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Oxytocin Receptor Gene Variant Interacts with Intervention Delivery Format in Predicting Intervention Outcomes for Youth with Conduct Problems

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Abstract Coping Power is an evidence-based preventive intervention program for youth with aggressive behavior problems that has traditionally been delivered in small group formats. Because of concerns about iatrogenic effects secondary to aggregation of high risk youth, the current study examined whether genetic risk may moderate intervention outcome when youth were randomly assigned to group versus individual formats of an intervention. The oxytocin receptor gene (OXTR) has been associated with social behavior and may influence susceptibility to social reinforcement in general and deviant peer influence in particular. One variant of OXTR (rs2268493) was examined in 197 fourth-grade African-American children (64% male) who were randomly assigned to Group Coping Power or Individual Coping Power (Lochman et al. 2015). Longitudinal assessments of teacher- and parent-reported behavior were collected through a 1-year follow-up. Growth curve analyses revealed a genotype by delivery format interaction. Youth with the A/A genotype demonstrated reductions in externalizing problems over the course of the intervention regardless of intervention format. In contrast, carriers of the G allele receiving the group-based intervention showed little improvement during the intervention and a worsening of symptoms during the follow-up year, while those receiving the individual format demonstrated reductions in externalizing problems. Given the associations between this OXTR variant and social bonding, carriers of the G allele may be more sensitive to social rewards from deviant peers in the group setting. This study suggests that genetic factors may be useful in predicting which type of intervention will be most effective for a particular individual.

Keywords Aggression · Conduct problems · Oxytocin receptor gene · Preventive intervention · Deviant peer

Interventions for behavior problems during childhood have the potential to prevent a cascade of negative outcomes, including criminal behavior, academic failure, and overreliance on government services in the future (Dodge 2009). Such programming may provide an opportunity to alter the developmental trajectory of aggressive behavior, thereby reducing rates of aggression and other negative outcomes such as school failure, substance use, and legal problems.

A number of programs have been developed to prevent the development of behavior problems in at-risk youth. One of the few rigorously tested school based programs currently available to address behavior problems among at-risk preadolescent children is called Coping Power (Lochman and Wells 2002, 2003, 2004). This multi-component program is designed for youth who display high levels of teacher- and parent-rated aggressive behaviors and are therefore at risk for later problem behaviors. It involves group sessions that take place at the students' schools, separate group sessions for parents, and supports to teachers.

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Efficacy and effectiveness studies indicate that youth receiving Coping Power demonstrate lower rates of youth substance use and delinquent behavior at post-intervention and at a 1-year follow-up than youth in a control condition who had not participated in the program (Lochman and Wells 2003, 2004). The intervention has also been found to significantly reduce teacher-rated externalizing behavior problems and callous-unemotional traits through 3-year follow-ups in two separate samples (Lochman et al. 2014; Lochman et al. 2013). Reductions in proactive aggression, improved social competence, improved concentration, and greater teacher-rated behavioral improvement at the end of intervention have also been found, compared to children who did not receive Coping Power (Lochman and Wells 2002).

Despite the overall positive effects of Coping Power, questions have been raised as to whether there are potentially negative effects of aggregating high-risk children into groups because of the opportunity for increased affiliation with deviant peers, thus making the program less effective than it could be (Dishion and Tipsord 2011; Dodge et al. 2006). Research suggests that involvement with deviant peers increases the risk for adolescent problem behaviors (Dodge et al. 2006). To assess this issue, Lochman et al. (2015) recently conducted a controlled trial in which youth were randomized to receive either the traditional Group Coping Power (GCP), or a version in which sessions were administered individually to youth (Individual Coping Power (ICP)). Results revealed that although children in both conditions demonstrated significant reductions in teacher- and parent-reported behavior problems at the end of a 1-year follow-up, the degree of improvement on teacher-reported outcomes was significantly greater for children receiving the individual version of the program, and this difference between formats was especially evident for children with poorer inhibitory control. Children's poor self-control has been proposed to contribute to poor outcomes because of these children's vulnerability to negative peer influences (Wills and Dishion 2004). In support of this hypothesis, Mrug et al. (2012) found that high levels of inhibitory control served a protective function for adolescents who had antisocial friends, limiting their involvement in delinquency and substance use. In contrast, low attention control has been associated with impulsive behavior, which then increases sensitivity to the reinforcement of deviant peer interactions (Snyder et al. 2010).

The finding that some youth respond poorly to group-based interventions presents a challenge for interventionists regarding feasibility. Delivering interventions in individual sessions is significantly more time intensive and costly. Under circumstances of limited resources, it is likely that intervention programs would not be able to reach as many youth if delivered in an individual format. Furthermore, we know that some youth do well in group-based interventions, and may benefit just as much as they might in an individual intervention. The problem is that prior to the intervention, we know very little about which youth may do well in a group-based intervention, and which youth would benefit more from the individual format. If research can identify children who do not fare as well in the group format, then the group intervention may be able to be modified to address the social mechanisms which may account for the differential impact of group intervention formats with aggressive children.

Emerging research suggests that individual characteristics of the youth participating in the intervention likely influence "what works for whom" (Albert et al. 2015). Specific characteristics of the individual may help us to predict which type of intervention would be best for a particular child, thus maximizing the cost-benefit ratio. In the case of group compared to individual interventions, factors that influence how an individual responds to social stimuli may be of particular importance because of the social element inherent in group-based interventions.

The oxytocin system is associated with various aspects of social cognition and behavior in both human and animal studies. Oxytocin has been found to be important for attachment, bonding, trust, and social motivation (Campbell 2010; Gordon et al. 2011). It also influences how individuals respond to others; intranasal oxytocin administration has been found to improve emotion recognition (Guastella et al. 2010) and increase the amount of time attending to the socially informative eye region of the face (Andari et al. 2010). Because of its important role in social cognition, the oxytocin system may influence how an individual responds to the social aspects of a group-based intervention. Although increased awareness to social stimuli and affiliative behavior is typically viewed as advantageous, in the context of a group-based intervention, in which the other members of the group are at-risk for aggression, this could potentially be detrimental as it may promote attachment to deviant peers and increase the likelihood of acting out in order to gain social approval from these peers. Conversely, youth with lower levels social awareness may benefit from the opportunities provided by the group context to practice social skills and become more aware of the emotions and perspectives of others.

In this study, we examine whether variation in a single-nucleotide polymorphism (SNP) of the oxytocin receptor (OXTR) gene, rs2268493, influences responses to the Coping Power program when delivered within a group format compared to being administered individually. This particular SNP was selected because it has been associated with social responding and behavior in a number of previous studies. First, several studies have identified associations between this SNP and the social impairments observed in autism spectrum disorder (Campbell et al. 2011; Di Napoli et al. 2014; Yrigollen et al. 2008). Another study found that the A allele of this SNP was associated with poorer performance on a measure of social cognition and on specific tests of

mentalizing and social perception in individuals with schizophrenia (Davis et al. 2014). Together these studies suggest that the A allele may be associated with reduced sensitivity to social cues, reduced interest in social rewards, and an impaired ability to take the perspective of others.

Second, individuals homozygous for the A allele rs2268493 have been found to have reduced activity in the mesolimbic reward circuitry during the anticipation of rewards (Damiano et al. 2014). Although this study did not examine social reward specifically, intranasal oxytocin administration has been found to influence mesolimbic responses to social stimuli (Rilling et al. 2012). Thus, through its effects on the reward circuitry of the brain, this SNP may influence how motivated individuals are by social rewards.

Finally, Beitchman et al. (2012) found that the haplotype consisting of the A allele of rs2268493 and the A allele of another SNP on the OXTR gene was associated with significantly higher callous-unemotional traits (e.g., blunted emotions, lack of guilt, and remorse). Callous-unemotional traits are associated with reduced responding to social cues, reduced affiliative behavior, and reduced empathy (Frick et al. 2000). Youth with callous-unemotional traits are described as being egocentric and showing a callous use of others for their own gain. The finding that rs2268493 is associated with callous-unemotional traits suggests that this SNP is important in social responding and may influence sensitivity to deviant peer effects.

Based on these studies, the goal of the present study was to test whether the rs2268493 SNP would affect responsiveness to the intervention differently in the group versus individual format. We hypothesized that this SNP would moderate responsiveness to the intervention in individuals in the group format of the intervention, but not in the individual format. Our primary outcome of interest was externalizing behavior, as rated by teachers and parents.

Methods

Sample

Children included in the analyses for this study were drawn from a randomized controlled trial (RCT) examining the relative effectiveness of group and individual formats of the Coping Power program. The RCT involved 360 children recruited from 20 different elementary schools. The recruitment process involved screening by both teachers and parents for eligibility. First, fourth grade teachers completed a rating of proactive and reactive aggression (Dodge et al. 1997) on each student in their classes. Across all schools, children who scored in the top 25th percentile were considered eligible for the parent screening.

A randomized list of eligible children was created for each school, and families were contacted according to their placement on the list. For interested families, the Behavior Assessment System for Children (BASC; Reynolds and Kamphaus 1992) Aggression scale was included in the parent assessment battery as a second screen in the recruitment process. Children whose parents rated them within the average range or above on the BASC Aggression scale were invited to enroll in the study. Families were contacted and assessed according to these procedures until six children were enrolled at each of the 20 schools.

The recruitment process was completed for each of the three annual cohorts, resulting in a total sample size of 360 parent-child pairs. Of the 360 children enrolled in the RCT, 71.4% (n = 257) provided a DNA sample that was successfully genotyped for rs2268493. Of this sample, 197 participants self-reported as African-American and 60 identified as Caucasian, Hispanic, or other (Fig. 1). In this study, we did not have the resources available to test the DNA for markers of genetic ancestry. Thus, in order to minimize the possibility that results could be affected by population stratification, or the fact that there are differences in allele frequencies between subpopulations due to different ancestries, we limited the analyses in the present study to the subsample of African-American participants. It should be noted that this solution does not entirely address the issue of population stratification, as there is still the possibility of population stratification within the African-American subsample (see Discussion).

The African-American sample included 105 participants from the GCP condition and 92 students from the ICP condition. Assignment to condition was made at the school level. Schools were paired on demographic factors and within the pairs one school was randomly assigned to each condition. There were no differences in proportion of gender, $\chi^2 = .31$, $p = .58$, or pre-intervention scores on the screening measure, $t(272) = .63$, $p = .53$, between African-American children who were successfully genotyped (n = 197) and those who declined to provide DNA or whose DNA was not usable (n = 77).

The 197 African-American children who were successfully genotyped ranged in ages from 9 to 11 years (mean = 9.75) at the time of recruitment. Participants included 126 boys (64%) and 71 girls (36%). Regarding yearly family income, 6.3% of parents reported no income, 28.4% less than $15,000, 33.6% between $15,000 and $29,999, 16.3% between $30,000 and $49,999, and 15.2% greater than $50,000. Table 1 includes gender and genotyping information for participants in the ICP and GCP conditions.

Intervention

Coping Power is an evidenced-based manualized intervention (Lochman et al. 2008) that is designed to target key social-

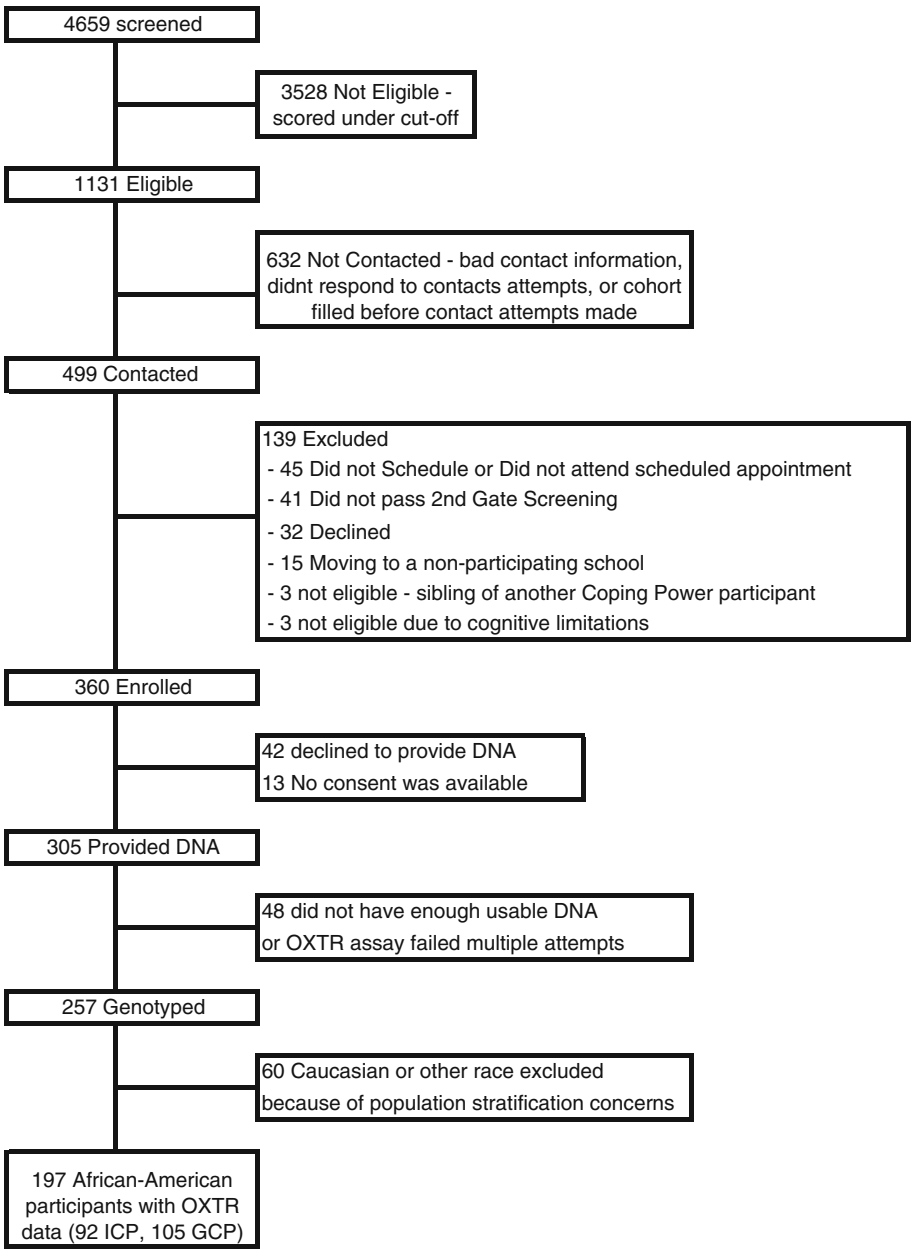

Fig. 1 CONSORT flow diagram for all the trial participants

cognitive deficits in children with aggressive behavior. Coping Power is based on a contextual social-cognitive model (Lochman and Wells 2002), and addresses aggressive children's social information-processing distortions (hostile encoding; hostile attributional biases) and deficiencies (dominance- and revenge-oriented social goals; problem solving that relies on direct action strategies rather than verbal assertion or help seeking; expectations that aggressive behavior will lead to satisfactory outcomes for the child). The model also addresses children's tendencies to become overaroused, especially when angry, when social problems are perceived. Contextual factors contributing to children's aggression include harsh, inconsistent parenting, and involvement with deviant peer groups. Using cognitive-behavioral strategies to influence mutable mechanisms in this contextual social-cognitive model, children are taught to use social problem-

Table 1 Sample characteristics

	ICP (n = 92)	GCP (n = 105)
Gender		
Male	55	71
Female	37	34
Genotype		
A/A	74	84
G/A	15	17
G/G	3	4

solving, goal-setting, and emotional regulation skills. The full curriculum includes a parenting component, but due to the RCT's focus on the child intervention, the parenting curriculum was not implemented in this study.

For both the ICP and GCP conditions, students attended 32 weekly meetings which took place during the school day at times that were arranged in consultation with classroom teachers. The intervention began during the second semester of students' fourth grade year, and continued through both semesters of fifth grade.

Group Coping Power GCP groups included the six children enrolled in the project at each GCP school. Sessions were scheduled for 50–60 min and were co-led by a Coping Power staff member and another clinician (e.g., graduate student, school counselor). Group leaders remained the same throughout children's involvement in the program. The majority of the groups were mixed gender; 17% consisted of all boys. The GCP and ICP curricula covered the same content, though specific activities were tailored for the condition. For example, children in GCP had opportunities to practice specific skills through role-plays with their peers, and received feedback from their peers at the end of each session. Children in GCP also participated in monthly individual meetings (approximately nine individual sessions total, lasting 15–30 min each), which is consistent with the standard Coping Power curriculum. The individual sessions were included to build rapport, assess comprehension of material, and address individual issues as needed.

Individual Coping Power Children in the ICP condition met one-to-one with a Coping Power staff member for each of the 32 sessions. Meetings were scheduled for 30 min, and included interactive activities (e.g., role plays) between the student and the Coping Power leader, rather than with peers (as in GCP).

Procedure

Questionnaire Data Pre-intervention (time 1) measures were completed with children and parents at the time of enrollment, during the spring semester of students' fourth grade year. Students participated in several sessions of the Coping Power intervention during the final months of fourth grade, and students and parents completed mid-intervention assessments (time 2) during the summer after fourth grade. The Coping Power intervention continued during fifth grade, and students and parents completed post-intervention assessments (time 3) in the summer following fifth grade. One-year follow-up assessments (time 4) were completed after sixth grade. Most assessments took place in participants' homes, but evaluations were also conducted in other locations chosen by the family (e.g., public library, research office) if requested. Children and parents were interviewed separately by research staff members who were blind to the children's condition assignment. Parents received $50 for each assessment, and children received $10.

Teachers provided baseline data (time 1) on participating students during spring of fourth grade, post-intervention assessments were collected in the late spring of fifth grade (time 3), and 1-year follow-up data were collected in the late spring of sixth grade (time 4). Mid-intervention (time 2) assessments were not collected from teachers. Teachers received $10 for each student assessed.

DNA Following their enrollment in the main study, families were given the option to participate in a supplemental study involving collection of DNA from children. Parents and children signed consent and assent forms specific to the DNA collection procedures. Families who chose not to participate in the DNA collection continued in the main study as planned.

Child DNA was collected via buccal cells by brushing the inside of the cheek with a buccal brush. Participants were instructed to gently rub the inside of each cheek with separate buccal brushes for approximately 30 s. The brushes were then placed in individual plastic cylinders marked with the participant's study ID number for storage and transport. Following collection, the cylinders were temporarily stored in a research lab refrigerator and then were transported to the Genomics Core Facility at the University of Alabama at Birmingham for genotyping. Parents and children each received $5 for participating in the collection of DNA. Figure 1 indicates the number of participants who declined to provide DNA or whose DNA was not usable.

Measures

The BASC (Reynolds and Kamphaus 1992) is a behavior problem checklist that was completed by children's teachers and parents, and which has demonstrated strong reliability and construct validity (Doyle et al. 1997; Reynolds and Kamphaus 1992). The Externalizing Composite scores were used.

Genotyping

Genotyping was conducted using DNA extracted from buccal cells. Genotyping was performed at the Heflin Center for Genomic Sciences at the University of Alabama at Birmingham. The single-nucleotide polymorphism (SNP) rs2268493 on the oxytocin receptor gene was genotyped using the pyrosequencing method. Briefly, 20 ng of genomic DNA was amplified with primers specific for each SNP. Primer selection was done using the PSQ Assay design software from Qiagen. Primer sequences were forward 5′ Biotin-GTTTGAGCAGCTTCCTTCCAACTAG 3′, reverse 5′ ATGGGGTGATGCTGTTATAGAGC 3′, and sequencing 5′

AACGGTGGACAGTTACTT 3′. Primer sequences for rs237885 were forward 5′ Biotin-AATGATGGCTGCTA TCACGACC 3′, reverse 5′ GCTCTGCCTGGAAA AACCATAG 3′, sequencing 5′ CCGGTGCCTACCTAA 3′. A standard PCR reaction was done with 5 PRIME Taq polymerase (Fisher Scientific) consisting of 500 mM KCl, 100 mM Tris-HCl pH 8.3, 15 mM $Mg(OAc)_2$, 1% Triton X-100, 0.1 mM each PCR primer, and 0.2 mM dNTPs. All sets of PCR primers were done with a touchdown PCR strategy but the annealing temperatures were locus specific. Final annealing temperature was 50 °C. All PCR products were checked on a 1.5% agarose gel to ensure amplification and specificity prior to running the pyrosequencing reactions. The pyrosequencing reactions were done as described by the manufacturer (Qiagen). Briefly, the resulting biotinylated PCR product was diluted in binding buffer (10 mM Tris-HCL, 2 M NaCl, 1 mM EDTA, 0.1% Tween 20) and bound to sepharose-streptavidin (SA) beads (GE Healthcare). The dsDNA-SA-beads complex was washed in 70% ethanol, denatured in 0.2 N NaOH, and washed in 10 mM Tris-acetate pH 7.6. The beads were then placed in annealing buffer (20 mM Tris-acetate, 2 mM $MgAc_2$) containing the appropriate sequencing primer (0.3 mM final), heated to 80 °C for 2 min and allowed to cool to 25 °C. Pyrosequencing was done in the PyroMark HS-96 pyrosequencing machine (Qiagen) as per the manufacturer's instructions. The genotyping call rate was 96.4%.

Minor allele (G) frequency of rs2268493 was 12%. The genotypes were not in Hardy-Weinberg equilibrium (HWE) ($\chi^2 = 8.89$, $p < .05$). To rule out potential problems with genotyping procedures, data from 24 randomly selected participants were genotyped again and concordance was 96%. The deviation from HWE may be because our sample is not normative; participants were selected for higher rates of aggressive behavior using the screening procedure described above. However, it remains possible that genotyping error could have led to an overabundance of G/G's in the sample, resulting in the deviation from HWE. In the analyses for this study, individuals with the G/A and G/G genotypes were combined into one group (i.e., carriers of the G allele) and compared to individuals with the A/A genotype. Because it is less likely that errors in genotyping would result in A/A individuals being categorized as G/G (rather, G/A individuals may have been categorized as G/G, resulting in the overabundance of G/Gs), the deviation from HWE may be less problematic for the results of this study.

Analytic Strategy

A three-level growth curve model was constructed by using HLM 7.0 with full maximum likelihood (FML) estimation method (Raudenbush and Bryk 2002). The model included three levels: (a) times of measurement, (b) nested within children, and (c) nested within the intervention units (with each group having a consistent group leader). For the teacher-rated BASC, 3 participants had missing data at pre-intervention, 26 at post-intervention, and 50 at the 1-year follow-up. For the parent-rated BASC, 14 participants had missing data at post-intervention, and 24 at the 1-year follow-up. Five participants withdrew from the study before the 1-year follow-up.

The individual growth trajectories were fitted in the level-1 model. Each child's outcome scores were modeled as a function of time. First, the unconditional curvilinear growth models were tested by adding a quadratic term for time to the level-1 model, and the deviance tests indicated that the outcomes changed over time with a significant quadratic pattern. For teacher outcomes, the data collection dates at each wave were very close in time. Therefore, the time variable for teacher outcomes is 0 as baseline, 1 as post-intervention, and 2 as 1-year-follow-up. For parent outcomes, the data collected with each wave were spread across several months, so we took the actual time interval from baseline as the time variable, setting baseline to zero. Each of the growth parameters in level-1 model has a substantive meaning and was estimated in level-1 model. The intercept was set as initial status at baseline. Time slope was the linear change rate over time, and the quadratic term represented the curvilinear change across time, capturing the curvature or acceleration in each growth trajectory.

At level-2, the person level, the child characteristics (gender and genotype, with genotype grouped into A/A and carriers of the G allele) were entered as control variables in the intercept, and child characteristic (gender and genotype and the interaction terms genotype by gender) was examined as a potential moderator of the child's rate of change and effect of intervention on behavior outcomes over time at level-1 model. Child characteristics were group mean centered. The intercept and time slope were treated as random effects at level-2. The quadratic term was treated as a fixed effect for teacher outcomes with three times of measurements, and as a random effect for parent outcomes at level-2 because of four times of measurement.

ICP and GCP intervention conditions (W_j, ICP = 1 and GCP = 0) were randomly assigned to schools, and the school received the same intervention condition in three successive years (cohorts). At level-3, we controlled for intervention condition on intercept and examined effects of children's characteristics on intervention (indicating interactions of intervention and child's characteristic) on child's behavior change rate. The intercept was random effect at level-3, and all interaction effects were fixed effects.

We fit the three-level growth curve model to capture children's behavior outcome changes over time in three growth parameters (intercept, time slope, and quadratic term). Parent and teacher outcomes were examined in separate models. The

variation in the growth parameters that was partitioned into (a) the variation among children within intervention unit was captured in the level-2 model, and (b) the variation among intervention units is represented in the level-3 model. Equations for the models are available online.

Results

Table 2 provides the means and standard deviations from the two outcome variables from the BASC by intervention condition at each of the four time points. Individuals with the A/A genotype did not differ from carriers of the G allele on teacher-rated externalizing behavior at baseline, $\gamma = 2.4$, SE = 2.7, $t(138) = 0.9$, $p = .37$, or in growth rates of teacher-rated externalizing behavior, $\gamma = -4.2$, SE = 3.1, $t(138) = -1.4$, $p = .18$. A significant interaction was observed between genotype and condition on teacher-rated externalizing behavior, $\gamma = 7.8$, SE = 4.0, $t(138) = 2.0$, $p = .05$.

As depicted in Fig. 2, children with the A/A genotype demonstrated reductions growth rates for teacher-rated externalizing behavior in both the individual ($d = 0.46$) and group ($d = 0.27$) formats. In contrast, intervention format influenced children carrying the G allele. In the group format, carriers of the G allele showed a modest reduction in externalizing problems from pre- to post-intervention, and then appear to demonstrate an increase in teacher-rated externalizing behavior during the 1-year follow-up. Carriers of the G allele receiving the individual format of the intervention demonstrated significant reductions in externalizing behavior over the course of the intervention, and showed continued reductions in externalizing behavior from post-intervention to the 1-year follow-up ($d = 1.16$ for the difference between groups).

Genotype was not associated with baseline levels or growth rates of parent-rated externalizing behavior problems (Table 3).[1]

Discussion

Growth curve analyses indicated that African-American children's genotype on the oxytocin receptor gene SNP rs2268493 significantly moderated the intervention format effect on teacher-rated externalizing problems. This finding is particularly important because differential effects of group versus individual delivery were previously found to be evident in teacher reports of children's behavior at school, but not parent reports of children's behavior at home (Lochman et al. 2015). For carriers of the G allele, intervention format significantly influenced responsiveness to the intervention. In the group format, children carrying the G allele were less responsive to the intervention, as indicated by teacher ratings of problem behavior 1 year later, than children in the individual format. In contrast, children with the A/A genotype showed reductions in externalizing behavior regardless of intervention format. The interaction between genotype and intervention condition was not observed for parent-reported externalizing problems.

Whereas children receiving A/A genotype showed reductions in externalizing behavior regardless of intervention format, for G allele carriers, the individual format of the intervention was more effective; carriers of the G allele did not respond well to the group format. This finding may be indicative of this gene's influence on social cognition and behavior. Given that the A allele of rs2268493 has previously been associated with conditions involving reduced social bonding (Beitchman et al. 2012; Campbell et al. 2011; Di Napoli et al. 2014; Yrigollen et al. 2008), it may be that in the context of a group-based intervention, individuals homozygous for this allele were less sensitive to the effects of deviant peers and were less likely to bond with and be influenced by other at-risk children in the group; thus, children with the A/A genotype were able to benefit from the group-based intervention. In contrast, carriers of the G allele did not demonstrate significant reductions in teacher-reported externalizing behavior over the course of the intervention, suggesting that for these individuals, the beneficial effects of the intervention may be counteracted by the effects of aggregating high-risk children into groups. During the intervention, children carrying the G allele may be more sensitive to social rewards from deviant peers and thus more distracted by them, and may be more susceptible to peer pressure. Furthermore, although such increasing ease in interacting with other at-risk children may have begun during the intervention year, for G allele carriers, the differential effects of intervention format on externalizing behavior become more pronounced the year after the intervention. One possibility is that carriers of the G allele may have been more likely to form new affiliations with deviant peers, a form of homophily (Hanish et al. 2005), that was enhanced after the intervention was over when interactions were not supervised by group leaders. In our sample, 70% of the youth remained in or continued on to the same school as the majority of participants in their intervention group at the 1-year follow-up. The middle school environment may further facilitate the maintenance of new affiliations, as students are less monitored by teachers, have less consistency in the adult who monitors them, and have more time for unsupervised child interactions (Bradshaw et al. 2008; Wilson 2004). Furthermore, children may also maintain affiliations via social media. In contrast, individuals with the A allele may have been less affected by the exposure to deviant peers while in the group, and less

[1] Based on previous findings by Lochman et al. (2015), models were also run including the child characteristic inhibitory control, but findings regarding genotype were similar to what is reported. Interactions with gender were also examined, but were not significant.

Table 2 Mean and standard deviations of behavioral outcomes across time

Measure	Time 1			Time 2			Time 3			Time 4		
	M	SD	*N*	*M*	SD	*N*	*M*	SD	*N*	*M*	SD	*N*
Coping Power: group format												
Externalizing (BASC)												
-Teacher-rated	39.31	17.62	103	–	–	–	29.29	17.40	98	33.67	23.04	87
-Parent-rated	27.09	13.61	105	25.07	13.21	104	23.20	12.00	98	23.81	12.93	97
Coping Power: individual format												
Externalizing (BASC)												
-Teacher-rated	43.55	16.95	91	–	–	–	37.39	20.71	79	31.56	19.23	66
-Parent-rated	32.73	13.89	92	28.04	13.70	92	27.90	14.65	89	28.65	13.80	84

Teacher ratings were not collected at time 2

BASC Behavior Assessment System for Children

likely to establish and maintain bonds with these peers once the intervention was over.

Another possible explanation for the improvements observed in children with the A/A genotype but not G carriers in the group intervention is that youth homozygous for the A allele may have limited social skills, and may be most in need of the opportunity to practice social skills with peers. In a group session, these individuals may benefit from the more natural practice of learned skills through role-playing. Such skills may include problem-solving in a social context, recognizing the perspectives and emotions of others, and regulating emotions in response to provocation. In addition, they may benefit from receiving peer reinforcement for attaining behavioral goals, and from the creation of a group norm that utilizes non-aggressive strategies. Although currently speculative, these interpretations regarding the social mechanisms underlying the observed interaction could be tested in future studies.

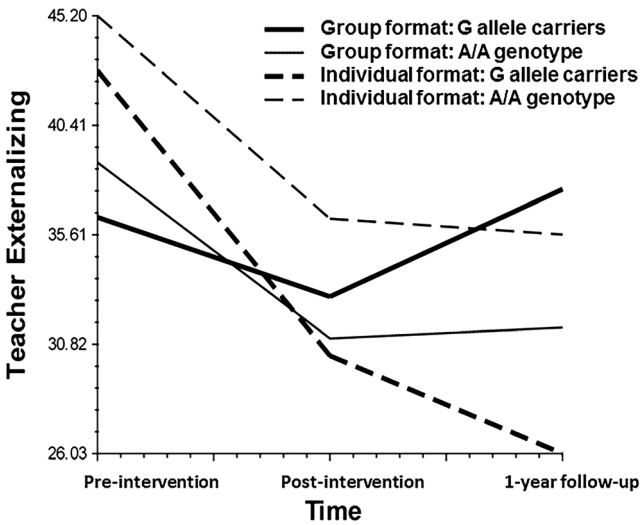

Fig. 2 Interaction between intervention condition and the oxytocin receptor gene on teacher-rated externalizing behavior

One of the most important contributions of the current findings about the oxytocin receptor gene SNP serving as a moderator of intervention format effects is that it raises the possibility that either or both of these putative active mechanisms (deviant peer effects; low social skills) may have accounted for the finding. The real gain for prevention science will be in future research that can target these active mechanisms to determine if they mediate effects.

There are several important general implications from the findings. First, when group interventions are being delivered, child characteristics, including genetic markers and the active mechanisms associated with them, should be considered. Second, more empirical understanding is needed of the type of therapist behaviors that may be able to buffer the limitations of the group format for children with the G allele of this variant of the oxytocin receptor gene. Research examining how different types of therapist behaviors affect children within the group sessions and in the years after the intervention continues to be crucially needed (Lochman et al. 2015).

Although we limited analyses to African-American participants, it remains possible that population structure may be confounding the results. Within the African-American subsample, there is undoubtedly variation in the amount of African and Caucasian ancestry between individuals. We were not able to test for genetic ancestry, and thus results should be interpreted with caution. However, because the design of the study involved randomizing participants to intervention conditions, we believe that population stratification may be less of an issue than in case-control designs in which participants are selected based on the presence or absence of a disease or disorder. In the present study, variation in genetic ancestry is more likely to be divided equally between groups in the randomization process. Future studies with larger sample sizes and that examine compute genetic ancestry will be required to test this.

Table 3 Summary of three-level growth curve analyses on growth rate

Variable	Fixed effect					Random effect								
						Level-3				Level-2				Level-1
	Coef.	SE	*t* value	DF	*p*	Var	χ^2	DF	*p*	Var	χ^2	DF	*p*	Var
Externalizing—teacher report														
Model for intercept, P0														
Intercept, G000	38.3	2.2	17.4	51	<.01	31.4	90.4	51	<.01	42.6	168.1	134	.02	209.0
IGCP, G001	6.4	3.1	2.0	51	.05									
Genotype, G010	2.4	2.7	0.9	138	.37									
Gender, G020	10.8	2.1	5.1	138	<.01									
Model for time slope, P1														
Intercept, G100	−11.0	3.6	−3.1	138	<.01					23.0	226.4	187	.03	
IGCP, G101	−2.7	2.1	−1.3	138	<.01									
Genotype, G110	−4.2	3.1	−1.4	138	.18									
Genotype*IGCP, G111	7.8	4.0	2.0	138	.05									
Model for TimeSQ slope, P2														
Intercept, G200	4.1	1.7	2.5	76	.02									
Externalizing—parent report														
Model for intercept, P0														
Intercept, G000	27.1	1.4	19.5	51	<.01	7.7	61.0	51	.16	143.3	953.8	140	<.01	36.54
IGCP, G001	4.4	2.1	2.1	51	.04									
Genotype, G010	−2.3	2.2	−1.0	138	.30									
Model for time slope, P1														
Intercept, G100	−5.6	0.9	−6.0	138	<.01					29.1	224.9	192	.05	
IGCP, G101	−0.4	0.6	−0.6	138	.55									
Genotype, G110	0.0	1.4	0.0	138	.99									
Genotype*IGCP, G111	0.0	2.1	0.0	138	.99									
Model for TimeSQ slope, P2														
Intercept, G200	2.0	0.4	5.2	138	<.01									

Estimates are reported with robust standard errors

Another limitation of the study is that this SNP was selected based on its associations with social responding and behavior in prior studies, and not agnostically arrived at in a genome-wide association study. Thus, it will be important to further test the effects of this gene as a moderator of intervention effects in future studies. In addition, we are unable to determine the specific biological mechanisms by which rs2268493 has an effect, as the functional effect of this SNP on the oxytocin system has not been explored (though see Di Napoli et al. 2014). Finally, we did not include a measure of social bonding in the present study, and therefore, cannot test whether this is the mechanism by which the genotype has an effect on outcomes in the group-based intervention.

In sum, the current findings emphasize the important influence of child characteristics, including biological factors, on group-based intervention outcomes. Lochman et al. (2015) previously reported that the child's level of inhibitory control moderated the format effect on intervention outcomes. Here we present a unique and different characteristic of the child that may influence how the child interacts with other youth in the sessions. These social mechanisms can be tested in future research. This study adds to a growing body of literature which has found that genes associated with dopamine (Bakermans-Kranenburg et al. 2008; Brody et al. 2014; African-American sample), serotonin (Brody et al. 2009; African-American sample), and glucocorticoids (Albert et al. 2015) moderate responses to interventions designed to reduce behavior problems and negative outcomes in disadvantaged youth. These studies put us closer to understanding what works for whom so that interventions could potentially be individualized based on child characteristics, and help to give insight into the reasons by which preventive interventions such as Coping Power work well for some individuals but not others.

Compliance with Ethical Standards

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Conflict of Interest None of the authors except for John Lochman has a conflict of interest. John Lochman is co-developer of the Coping Power program and receives royalties for the implementation guide published by Oxford University Press.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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