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Reducing Aggression and Impulsivity Through School-based Prevention Programs: A Gene by Intervention Interaction

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Abstract

A variety of school-based, universal preventive interventions have been developed to address behavioral and mental health problems. Unfortunately, few have been evaluated within the context of randomized controlled trials with long term follow-up. Even fewer still have examined the potential genetic factors that may drive differential impact of the intervention. In the present analysis, we examine the extent to which the longitudinal effects of two elementary school-based interventions were moderated by the brain derived neurotrophic factor (BDNF) gene, which has been linked with aggression and impulsive behaviors. The sample included 678 urban, primarily African American children who were randomly assigned along with their teachers to one of three first grade classrooms conditions: classroom-centered (CC) intervention, Family School Partnership (FSP), or a control condition. Teacher ratings of youth's aggressive and impulsive behavior were obtained at baseline and in grades 6-12. Single nucleotide polymorphisms (SNPs) from the BDNF gene were extracted from the genome wide data. Longitudinal latent trait-state error models indicated a significant interaction between a particular profile of the BDNF SNP cluster (46% of sample) and CC intervention on impulsivity ($\beta = -.27, p < .05$). A similar interaction was observed for the BDNF SNP cluster and the CC intervention on aggression ($\beta = -.14, p < .05$). The results suggest that the impacts of preventive interventions in early elementary school on late adolescent outcomes of impulsivity and aggression can be potentially modified by genetic factors, such as BDNF. However, replication of these results is necessary before firm conclusions can be drawn.

Keywords

Aggression; impulsivity; genes; brain derived neurotrophic factor; intervention; schools

An early-onset of aggressive and impulsive behavior problems in childhood is associated with increased risk for mental health and problems in adolescence and adulthood (Bradshaw, Schaeffer, Petras, & Ialongo, 2004; Ialongo et al., 2006; Moffitt, 2006; Petras, Chilcoat, Leaf, Ialongo, & Kellam, 2004). The need for efficacious prevention programs is particularly great in urban communities, where the risk for behavioral, mental health, and

academic concerns are considerably increased (IES, 2011; IES, 2012; Perie, Grigg, & Donahue, 2005). Only a select number of school-based prevention programs have been effective at reducing rates of behavioral and mental health problems through late adolescence (Wilson & Lipsey, 2007). One such program is the Good Behavior Game (GBG). Another program of interest is the Family School Partnership (FSP), which was designed to reduce early risk behaviors by enhancing family-school communication and parent behavior management and academic instruction skills. These interventions are designed to target the early antecedents of problem behaviors such as substance abuse, depression and antisocial behavior. This work is supported by previous work showing that learning problems in childhood can predict psychiatric distress (Shaffer et al., 1979) and that early aggressive behavior can predict later antisocial behavior and substance use (Kellam et al., 2008; Petras et al., 2008).

The preventive effects of the GBG and FSP interventions were evaluated within the context of a randomized controlled trial by the Johns Hopkins Prevention Intervention Research Center (JHU PIRC). The theoretical basis for the interventions and their hypothesized mechanisms were derived from the life course and social fields framework (Kellam et al., 2008) and Patterson and colleagues' (1992) model for the development of antisocial behavior. It was hypothesized that both interventions would reduce the early antecedents of risk behaviors of poor achievement and aggressive/disruptive behavior, by improving teacher and parent child behavior management practices and support for child academic performance. In turn, the reduction in early antecedents risk behaviors would lead to improved academic achievement and occupational success and lower levels of antisocial behavior and drug use in adolescence and emerging adulthood. The GBG has been shown to reduce rates of aggressive/impulsive behavior, substance use, and violence and improve a range of academic outcomes, such as high-school graduation and standardized test performance (Ialongo et al., 1999; Ialongo, Poduska, Werthamer, & Kellam, 2001; Kellam et al., 2008). The FSP focused on promoting parental involvement in educational activities and bolstering parents' behavior management strategies. The FSP intervention has demonstrated significant impacts on suspensions and other academic outcomes (Bradshaw, Goldweber, Fishbein, & Greenberg, 2012; Ialongo et al., 2001). Yet, there has been some variation in the impacts of these programs based on the child's trajectory of aggressive behavior, for example males with greater baseline levels of aggressive behavior showed a more marked improvement after the intervention as compared to males with lower levels of baseline aggressive behavior (Ialongo et al., 2001; Kellam et al., 2008). Reasons behind this phenotypic variation have been postulated (e.g., Ialongo et al., 1999), but to date we have been unable to explore the potential genetic underpinnings of variation among the participants.

This paper integrates recent advances in developmental neuroscience and prevention science to explore variation in the impact of the GBG and FSP preventive interventions based on the brain-derived neurotrophic factor gene (BDNF; Bradshaw et al., 2009; Howe, Beach, & Brody, 2010). Located on chromosome 11, the BDNF gene codes for a protein involved in neurogenesis, neuronal survival, and synaptic plasticity. This protein has been shown to be related to reward pathways and plays a role in the dopaminergic pathway. BDNF influences the mesolimbic and corticolimbic reward pathways by modulating responses to dopamine

(Gizer, Ficks & Waldman, 2009). More specifically, BDNF works to elicit long term neuronal changes by altering the responsiveness of target neurons to dopamine by controlling dopamine D3 receptor expression (Guillin et al., 2001). The unit of analysis for this gene is a single nucleotide polymorphism (SNP), which is a variation in a single nucleotide that differs between members of a particular species. These variations may or may not lead to alterations in protein production. Though this gene is only one of many that could play a role in this behavioral pathway, it shows the most promise in terms of links to both aggressive and impulsive behaviors (Lee et al., 2007; Oades, 2008; Spalletta et al, 2009).

Interest in the BDNF gene originated in animal studies of BDNF-knockout mice (Ito, Chehab, Thakur, Li, & Morozov, 2011). Without production of BDNF, these mice displayed high levels of aggression when compared to mice with appropriate levels of BDNF (Ito et al., 2011). There has also been investigation into the BDNF gene as a potential candidate for various psychiatric problems, such as aggression, impulsivity, and ADHD. For example, a series of studies reported that single nucleotide polymorphisms (SNPs) within this gene significantly interacted with socioeconomic status (SES) and stressful life events to predict inattentive symptoms in individuals with ADHD (Lasky-Su et al., 2007; Wagner, Baskaya, Dahmen, Lieb, & Tadic, 2010). More specifically, Lasky-Su and colleagues (2007) genotyped 10 SNPs in the BDNF gene and found significant SNP by SES interactions on inattentive symptoms of ADHD. Three of the ten SNPs (rs1387144, rs1013442, and Val66Met) had significant SNP by SES interactions. Presence of an 'a' allele in rs1013442, a 't' allele in Val66Met, and a 'c' allele in rs1387144 were associated with higher levels of inattentive symptoms in lower SES (Lasky-Su et al., 2007). A main effect of SNPs within the BDNF gene has also been found in individuals diagnosed with ADHD (Lee et al., 2007; Oades, 2008).

Links between ADHD and the BDNF gene are important as the ADHD phenotype overlaps significantly with aggression and impulsivity phenotypes. Additionally, polymorphisms found within the BDNF gene have been predictive of aggressive behavior in schizophrenic patients (Spalletta et al, 2009). Similar work from Brody and colleagues (2009) has found an interaction between environmental factors and the serotonin transporter gene in relation to prevention efforts. As a result of these lines of research linking the BDNF gene with aggression, we hypothesized an interaction between the GBG and FSP interventions and variants of the BDNF gene, such that children with particular variants of the BDNF gene would be more responsive to the intervention than those without this particular genetic profile.

In addition to the recent advances in developmental neuroscience, advances in statistical methodology have generated a novel analytic method that allows us to parse out variance associated with trait-like or stable behavior. These analytic models, often described as latent trait models, use either single repeated observed measurements or multiple repeated measurements to model the longitudinal structure of a particular psychological process. One model of interest is the latent trait-state-error model, which extracts a latent state and trait factors from single repeated measures (Cole, Martin, & Steiger, 2005). Similar models have been used to explore continuous and discontinuous processes of psychological functioning

such as the longitudinal structure of depressive or anxious symptoms (Cole et al., 2005; Cole, Nolen-Hoeksema, Girgus, & Paul, 2006; Olatunji, & Cole, 2009).

The trait-state-error model was developed by Kenny and Zautra (1995) to explore sources of variance in a given construct. The model assumes that an individual's value of a particular variable is caused by three different sources of variability. The first, which Kenny and Zautra (1995) called the trait, is said to be stable across time. The other source of variance, called the state, changes across time. Finally, a random source, called error, contributes to the individual's value of a particular variable. This model will allow us to study the effects of the intervention on trait-level aggression and impulsivity along with the effects of the BDNF SNPs and the interaction between these SNPs and intervention impact.

Methods

Sample

The primary data from this study come from a longitudinal randomized controlled trial (RCT) testing the impact of the Family School Partnership (FSP) and Classroom-Centered (CC) interventions, the latter featured the GBG as its primary behavior management component. A detailed description of the participants and design is provided elsewhere (Ialongo et al., 1999). Data collection began in 1993 with 678 first graders and their caregivers. The evaluation battery consisted of structured teacher, parent, and child interviews. A randomized block design was employed with schools serving as the blocking factor. Children and teachers were randomly assigned to classroom and then classrooms were randomly assigned to intervention condition with each of the three conditions being represented in each of the 9 participating schools. The interventions were provided over the first grade year only, following a pretest in the early fall.

Of the original 678 participants, written parental consent for participation in the assessments was received for 653 students. Fifty-three and two-tenths % were male, 86.8% were African American, and 13.2% were Caucasian. Additionally, 63.4% of the participants qualified for free or reduced lunch, a proxy for low socioeconomic status (Ensminger et al., 2000). As for the racial breakdown by design, 188 African Americans were in the control condition, while 201 African Americans were in the CC intervention and 196 African Americans were in the FSP intervention conditions. Additionally, 31 Caucasians were in the control condition, and 28 Caucasian and 33 Caucasian participants were in the CC intervention and FSP intervention conditions, respectively. The participants ages at the start of first grade ranged from 5.3 years to 7.7 years (mean 6.2, $SD \pm .34$). Assessments were carried out in the fall of grade 1, with annual follow-up assessments in the spring of grades 6 through 12. Genetic samples were collected shortly after high school. Written informed consent was obtained from each participant and the Institutional Review Board approved the study. For additional information on the design of the trial, see Bradshaw and colleagues (2009); Ialongo and colleagues (1999); or Ialongo and colleagues (2001).

Missing data—As with any longitudinal study, some amount of attrition and missing data is expected. Full information maximum likelihood (FIML) estimation under the missing at random assumption was utilized as implemented in Mplus (Muthén & Muthén, 1998-2011).

This assumption suggests that the reason for missing data is either random or random after incorporating other measured variables (Arbuckle, 1996; Little, 1995). FIML is widely accepted as an appropriate way to handle missing data (Muthén and Shedden, 1999; Schafer & Graham, 2002). The bivariate data coverage for the present analysis ranged from 40.4% to 97.0%. The pre-intervention sample contained 678 participants; of this sample 100% had complete teacher data during the fall of first grade. Additionally, 67% of the participants had at least 5 of the 7 time points between 6th and 12th grades, and 73% of the original sample agreed to participate in the genetic portion of the assessment, giving blood or saliva during the 19-21 year follow-up.

Interventions

The *Classroom-Centered (CC)* intervention was designed to reduce the early risk behaviors of poor achievement and aggressive behavior through enhancements to the curriculum, improvements in teacher instructional and classroom behavior management practices, and specific strategies for children not performing adequately (Ialongo et al., 1999). Each intervention classroom was divided into three heterogeneous groups, which provided the underlying structure for the curricular and behavioral components of the intervention. Additionally, the intervention program enhanced the Baltimore City Public School curriculum in language arts and mathematics by adding material to increase critical thinking, composition and comprehension skills (Petrus, Masyn, & Ialongo, 2011). The primary behavior management component was a behaviorally-focused classroom management program called the Good Behavior Game (GBG), which in previous trials demonstrated a beneficial impact on student behavior (Barrish, Saunders, & Wolf, 1969; Kellam et al., 2008). The GBG is a whole-class strategy that aims to decrease disruptive behaviors by assigning children to teams and only allowing the teams that do not exceed a specified criterion of precisely defined off-task, disruptive, and aggressive behaviors to “win” the Game. The winners receive praise and small material rewards.

The *Family-School Partnership* intervention (FSP) was developed to improve collaboration between parents and teachers and school mental health professionals and to enhance parents’ “teaching” and behavior management skills (Ialongo et al., 1999; Canter & Canter, 1991). The major features of the FSP intervention were: (1) training teachers, school mental health professionals, and other relevant school staff in parent-school communication and partnership building (Canter & Canter, 1991); (2) weekly home-school learning and communication activities; and (3) a series of nine workshops for parents led by a first grade teacher and a school psychologist or social worker. The initial parent workshops were aimed at establishing an effective and enduring partnership between parents and school staff, and set the stage for parent-school collaboration to support children’s learning and behavior. Subsequent workshops focused on effective disciplinary strategies. The Parents and Children series, a videotape modeling and group discussion program, formed the basis for the positive discipline component of the FSP intervention (Webster-Stratton, 1984). The fidelity of both first grade interventions were carefully monitored (Ialongo et al., 1999). For the CC intervention, five of the nine classrooms were identified as high-implementing. For the FSP intervention, parents attended 4.02 (SD=2.38) of the seven core parent sessions. In total, 13% of parents failed to attend any sessions and even a smaller percentage failed to

complete any of the weekly home learning activities designed to foster their child's intellectual development.

Measure of Aggression and Impulsivity

The Teacher Observation of Classroom Adaptation-Revised (TOCA-R) was used to assess the participants' aggressive behaviors and impulsivity at baseline (i.e., fall of grade 1 prior to randomization; Werthamer-Larsson, Kellam, & Wheeler, 1991). Teachers completed the Teacher Report of Classroom Behavior (TRCBC), an adolescent adaptation of the TOCA-R, in the spring of grades 6 through 12. Both measures included items such as, harms or hurts others physically, starts fights with classmates to assess aggression, whereas impulsivity was measured using items such as waits for turn and blurts out answer. Teachers rated student behavior on a six-point Likert scale from "almost never" to "always". Previous research on the TOCA-R has demonstrated a high level of predictive validity (Petras et al., 2004; Petras et al., 2011). See Petras and colleagues (2011) for additional information on the reliability and validity of these measures. The coefficient alphas for the TRCBC subscales in middle school were .91 (aggressive behavior) and .79 (impulsivity).

BDNF Gene

Blood or buccal samples were collected from participants and genotyped using a genome wide assay (see Uhl et al., 2012 for additional details). SNPs from the BDNF gene were extracted from the genome wide data on the Affymetrix 6.0 microarray. Genome wide results were then imported into Plink Version 1.07 (Purcell et al., 2007), and SNPs extracted that fell within the boundaries of the BDNF gene. Nineteen SNPs from this gene were found on the microarray; however, 7 were not included in this analysis because of minimal variance, thus 12 were included in the analysis. For example, for one of these SNPs, all members of the sample population possessed the same genotype, therefore inclusion of this SNP in any model would not provide variation. The SNPs were recoded in Plink in a single allele dosage number. The result of this recode was three categories indicating the number of minor alleles present (see Table 1 for the reference SNP numbers; Purcell et al., 2007). Information about linkage disequilibrium among the included SNPs can be seen in Supplemental Figure 1.

Population stratification—Due to the admixture nature of the sample, population stratification was controlled for at a genetic level. This variable is akin to genomic race and was created with a randomly selected set of 50,000 SNPs using the multidimensional scaling option in PLINK (Purcell et al., 2007).

Analyses

Two latent trait-state error (LTSE; Kenny & Zautra, 1995) models were fit in Mplus 7.11 (Muthén & Muthén, 1998-2011) to explore the longitudinal structure of aggression and impulsivity from middle childhood to adolescence (see Supplemental Figure 2). This model assumes that an individual's value of a particular variable is caused by three different sources of variability, including the stable trait variable, the occasion specific state variable, and random error. The stable trait variables within these models are of interest because we believe that this stable aspect of behavior is most likely to be influenced by biological

mechanisms (DeYoung & Clark, 2012). Each LTSE model was fit separately and then the latent trait variables were allowed to correlate.

SNP clusters within the BDNF gene were modeled using latent class analysis, with each SNP as indicators of class membership. This method offers us the opportunity to identify structural clustering of genetic markers within our sample and create SNP clusters for association testing. Previous research has used LCA for data reduction of SNPs, and demonstrated a functional association between the latent class membership and health outcomes (e.g., Crohn's disease; Cleynen et al., 2010). The class enumeration process begins by fitting a single class (i.e., unconditional) model and then additional classes are added to the model, examining fit statistics to determine whether the additional class improved model fit. Fit statistics commonly used for mixture modeling include the Bayesian information criterion (BIC) value, the Lo Mendell Rubin likelihood ratio test (LMR-LRT) and the bootstrap likelihood ratio test (BLRT). The standardized residuals of allelic patterns also were evaluated to optimize the fit of the model to the data. The influence of SNP cluster found within the BDNF gene on the stable trait variables of impulsivity and aggression was explored. This is accomplished by adding a mixture component to the LTSE models and allowing the mean of the latent trait variables to vary.

Intervention status, gender, genetic race, and free or reduced lunch status were included as fixed effects in the models on the stable traits. No significant pre-test differences were found using chi-square tests among the different intervention groups in terms of gender ($\chi^2=2.19$, $df=2$, $p=.33$), race ($\chi^2=2.70$, $df=2$, $p=.61$), or free or reduced lunch status ($\chi^2=1.34$, $df=2$, $p=.51$) in the fall of first grade. Classroom was included as a random effect to account for the clustering of students in classrooms. Intervention status was included using dummy coding of the intervention variable, resulting in two intervention variables with one representing the CC intervention and the second representing the FSP intervention. Finally, an interaction between BDNF SNP cluster and each intervention status was tested on the impulsivity and aggression outcomes to test the hypothesized genetic modification. The interaction between a latent categorical variable and an observed categorical variable was modeled by allowing the observed categorical variable to have a different influence on the dependent variable for different categories of the latent variable (Muthén, 2001). This results in a different regression coefficient for the observed categorical variable for each of the latent variable categories. In this analysis, the regression coefficient of intervention status on the stable trait variables for aggression and impulsivity differed by SNP cluster group. A significant regression coefficient indicated a significant interaction between SNP cluster and intervention status (Muthén, 2001). Analyses also adjusted for baseline teacher TOCA-R ratings of impulsivity and aggression on the latent trait variables. Analysis of Covariance (ANOVA) was used to examine group differences in pre-intervention ratings of aggression and impulsivity. Results revealed significant but modest mean differences between the intervention groups in terms of pre-intervention teacher ratings of aggression ($F(2,677)=6.74$, $p=.001$) and impulsivity ($F(2,677)=5.31$, $p=.005$). Specifically, post-hoc Tukey tests showed that individuals in the control group ($M=1.50$, 95%CI [1.39, 1.60]) had significantly lower teacher ratings of aggression as compared to individuals in the CC intervention ($M=1.78$, 95%CI [1.65, 1.90]). Additionally, individuals in the control condition ($M=2.08$,

95%CI [1.92, 2.24]) had significantly lower levels of teacher ratings of impulsivity as compared to those in the CC intervention ($M=2.43$, 95%CI [2.28, 2.57]). As with teacher ratings of aggression, the differences in means were modest in size—about 1/5 of a standard deviation. Accordingly, baseline teacher ratings of aggression and impulsivity were included as a covariate in all analyses in order to control for pre-intervention ratings of the children's behavior.

Results

Descriptive statistics for the externalizing means and impulsivity means from the TOCAR are reported in Table 2. A latent class analysis was performed on the BDNF gene using the 12 SNPs as indicators of class membership. A three-class model best fit the data, as indicated by changes in log-likelihood and BIC values (see Table 3). There was a significant change in the log likelihood with the addition of the third class, which suggested that a third class was warranted. Additionally, the elbow in a scree plot of the BIC values at the third class provided further support for the three-class model. Issues with the theta matrix, primarily a negative variance of one of the latent factors, with the five and six class models suggested the need for fewer classes. The first SNP cluster contained approximately 33% of the sample, with the second and third SNP clusters containing 21% and 46% of the sample, respectively. Latent class 1 and 2 were characterized by greater proportions of minor alleles across the SNPs that were used as indicators. Conversely, the third latent class was dominated individuals with none or one minor alleles across the SNPs (see Figure 1).

With regard to the LTSE results, the regression coefficient for the autoregressive function for impulsivity was .45 ($p<.05$), whereas it was .59 for aggression ($p<.05$), suggesting a moderate level of stability in state specific factors across time. This is likely due to the fact that teachers used similar measures to assess the constructs across the multiple time points. With respect to the aggression outcome, the proportion of total variance accounted for by the trait factor ranged from .30 to .67, increasing from grades 6 through 12. The proportions were calculated using the variance of the latent trait variable, the state latent variables, and the total variance of the construct. The total variance at each wave was made up of the trait variance, the state variance, and the error variance. The proportion of total variance accounted for by the state factors ranged from .22 to .0, decreasing from grades 6 to 12. With respect to impulsivity, the proportion of total variance accounted for by the trait factors ranged from .35 to .60, increasing from grade 6 to 12. The proportion of total variance accounted for by the state factors ranged from .15 to .31, increasing from grades 6 through 12. See Table 2 for a complete breakdown of the variance decomposition for impulsivity and aggression.

We explored the influence of gender and genetic race on the latent trait variable for both impulsivity and aggression and found that genetic race was a significant predictor of impulsivity ($\beta = 18.5$, $p < .01$) and aggression ($\beta = 4.4$, $p < .01$). Additionally, gender was a significant predictor of impulsivity ($\beta = .34$, $p > .01$) and aggression ($\beta = .27$, $p > .01$). Finally, free or reduced lunch status was a significant predictor of trait level impulsivity ($\beta = .24$, $p < .01$) and aggression ($\beta = .22$, $p < .01$). Baseline impulsivity was a significant

predictor of trait levels of impulsivity ($\beta = .15, p < .01$), and baseline aggression was a significant predictor of trait levels of aggression ($\beta = .132, p < .01$).

We then examined a main effect of the interventions on the stable traits of impulsivity and aggression and found that the FSP intervention had a significant effect on impulsivity ($\beta = -.19, p < .01$) and aggression ($\beta = -.13, p < .05$), such that trait level impulsivity and aggression were lower in the FSP than in the control conditions. Similarly, the CC intervention had a significant effect on impulsivity ($\beta = -.17, p < .05$) and for aggression ($\beta = -.12, p < .01$), with lower levels of impulsivity and aggression than in the control condition.

With regard to intervention effect modification, we observed a significant interaction (Baron & Kenny, 1986) between the third BDNF SNP cluster and intervention status, such that there was an interaction between the third BDNF SNP cluster and the CC intervention ($\beta = -.27, p < .05$) on impulsivity. Individuals who received the CC intervention and were in the third BDNF SNP cluster were more likely to show lower levels of impulsivity in grades 6 to 12 than individuals in the CC intervention and in the first or second BDNF SNP cluster. There also was an interaction between the third BDNF SNP cluster and the CC for aggression ($\beta = -.14, p < .05$). Specifically, individuals in the third BDNF latent class were less likely to have high levels of aggressive behaviors if they were in the CC condition as compared to the control condition. In terms of the FSP condition, the BDNF cluster did not significantly interact with condition in predicting aggression ($\beta = -.04, p = .08$) or impulsivity ($\beta = -.14, p = .07$), but these relationships were in the expected direction.

Discussion

The current study used a longitudinal RCT design to explore whether the impacts of the CC and FSP preventive interventions on aggression and impulsivity in late adolescence were modified by a particular profile of BDNF SNPs. Our interest in latent classes of SNPs within the BDNF gene was theoretically and empirically motivated by prior research linking it with aggressive behavior, impulsivity, and related psychiatric concerns, like ADHD. The latent class analyses indicated 3 distinct BDNF SNP latent classes, the third of which comprised 46% of the sample; this class was the only one to produce a significant interaction with intervention status. Specifically, we found that youth in this third BDNF latent class who were randomly assigned to CC intervention classrooms were more likely to experience impacts on aggression and impulsivity in adolescence. These interactions were observed in addition to the main effects of the intervention on impulsivity and aggression (for CC only). Taken together, these findings provide preliminary evidence for a gene by intervention interaction involving SNP cluster within the BDNF gene; these effects may account for some of the variability in the impacts of the CC intervention as noted in previous studies (Ialongo et al., 1999; Ialongo et al., 2001; Kellam et al., 2008). Previous work found that the CC intervention effects varied based on early level of aggressive behavior, whereby those at higher levels benefitted the most (Petras, Masyn, & Ialongo, 2011). The current results add support to the hypothesis that genetic differences among individuals may contribute to the variation in these effects. We did not find a significant interaction between the BDNF gene cluster and the FSP intervention, however; the relationship approached significance and in the expected direction. This suggests that with more power a significant interaction would

be found between the BDNF SNP cluster and the FSP intervention related to aggression and impulsivity.

Previous work has shown significant links between variants within the BDNF gene and externalizing behaviors such as aggression and impulsivity (Lee et al., 2007; Oades et al., 2008; Spalletta et al., 2009). Our findings, consistent with previous work, suggest that variants within this gene play a significant role in these types of behaviors. For example, Gizer et al., 2009 as well as others (Guerin et al., 2007; Lasky-Su et al., 2008; Lee et al., 2007; Spalletta et al., 2010) found a relationship between aggressive and impulsive behaviors and one particular SNP within the BDNF gene (rs6265), which is included in the genetic LCA in this paper. Perhaps this SNP (rs6265) is driving tclass membership, and thereby driving the link between the BDNF LCA and the outcome behaviors. It is possible that this SNP class is vulnerable to environmental factors that promote aggression and impulsivity, thereby making these individuals more susceptible to intervention. More work must be done to understand this relationship in its entirety. Additionally, this study adds knowledge related to a gene by intervention interaction, which was found to be statistically significant. No work to date has posited a mechanism for how this relationship works, but it is possible that it functions by altering gene expression and changing neural substrates (Caspi & Moffitt, 2006).

Previous work has explored the utilization of genetics information in intervention work. For example, Brody and colleagues (2009) found a significant interaction between a prevention program (Strong African American Families) and polymorphisms in the serotonin transporter gene, which was predictive of risk behavior initiation. It is quite possible that the genetic modification revealed in the current study could explain some of the variability in program impacts noted in previous studies. Therefore, these findings represent an important and novel extension of prior work on the outcomes of these universal preventive interventions. Future studies should aim to elucidate genetic modifiers of other preventive interventions in order to understand variation in the impact of preventive interventions and identify for whom interventions are most effective (Bradshaw et al., 2012). These findings, coupled with work by Brody and colleagues (2009), support hypotheses set forth by Rutter (1985) which suggested that interventions that involved improvement of protective factors would have the greatest impact on individuals at highest risk.

It is important to keep in mind some limitations when reviewing these findings. To begin, any longitudinal study faces certain amounts of attrition. In order to handle missing data in this study, we used FIML, which assumes data is missing at random. Though this is the standard approach for handling missing data (Muthén and Shedden, 1999; Schafer & Graham, 2002), there is no way to confirm that this data is, in fact, missing at random. Therefore, it is possible that there is difficulty in the generalization of these findings to the population from which the sample is drawn. As a result, the findings must be interpreted with caution.

Additionally, any prevention or intervention trial where participants are clustered within classrooms or clinics, respectively, raises the possibility of a violation of the strongly ignorable treatment assignment assumption (SITA). The following reasons serve to instill

confidence that the SITA was not violated in the present study. First, children and teachers were randomly assigned to classrooms within schools and classrooms were randomly assigned to intervention conditions. Second, gender, ethnicity, free lunch status and levels of aggressive and impulsive behavior at baseline were used as covariates in our outcome analyses. Third, the clustering of students within classrooms was taken into account in our outcome analyses. A second assumption intervention researchers should be concerned with is the stable unit value assumption (SUTVA). SUTVA suggests that the outcome should not be affected by assignment of treatments to the other units. For example, one could imagine that parents assigned to the control condition may have been motivated to make a greater effort to support their child's behavior and learning. Consequently, their children's outcomes may have been more positive than expected based on their randomization to the control group. The SUTVA would be difficult to prove in any randomized control trial, but Jo (2002) offers some insights into how one might test for such a violation.

An additional limitation of the present study is that we are unable to determine the specific biological mechanisms mediating the change process in the current study. However, we hypothesize that these effects are mediated by proximal impacts on impulsive and aggressive behavior, which shift the youth's developmental trajectory of aggression over time. An important area for future research is the exploration of the biological pathways or mechanisms through which the CC and the FSP interventions influence aggression and impulsivity, and the specific time points at which these is greatest sensitivity to both environmental and genetic influences. There are a variety of child, family and community factors, which are not included in the present analysis, which may serve as potential moderators of intervention outcomes. These and other factors warrant further exploration as potential modifiers. Although the LCA method used to reduce the genetic data into a set of latent classes has been employed in previous genetic studies (e.g., Cleyne et al., 2010), the LCA does treat each SNP equally. This may be problematic as SNPs may vary in terms of their functionality and subsequent impact on protein production. Future work should focus on identifying the functionality of the SNPs within the SNP cluster to determine the significance of having a given SNP cluster on gene expression, because the functionality of the SNPs within each cluster can determine levels of gene expression. This would thus cause alterations in protein levels, potentially leading to behavior changes.

In conclusion, the current findings highlight the significant impact of relatively modest one-year preventive interventions on aggressive and impulsive behavior through adolescence among economically disadvantaged, urban, primarily African American youth. The current findings further bolster the available data indicating the effectiveness of these two interventions on impulsivity and aggression with regard to longer-term impacts through late adolescence (Ialongo et al., 1999; Ialongo et al., 2001; Bradshaw et al., 2009). The results also suggest that early intervention with youth can have a positive impact over 14 years later, and that those effects are greatest among youth with a particular pattern of genotypes within the BDNF gene. Although genetic factors have been hypothesized to influence the effects of preventive interventions (Bradshaw et al., 2010), relatively few longitudinal RCT have explored such genetic effect modifiers (Howe et al., 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Stacked bar plots of the SNP categories across the SNPs included as indicators in the BDNF latent class analysis.

Table 1

Reference numbers and genotypes (number of minor alleles present) for the 12 SNPs on the BDNF gene included in analysis

SNP	Reference Number	Position	Allele	0 minor alleles	1 minor allele	2 minor alleles
SNP 1	rs7124442	27633617	T/C	34%	47%	19%
SNP 2	rs2353512	27636238	C/G	99%	1%	0%
SNP 3	rs6265	27636492	C/T	87%	13%	0%
SNP 4	rs11819808	27637964	C/T	65%	28%	7%
SNP 6	rs11030102	27638172	C/G	75%	22%	3%
SNP 7	rs12273539	27639887	C/T	56%	35%	9%
SNP 8	rs11030104	27641093	A/G	86%	13%	1%
SNP 9	rs11030108	27652040	A/G	56%	37%	7%
SNP 10	rs10835210	27652486	A/C	71%	24%	5%
SNP 13	rs11826087	27658097	A/G	83%	15%	2%
SNP 15	rs7127507	27671460	T/C	35%	47%	18%
SNP 16	rs4923468	27682351	A/C	73%	24%	3%

Table 2

Wave	Descriptive Data				Trait Variance		State Variance		Total Variance
Impulsivity									
	Mean	SD	Skew	Kurtosis	Amount	Proportion	Amount	Proportion	
6 th grade	2.38	1.08	.70	−.05	.412	.35	.175	.15	1.19
7 th grade	2.22	1.03	.90	.20	.412	.41	.208	.21	1.01
8 th grade	2.28	1.03	.75	.11	.412	.37	.214	.19	1.10
9 th grade	2.17	1.00	1.04	.76	.412	.40	.215	.21	1.03
10 th grade	2.02	.97	1.32	1.73	.412	.44	.216	.23	.94
11 th grade	1.86	.83	1.18	1.60	.412	.57	.216	.30	.72
12 th grade	1.76	.81	1.53	2.94	.412	.60	.216	.31	.69
Aggression									
6 th grade	1.84	.81	1.54	2.43	.188	.30	.136	.22	.628
7 th grade	1.73	.70	1.37	1.78	.188	.42	.044	.10	.452
8 th grade	1.74	.69	1.56	1.24	.188	.41	.014	.03	.464
9 th grade	1.67	.72	1.75	3.37	.188	.38	.005	.01	.491
10 th grade	1.57	.59	1.89	4.74	.188	.57	.001	.003	.327
11 th grade	1.49	.53	1.74	3.49	.188	.60	0	0	.313
12 th grade	1.44	.49	2.05	6.18	.188	.67	0	0	.282

Impulsivity And Aggression Descriptive Data And Variance Decomposition Based On The Latent Trait State Error Models

Note. The left side of the table reports means, standard deviations, skewness, and kurtosis for teacher rated impulsivity and aggression from 6th grade to 12th grade. The right side of the table reports variance decomposition for teacher ratings of impulsivity and aggression as a result of the latent trait state error models.

Table 3

Model Fit Statistics for The LCA for the BDNF SNP clusters

Number of Latent Classes	LL ^a	# of free parameters	BIC ^b	VLMR-LRT ^c	BLRT ^f	Entropy	Smallest class <i>g</i>
1 class	-3882.48	23	7907.05	na	na	na	na
2 classes	-3206.24	47	6702.84	0.0	0.0	.99	.33
3 classes^h	-2812.80	71	6064.24	0.0	0.0	.99	.19
4 classes	-2600.61	95	5788.13	0.0	0.0	.99	.19
5 classes ⁱ	-2435.20	119	5605.58	0.0	0.0	.99	.16
6 classes ⁱ	-2333.48	143	5550.41	0.0	0.0	.99	.14

^aNotes. Loglikelihood,^bBayesian Information Criterion,^cVuong-Lo-Mendell-Rubin Likelihood Ratio Test *p*-value,^fBootstrap Likelihood Ratio Test *p*-value,^gModel based estimated frequency,^hElbow in BIC value,ⁱProblem with Theta Matrix. The bolded class represents the selected class.