 0.05,

** *p* 0.01,

*** *p* 0.001