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Testosterone Reactivity to Provocation Mediates the Effect of Early Intervention on Aggressive Behavior

Justin M. Carré[1], Anne-Marie R. Iselin[2,3], Keith M. Welker[4], Ahmad R. Hariri[5,6], and Kenneth A. Dodge[7]

[1]Department of Psychology, Nipissing University; [2]Department of Psychology, University of North Carolina Wilmington; [3]Center for Child and Family Policy, Duke University; [4]Department of Psychology, Wayne State University; [5]Department of Psychology and Neuroscience, Duke University; [6]Institute for Genome Sciences and Policy, Duke University; and [7]Center for Child and Family Policy, Duke University

Abstract

We tested the hypotheses that the Fast Track intervention program for high-risk children would reduce adult aggressive behavior and that this effect would be mediated by decreased testosterone responses to social provocation. Participants were a subsample of males from the full trial sample, who during kindergarten had been randomly assigned to the 10-year Fast Track intervention or to a control group. The Fast Track program attempted to develop children's social competencies through child social-cognitive and emotional-coping skills training, peer-relations coaching, academic tutoring, and classroom management, as well as training for parents to manage their child's behavior. At a mean age of 26 years, participants responded to laboratory provocations. Results indicated that, relative to control participants, men assigned to the intervention demonstrated reduced aggression and testosterone reactivity to social provocations. Moreover, reduced testosterone reactivity mediated the effect of intervention on aggressive behavior, which provides evidence for an enduring biological mechanism underlying the effect of early psychosocial intervention on aggressive behavior in adulthood.

Keywords

aggressive behavior, antisocial behavior, intervention, neuroendocrinology

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Violence is a major public-health concern, resulting in costs of more than $70 billion in medical expenses and loss of productivity in the United States alone (Corso, Mercy, Simon, Finkelstein, & Miller, 2007). Substantial efforts have been made toward developing intervention programs to prevent aggression (Brotman et al., 2008; Dodge, Godwin, & Conduct Problems Prevention Research Group, or CPPRG, 2013). One such program, Fast Track, was based on the hypothesis that risk for chronic antisocial behaviors can be identified early in life (Moffitt, 1993) and prevented through long-term psychosocial intervention. Much violence occurs during social conflict, so Fast Track was designed to build social competencies and self-regulatory skills that enable children to respond more calmly and less vociferously to provocation. Fast Track used a multistage screening process to identify kindergarteners who displayed high rates of aggression on parent and teacher reports. A major premise of Fast Track was that effective intervention should be comprehensive, targeting age-relevant skills across multiple life domains and time points. Fast Track targeted primary risk factors for antisocial behavior, including poor parental behavior management, deficient social-cognitive and emotional-coping skills, poor peer relations, weak academic skills, disruptive and rejecting classroom environments, and poor parental monitoring and supervision.

Corresponding Author:
Justin M. Carré, Department of Psychology, Nipissing University, North Bay, Ontario, Canada
E-mail: justinca@nipissingu.ca

A number of studies now support the efficacy of Fast Track across a variety of outcomes, including academic and social competence (CPPRG, 1999), aggression and peer relations (CPPRG, 1999, 2002), use of medical and mental-health services (Jones, Godwin, Dodge, & CPPRG, 2010), frequency and onset of juvenile arrests (CPPRG, 2010), antisocial behaviors (CPPRG, 2007), and lifetime prevalence rates of externalizing disorders (CPPRG, 2007, 2011).

Although the positive effects of the Fast Track intervention are clear in childhood and adolescence, it is less clear whether its effects are sustained into adulthood and what the mechanisms of long-term impact are. The intervention was successful throughout preadult life in equipping its recipients with self-regulatory skills in response to social conflict and provocation. In elementary school, children randomly assigned to treatment ascribed fewer hostile attributions to ambiguous peer interactions (CPPRG, 2002), generated more competent solutions to social conflicts, and were less likely to react aggressively to provocations (CPPRG, 1999, 2002), compared with children assigned to a control condition. Furthermore, social-cognitive responses to provocations mediated the effect of intervention on adolescent antisocial behavior (Dodge et al., 2013). We hypothesize here a biological mechanism underpinning recently established social-cognitive mediators of the long-term impact of Fast Track: Intervention will improve biological stasis during peer provocations, and such stasis will mediate the effect of intervention on aggressive behavior in adulthood.

Notably, no studies have examined the biological processes underlying the beneficial effects of Fast Track. In the current study, using a subset of the Fast Track sample from one site (Durham, North Carolina), we tested the extent to which early intervention in childhood reduced reactive aggression in adulthood. We assessed this outcome using the point-subtraction aggression paradigm (PSAP; Cherek, Tcheremissine, & Lane, 2006). This laboratory paradigm exposes participants to provocation by another (fictitious) participant. We also tested the hypothesis that intervention would reduce the responsiveness of the hypothalamic-pituitary-gonadal (HPG) axis during peer provocation and that this effect would mediate the impact of intervention on aggression. We focused on testosterone, the end product of the HPG axis, because of compelling research in animal models indicating that situation-specific changes in testosterone map onto aggression (see Gleason, Fuxjager, Oyegbile, & Marler, 2009, and Oliveira, 2009, for a review). Similarly, in men, evidence indicates that acute fluctuations in testosterone during social provocation positively predict aggression (Carré, Campbell, Lozoya, Goetz, & Welker, 2013; Carré, Putnam, & McCormick, 2009; Geniole, Carré, & McCormick, 2011).

Method

Participants

The sample was drawn from the larger Fast Track sample (CPPRG, 1999), which included children from each of three kindergarten cohorts (1991–1993) at each of four geographic sites: Durham, North Carolina; Nashville, Tennessee; rural Pennsylvania; and Seattle, Washington (the full protocol can be found at fasttrackproject.org). Within sites, schools were clustered, matched, and randomly assigned to the intervention or control condition. A multiple-gating screening procedure that combined teacher and parent ratings of aggressive-disruptive behavior was applied to all 9,594 kindergarteners in 55 schools, yielding a severity-of-risk screen score. We selected children based on this risk score, moving from highest down until the desired sample sizes were met within each condition and cohort. A total of 979 children (~10% of the number of kindergarteners screened) were selected to yield a consenting sample of 891 (a 91% consent rate), which consisted of 445 children from intervention schools and 446 from control schools.

The mean externalizing-scale *T* score on the Kindergarten Teacher's Report Form of the Child Behavior Checklist (Achenbach, 1991) was 66.4 (national mean = 50, *SD* = 10). (See Table S1 in the Supplemental Material available online for mean scores on 20 measures in both the intervention and control conditions.) At the time of selection, participants' mean age was 6.5 years (*SD* = 0.48). Across all childhood waves of data collection, written consent from parents and oral assent from children were obtained. All procedures were approved by the institutional review boards of participating universities.

The current subsample consisted of African American men from the Durham site meeting eligibility (described in the Current Study Procedures section) at a mean age of 26 years (in 2011; age range = 25–27 for cohorts recruited from 1991–1993, respectively). The final sample consisted of 34 participants from intervention schools and 29 from control schools. We restricted our recruitment to men because 77% of the Durham cohort was male. Moreover, of the men sampled, 94% were African American, and thus, we decided to restrict our analyses to those individuals.

Intervention procedures

Elementary school phase. During Grades 1 through 5, intervention families were offered parent training with supplemental trainings visits at home, academic tutoring, peer coaching, social-cognitive skills training, and classroom curricula in social-emotional learning. Group interventions were conducted during a 2-hr "enrichment program" that included social skill training "friendship groups," parent-training groups, guided parent-child-interaction sessions,

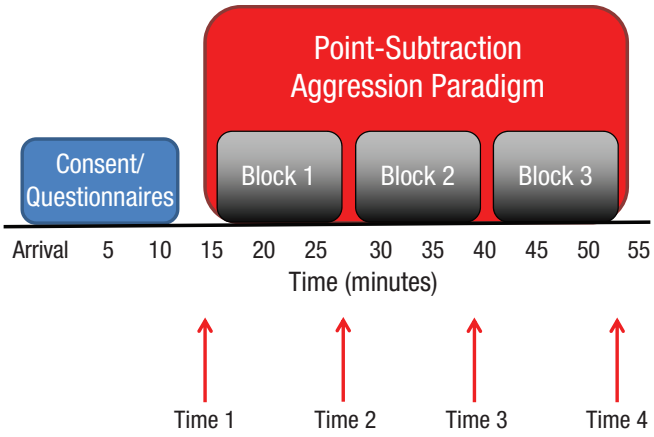

Fig. 1. Experimental timeline. Participants performed three blocks of the point-subtraction aggression paradigm, and saliva samples were taken at Times 1 through 4.

and paraprofessional tutoring in reading. Tutors provided three additional 30-min sessions per week in reading and playing with a peer to improve friendships with classmates.

Enrichment programs were held weekly during Grade 1, every other week during Grade 2, and monthly during Grades 3 through 5. In addition, home visiting helped parents generalize their skill learning and addressed individual needs. After Grade 1, criterion-referenced assessments were used to adjust the number of home visits to match each participants' need. An adaptation of the Promoting Alternative Thinking Strategies (PATHS) curriculum (Modules 502046 and 502047; Kusche & Greenberg, 1993) and teacher consultation were implemented universally in Grade 1 through 5 classrooms in intervention schools to promote social and emotional competence.

Middle and early high school phase. During Grades 5 and 6, children received a middle school transition program and attended four parent and youth groups on topics of adolescent development; alcohol, tobacco, and drugs; and decision making. In Grades 7 and 8, eight youth forums addressed vocational opportunities, life skills, and summer employment opportunities. In Grades 7 through 10, individualized interventions, assigned on the basis of need, addressed parent monitoring, peer affiliation, academic achievement, and social cognition.

Current study procedures

When participants were 26 years old, a trained research assistant contacted them by telephone, mail, or e-mail to inform them of the study details and screen for magnetic-resonance-imaging eligibility.[1] Participants were excluded if they (a) were receiving pharmacological treatment that may have affected steroid hormone concentrations or taking psychotropic medications, (b) were unable to stop taking stimulant medications for at least 24 hr, (c) were unable to understand the procedure and sign the consent form, (d) tested positive for drug use, or (e) were currently incarcerated. Seventy-six African American men from the Durham site qualified to participate. Of these participants, 63 (83%) consented, completed the laboratory procedure, and provided sufficient saliva for testosterone analyses. All procedures were conducted in accordance with the practices of the medical center institutional review board.

After providing informed consent and supplying a saliva sample via passive drool, participants performed the PSAP, a well-validated behavioral measure of reactive aggression (Cherek et al., 2006). Participants were asked to play a game with another male participant (actually fictitious) in which the goal was to earn as many points as possible, which were later exchangeable for money. Participants had three response options: Button 1 earned points after 100 consecutive presses, Button 2 stole points from the other male participant after 10 consecutive presses, and Button 3 protected points from being stolen after 10 consecutive presses.

Throughout the task, points were randomly stolen from participants, who were told that the other participant had taken them and got to keep them. Participants were told they could steal points from the other participant but could not keep them, which rendered stealing purely an act of reactive aggression. Participants were told that at the end of the game, they would be paid based on how many points they accumulated during the task and that the other participant would be paid based on how many points he accumulated during the task.

The PSAP consisted of three 10-min blocks. To quantify testosterone concentrations, we collected saliva samples four times, once prior to the PSAP and once after each block (Times 1–4, respectively; see Fig. 1). Samples were collected in polystyrene culture tubes and stored at −20° C until assayed. All samples were assayed in duplicate using commercially available enzyme immunoassay kits (DRG International, Springfield, NJ). Mean intra- and interassay coefficients of variation were 9.92% and 12.6%, respectively. (See Postintervention Measures and Table S2 in the Supplemental Material for details on further measures administered.)

Dependent variables

Aggression was calculated within each of the three blocks as the number of points stolen from the fictitious opponent divided by the number of provocations received (Gowan et al., 2013). Because aggressive behavior was positively correlated with time of day ($r = .26$, $p = .046$),[2] time of day was included as a covariate in all analyses.

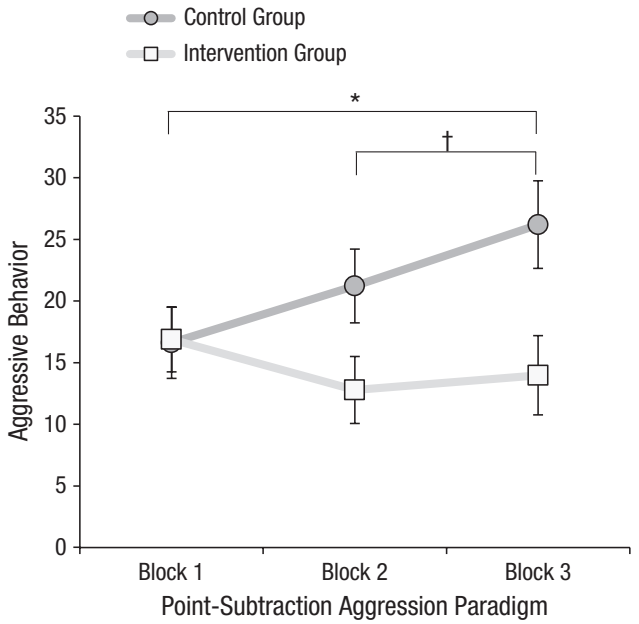

Fig. 2. Mean aggression score as a function of block and treatment group. The dagger indicates a marginally significant result ($p < .06$), and the asterisk represents a significant result ($p < .05$). Error bars show standard errors of the mean.

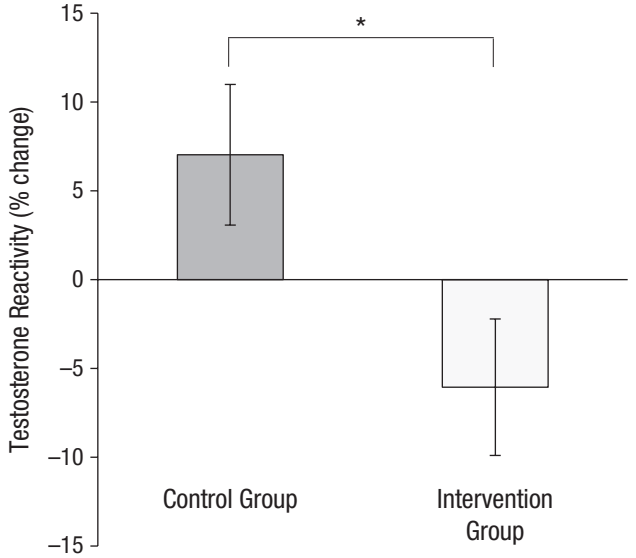

Fig. 3. Mean testosterone reactivity within the first 10 min of the point-subtraction aggression paradigm as a function of treatment group. The asterisk indicates a significant difference between conditions ($p < .05$). Error bars show standard errors of the mean.

One control participant had aggression scores more than 3 standard deviations higher than the mean and was removed from all analyses.

Because previous evidence has indicated that testosterone reactivity within the first 10 min of the PSAP predicts aggressive behavior (Geniole et al., 2011), we were interested in whether the experimental groups would differ in their early neuroendocrine response to the PSAP. Moreover, examining this early response pattern enabled us to determine the extent to which changes in testosterone at the beginning of the task predicted future aggressive behavior (i.e., in Blocks 2 and 3) during the PSAP. We quantified this response as a percentage change from baseline ([Time 2 testosterone – Time 1 testosterone]/Time 1 testosterone × 100). Two participants (1 control and 1 intervention) had testosterone-reactivity scores more than 3 standard deviations from the mean and were removed prior to all analyses.

Mediation analyses were conducted to test the hypothesis that changes in testosterone within the first 10 min of the PSAP mediate the impact of intervention on aggressive behavior. These analyses used bootstrapping, a nonparametric resampling procedure designed for conducting mediation analysis with smaller sample sizes. Bootstrapping analysis is more powerful than testing the significance of indirect effects through the conservatively biased Sobel test (Sobel, 1982). The tools we used for mediation analysis were provided through the SPSS dialog PROCESS (Hayes, 2012, Model 1). This procedure generated a 95% confidence interval (CI) for the indirect effect with 10,000 iterations.

Results

Aggressive behavior

A repeated measures 3 (block: 1–3; within subjects) × 2 (group: intervention, control; between subjects) analysis of variance revealed a marginal effect of group on reducing aggression (control: $M = 21.25$, $SE = 2.55$; intervention: $M = 14.55$, $SE = 2.31$), $F(1, 57) = 3.89$, $p = .053$, $\eta_p^2 = .064$. The group-by-block interaction and cell contrasts were significant, $F(2, 114) = 4.312$, $p = .016$, $\eta_p^2 = .070$, which indicates that the intervention group displayed less reactive aggression than the control group in Blocks 2 ($p < .05$) and 3 ($p < .05$; see Fig. 2).

Testosterone concentration

Baseline testosterone concentrations did not differ significantly in the two experimental groups (intervention: $M = 153.49$; control: $M = 152.48$; $p = .967$). However, the groups did demonstrate a significantly different testosterone response pattern within the first 10 min of the task (i.e., from Time 1 to Time 2); there was a 6.05% decrease in testosterone in the intervention group and a 7.03% increase in testosterone in the control group, $t(58) = 2.35$, $p = .022$, Cohen's $d = 0.61$ (see Fig. 3).

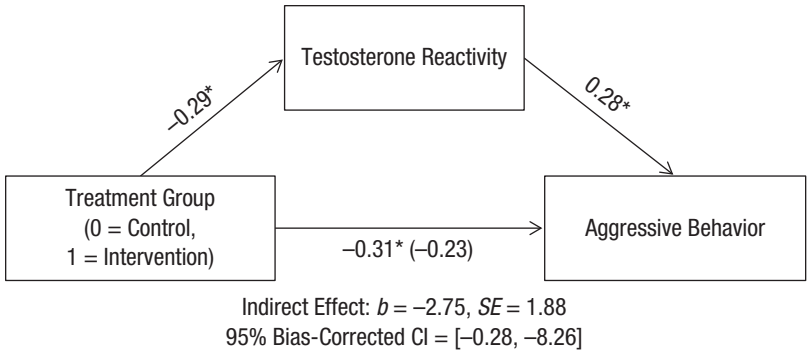

Fig. 4. Mediation model showing the effect of treatment group on aggressive behavior in Blocks 2 and 3 of the point-subtraction aggression paradigm, as mediated by testosterone reactivity within the first 10 min of the task. An asterisk indicates a significant result ($p < .05$). Unstandardized regression coefficients are shown. Along the lower path, the number outside parentheses is the total effect, and the number inside parentheses is the direct effect. CI = confidence interval.

Mediation

As already indicated, intervention had a significant effect on reactive aggressive behavior in Blocks 2 and 3 of the PSAP, and the intervention had a significant effect on testosterone reactivity within the first 10 min (i.e., in Block 1) of the PSAP. Thus, we were interested in the extent to which testosterone reactivity within Block 1 of the PSAP would mediate the association between the intervention and aggressive behavior in Blocks 2 and 3. Testosterone reactivity significantly mediated the effect of intervention on average aggression across Blocks 2 and 3 of the PSAP ($b = -2.75$, $p < .05$; see Fig. 4), with testosterone reactivity accounting for 26% of the intervention's impact on reducing reactive aggression (calculated as direct-effect coefficient/total-effect coefficient, or −0.23/−0.31). As a counterfactual test of directional sensitivity of mediation, testosterone reactivity did not mediate the effect of intervention on aggression that occurred before the change in testosterone (i.e., in Block 1; 95% CI = [−3.947, 2.298]).

Discussion

These findings indicate that the Fast Track early intervention for at-risk youth at age 5 years substantially reduces retaliatory, reactive aggressive behavior in adulthood, as assessed in a controlled laboratory setting. This finding is consistent with previous evidence that Fast Track decreases rates of externalizing and antisocial behavior in children and adolescents (CPPRG, 2007, 2011). The most novel contribution is discovery of a biological mechanism for the effect of this psychosocial intervention. Reduction in testosterone reactivity to social provocation mediates the effect of early intervention on aggressive behavior. Specifically, we found that as young men, high-risk individuals who had been assigned to early intervention as boys demonstrated decreased testosterone reactivity when exposed to social provocation, whereas high-risk boys not assigned to the intervention demonstrated increased testosterone reactivity as adults. This difference significantly mediated the effect of early intervention on reduced aggression. These findings suggest a biological mechanism that may underpin recently established social-cognitive mediators of the long-term effects of Fast Track (Dodge et al., 2013). Together, these results suggest that the Fast Track intervention creates persistent changes in psychological processes underpinning how individuals encode, interpret, and process social threat and provocation. These mental processes, in turn, influence the pattern of testosterone responses to provocation, which in turn influence aggressive behavior.

The finding that testosterone reactivity to provocation, but not baseline levels of testosterone, maps onto variability in aggression is consistent with a growing body of evidence in social neuroendocrinology (Carré et al., 2013; Carré et al., 2009; Geniole et al., 2011). In the past, we proposed that change in testosterone in the context of social provocation may modulate aggressive behavior through its effect on amygdala function (Carré, McCormick, & Hariri, 2011). Notably, neuroimaging work indicates that acute elevations of testosterone through pharmacological challenge are associated with heightened amygdala reactivity to social signals of threat (Goetz et al., in press; Hermans, Ramsey, & van Honk, 2008; van Wingen et al., 2009). Moreover, individuals at risk for engaging in reactive aggression also demonstrate heightened amygdala reactivity to angry facial expressions (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). These findings converge to suggest that heightened amygdala reactivity to social signals of threat, modulated by fluctuation in testosterone, may represent a neural marker for one's propensity to react aggressively. The extent to which the relation between early intervention, reduced testosterone reactivity, and reduced aggression is

mediated through alterations in amygdala function is an intriguing question that warrants further study.

In summary, we demonstrated for the first time that early psychosocial intervention can decrease testosterone reactivity to social provocation and that this effect represents a biological mechanism mediating the beneficial effects of intervention on long-term adult aggressive behavior.

Author Contributions

J. M. Carré, A.-M. R. Iselin, A. R. Hariri, and K. A. Dodge designed the study. J. M. Carré and K. M. Welker analyzed the data. J. M. Carré took the lead in writing the manuscript. A.-M. R. Iselin, K. M. Welker, A. R. Hariri, and K. A. Dodge provided critical edits to the manuscript. All authors approved the final version of the manuscript.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information may be found at http://pss.sagepub.com/content/by/supplemental-data

Notes

1. This study was part of a larger project examining the neural endophenotypes of aggression and antisocial decision making.
2. The results remained unchanged when time of day was removed from the statistical models.

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