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Unpacking the association: Individual differences in the relation of prenatal exposure to cigarettes and disruptive behavior phenotypes

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1. Introduction

This special issue is a cherished opportunity to pay tribute to our esteemed colleague, Vincent Smeriglio, Ph.D. Vince's dedication and commitment as a NIDA Program Officer is legendary. For those of us privileged to be investigators in Vince's prenatal exposure portfolio, he has been an inspiration and a scientific advisor and advocate *par excellence*. We are particularly delighted to honor Vince with this paper on unpacking associations between exposure and developmental patterns. This is because his quest to facilitate scientific investigations that would go “ever deeper” exemplifies his devotion to promoting high-quality, developmentally-based investigation of prenatal exposure effects. As such, the present findings are just one reflection of a much larger “unfolding story” that splendidly reflects the broad scope and enduring nature of Vince's legacy.

Over the past decade, a robust association between prenatal exposure to cigarettes (“exposure”) and disruptive behavior has been established across diverse samples and developmental periods [69]. These include DSM-based Oppositional Defiant and Conduct Disorders [31,44,68], delinquency and criminality [10,68], checklist ratings of externalizing problems [3,19,61], observed disruptive behavior [67] and its developmental substrates in early childhood [47,51]. However, disruptive behavior syndromes and corollary delinquent behaviors represent a very broad and heterogeneous set of behaviors [34]. Thus, greater specification of disruptive behavior dimensions is needed to map discrete mechanisms by which exposure may exert its effects [17,56,65]. In this paper, we examine the relation of exposure to four dimensional disruptive behavior phenotypes and examine moderation of these pathways by youth sex and parental responsive engagement.

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1.1. Specifying the Association of Exposure and Disruptive Behavior

Initial efforts to specify the relation of exposure to narrower components of disruptive behavior provide empirical support for this approach. Differential associations have been demonstrated between exposure and: (a) adolescent history of overt but not covert behaviors [43]; and (b) observed aggression and noncompliance but not temper loss at toddler age [67]. These studies provide preliminary evidence that specification is likely to be illuminating. However, the relation of exposure to each of the defining elements of disruptive behavior syndromes has not been comprehensively tested.

1.2 Dimensional Approaches to Disruptive Behavior

There is increasing evidence that multidimensional approaches enhance phenotypic characterization and identification of mechanisms. A number of approaches have been developed to characterize sub-groups of youth with conduct problems including the DSM distinction between oppositional and conduct problems and corollary distinctions between aggressive and non-aggressive rule breaking and distinguishing a callous/unemotional subtype [12,29]. Building on this work and incorporating recent research on phenotypic heterogeneity and specification of developmental processes that go awry in disruptive behavior syndromes, we have recently proposed a four dimensional framework of disruptive behavior [70]. This framework is designed to move beyond aggression as a central organizing frame to more fully capture defining elements of the full disruptive behavior spectrum as well as to provide an approach that can be meaningfully applied across developmental periods. This dimensional framework incorporates a developmental conceptualization. This includes recognition that some disruptive behaviors are normative within a particular period (e.g. the noncompliance of adolescence) and that atypicality is manifest in terms of higher than expectable frequencies and in extreme forms of the behavior. Although the present sample is adolescent, employing a conceptual framework that has coherence across developmental periods will be especially useful for replication and extension.

1.2.1 Proposed multidimensional approach and theorized associations to exposure—We have proposed these four core dimensions of disruptive behavior as: (1) Aggression; (2) Noncompliance; (3) Temper Loss; and (4) Low Concern for Others [70]. The *Aggression* dimension characterizes a tendency to respond aggressively across a variety of contexts, ranging from appropriate self-protection to severe violence. The *Noncompliance* dimension captures failure to comply with directions, rules, and social norms, ranging from developmentally appropriate resistance to pervasive and provocative rule breaking. The *Temper Loss* dimension encompasses overt expression and management of anger, ranging from mild expressions of frustration to rage and extreme and dysregulated temper loss. The *Low Concern* dimension captures active disregard of others, including lack of guilt for transgressions and lack of concern for others' feelings. Behaviors along this dimension may include mild insensitivity within expectable contexts to extreme and persistent disregard of others needs and feelings. In two independent early childhood samples [64], this four dimension model has demonstrated a superior fit compared to traditional models including: (a) a DSM-based (ODD/CD) model [4], and (b) a model distinguishing a general disruptive group from a group high on the Low Concern dimension, along the lines of the callous-unemotional subtype described and extensively studied by Frick and colleagues [29]. The superior model fit was demonstrated across child age and sex. Concurrent and predictive validity were also demonstrated [64].

With this preliminary empirical evidence as foundation, we here draw on this multidimensional model as a framework for testing specificity of relations of exposure and disruptive behavior dimensional phenotypes. Distinguishing multiple narrow-band

phenotypes that include a broad range of behavior from mild to severe is likely to provide enhanced precision for linkage to mechanisms. Although we do not directly test neurocognitive mechanisms here, we hypothesized that exposure would predict elevated scores on the Aggression and Noncompliance dimensions based on recent neuroscientific findings. Reduced lateral orbital frontal cortex (OFC) thickness and inefficient recruitment of brain regions implicated in response inhibition have been demonstrated in exposed youth [60, 6]. OFC disruptions and concomitant impairments in emotional regulatory mechanisms are associated with impulsive and reactive aggression [8]. Lateral regions of OFC and inferior frontal cortex also regulate social response reversal, i.e. the putative system that promotes changes in behavior in response to others' aversive social cues such as anger and social disapproval [9]. Damage to these regions can lead to reduced concern for social rules and the capacity to generate alternate behavioral responses to others' negative social cues as well as punishment more generally [7,9]. Impaired anger discrimination has been demonstrated in exposed girls [65]. Processing of these social cues is a critical aspect of compliant behavior and thus, impairments in social response reversal are likely to be associated with increases in Noncompliance.

1.3 Moderational Pathways

Enhanced phenotypic specification is also critical for elucidating individual differences in pathways. A number of moderators have been demonstrated in pathways from exposure to disruptive behavior including sex [63], genotype [37,65], socioeconomic status [35,43], maternal antisocial behavior [35], and maternal responsiveness [71]. Based on prior work, we focus on two particular promising areas for elucidating salient individual differences: sex differences in exposure-related patterns and moderation of these patterns by the parenting environment. Whether or not exposure-related disruptive behavior is specific to males remains a pressing question for the field. The more precise, dimensional specification approach employed here provides a unique opportunity to shed light on this issue by capturing a broader phenotype that encompasses individual variation. We also focus on the potential moderating role of responsiveness, because it is unique amongst established moderators due to its modifiability [62].

1.3.1 Moderation by sex of youth—Initial investigations suggested that links between exposure and disruptive behavior were specific to boys [27,71,73]. However, a number of recent studies have reported contradictory findings. In particular, multiple studies of exposure-related patterns in early childhood have employed dimensional measures of externalizing problems and found no evidence that exposure-related patterns are specific to boys [13,35-36,54,67]. In older youth and adults, studies that have considered a broader phenotypic range and applied dimensional approaches have also demonstrated exposure-related patterns for both males and females [10,65]. Given both developmental and methodological differences across these studies, reconciliation of these contradictory findings is difficult. One possibility is that these varying patterns reflect true differences across developmental periods (e.g. absence of sex differences in early childhood and stronger associations for boys during adolescence). Another alternative is that these inconsistencies are due to methodologic artifacts (e.g. studies of adolescents tend to focus on severe forms of behavior common in teenage boys). Here we attempt to shed light on this issue by employing dimensional assessments of disruptive behavior to test for sex differences in exposure-related patterns at adolescence including relations to specific dimensions and whether or not there are sex differences in moderated patterns. We hypothesized that exposure-related patterns would be evident in both male and female teens using this dimensional approach.

1.3.2 Moderation by parental responsiveness—To our knowledge, only two studies have tested for the interaction of exposure and parental responsiveness. The first was in a small pregnancy cohort of African-American women at very high-risk due to extreme poverty and over-sampling for prenatal opiate exposure [71]. In this sample, the association of exposure and heterogeneous disruptive behavior symptoms in was moderated by observed maternal responsiveness during the first years of life [71]. However, sex differences were not examined, as moderational effects were tested for boys only. In contrast, observed maternal responsiveness did not modify impact of exposure on early childhood aggression for male or female toddlers in the predominantly Caucasian, socio-demographically diverse Quebec Longitudinal Study of Child Development [35]. These discrepant findings may result from a number of differences across the two studies including differences in: demographic composition (high-risk vs. community), developmental periods in which disruptive behavior was measured (adolescence vs. early childhood), exposure rates (75% vs. 25%) and measurement of exposure (prospective, repeated measures vs. retrospective, single time-point), and the nature of the outcome (e.g. heterogeneous disruptive behavior vs. aggressive behavior). The present sample enables us to further elucidate the role of responsiveness in pathways from exposure to disruptive behavior by testing for moderation by *paternal*, as well as maternal, responsiveness during adolescence. We hypothesized that maternal and paternal responsive engagement would moderate exposure patterns for both girls and boys.

2. Methods

2.1 Participants

Participants are derived from the Maternal Infant Smoking Study of East Boston (MISSEB) pregnancy cohort [58]. The present study reports on data from the East Boston Family Study (EBFS), an adolescent follow-up of the non-Hispanic White families of MISSEB (n=348 families, 388 youth). (Hispanic MISSEB participants were excluded because of very low rates of prenatal smoking). Seventy-seven percent of eligible MISSEB families agreed to participate in EBFS (n=251 families, 282 youth including 30 sets of siblings) (see study timeline Figure 1). EBFS participants did not differ from eligible non-participants from MISSEB in terms of maternal smoking status. However, mothers participating in EBFS had higher education levels (75% vs. 62% high school completion, $\chi^2 = 6.0$, $p<.01$) and were slightly older (mean age at pregnancy= 27 vs. 25.5 years, $t=2.5$, $p<.01$). (For further sample description, see [65]).

Because the focus of the present paper is on links between exposure and disruptive behavior and moderation by parenting, the analytic sample is comprised of the 75% of youth who had data in these key domains and who participated with a biologic parent. Two hundred and sixty-five of the 282 EBFS youth participated with a biologic parent. Of these 265, 211 teens reported baseline disruptive behavior data and parenting data for both parents. Thus, the analytic sample is comprised of 211 youth (including 25 sets of siblings). With the exception of prenatal active and second hand exposure, all data are derived from the EBFS baseline interview. Ninety-nine percent of youth participated at baseline with their mothers. The remaining 1% (n=3) participated with their fathers. However, information on both mothers' and fathers' parenting was solicited from the teen at this interview. Virtually all of the mothers were biological and 88% of the fathers were biological (with the remaining 12% being father-figures such as step-fathers.) Ninety-three percent of the youth co-resided with their mothers and 76% co-resided with their fathers or father-figures.

Descriptive information on the analytic sample by exposure status is provided in Table 1. Mean age of the youth in this sample was 14.9 years (SD=1.7) and 54% were girls. Teens in the analytic sample did not differ significantly from the remaining EBFS teens in terms of

sex, exposure status, or mothers' educational attainment. However, compared to those in the analytic sample, excluded teens were older (15.7 versus 14.9 years, $t = 3.40$, $p < .01$), had fathers with lower educational attainment (31% vs. 15% with less than high school education, $\chi^2 = 7.44$, p< .01), had lower household income (median category $20,001-30,000 versus $50,001-75,000, Wilcoxon z = -3.46, $p < .01$), and were more likely to live in a single parent household, (68% versus 29%, $\chi^2 = 31.0$, p< .01). These were controlled in the multivariate analyses.

2.2 Measures

2.2.1 Exposure—At the first prenatal visit, smoking from the start of pregnancy was queried. At each subsequent prenatal visit (median number of visits = 6, range 1-12), women reported current smoking habits, including the number of cigarettes being smoked per day. Blood samples were collected to obtain maternal serum cotinine levels, which are more stable than urinary cotinine. Blood samples were typically collected at the first prenatal visit. Self-reported smoking intensity and cotinine were highly correlated (r=.75). Mean (SD) self-reported smoking was 5.3 (7.8) cigarettes per day and mean serum cotinine was 72.1 (103.4) ng/ml.

Second hand exposure was assessed prenatally and during the EBFS adolescent follow-up visit. Prenatal second hand exposure (presence of other smokers in the household) was assessed by maternal report at the initial prenatal visit and by parent report of maternal and paternal smoking at the adolescent follow-up. For the present analyses, we used these two measures as dichotomous indicators of second hand exposure. Forty-five percent of youth were exposed to second hand smoke prenatally and 36% during adolescence. Second hand exposure was not significantly associated with active prenatal exposure ($\chi^2 = 1.64$, p = .20) but was associated with adolescent second hand exposure ($\chi^2 = 36.1$, p < .001). Prenatal and concurrent secondhand exposures were controlled in all models.

Utilizing methods developed by Dukic and colleagues [22-23], a “best-estimate” prenatal exposure measure was generated using all available data on each woman's exposure [22-23]. This best estimate method mathematically combines self-reported and biologic exposure measures. Hierarchical (subject-specific) modeling of cotinine metabolism was used to generate a cotinine-based correction factor to account for inconsistencies due to nondisclosure or underreporting. This “cotinine-calibration method” algorithm estimates the average relationship between cotinine (taking into account its exponential decay in serum [20] and the timing of samples) and the number of cigarettes self-reported as smoked in a sample of pregnant women. Based on this relationship, the model uses the cotinine measurements to “probabilistically correct” the self-reported number of cigarettes. The threshold for determining prenatal smoking via serum cotinine has been established as 15/ ng/ml. Based on guidelines previously established by the EPA [25], we determined that serum cotinine values due to second-hand prenatal exposure would be between 13-15 ng/ml. Thus, second hand exposure would affect cotinine levels by ≤ 1 cig/day. As a result, calibrations ≤1 were discounted to ensure that the calibrated measure was based solely on exposure to active smoking.

Using this best estimate method, mean upward adjustment was 2.62 cigarettes/day (SD=3.25; range=.32-9.24). Based on this correction, rates of non-disclosure were 8.5% in the group classified as non-exposed by maternal report. Exposure levels of 82.8% of exposed youth were also adjusted upward based on cotinine-identified underreporting. Based on these corrected exposure levels, 49% of the analytic sample were classified as exposed. The mean adjusted number of cigarettes per day in the smoking group was 12.9±7.6, with 64% of these exposed to ½ pack per day or more. For the present analyses,

we used this continuous serum-cotinine corrected measure of average cigarettes per day across the pregnancy.

2.2.2 Disruptive behavior dimensions—We drew on multiple measures to generate the disruptive behavior dimensions (see Table 2). This approach was designed to go beyond categorical, extreme measures of disruptive behavior to assess a broad range of conceptually-linked behaviors that would also include female manifestations. While this approach resulted in some unevenness in coverage across the dimensions, it used all available data to encompass the broadest range of salient behaviors. Youth served as informants for all disruptive behavior measures. Since dimensions included items from multiple measures, scores were range standardized for comparability. Items were recoded to a minimum value of 0 and a maximum value of 1 and to agree in direction (1 = disruptive behavior). Drawing on our prior dimensional validation work, items were first assigned based on their conceptual link to the dimensional construct. These conceptually derived dimensions were then pared down via examination of internal consistency and to reduce inter-dimension correlations. Inter-correlations of the dimensions were relatively high (mean r = .60, range = .49-.79). This level of inter-relatedness is not unexpected given the common variance underlying all four dimensions and indicates overlapping but independent dimensions. Four dimensions were generated:

1. The *Aggression Dimension* was comprised of 22 items tapping into fighting and reactive aggression (Cronbach's α=.83). It was derived from: (a) Conduct Disorder (CD) symptoms from the Diagnostic Interview Schedule for Children (C-DISC-IV:C) [53] (e.g. “participated in a physical fight in which someone was injured”); (b) delinquency items from the Antisocial Behavior Checklist (ASBC) (e.g. “took part in gang fight”) [75] and; (c) items from the Adolescent Anger Rating Scale(AARS) (e.g. “I hit right back if someone hits me”) [11].
2. The *Noncompliance Dimension* was comprised of 42 items (α=.92) tapping into rule-breaking and norm-violation. It was derived from: (a) DISC Oppositional Defiant Disorder (ODD) and CD symptoms (e.g. “refused to do what caretakers asked, “broke curfew”); (b) ASBC delinquency items (e.g. “carrying a fake id”) and; (c) items from the Youth Psychopathy Index (YPI) (e.g. “skipping school”) [2].
3. The *Temper Loss Dimension* was comprised of 10 items (α = 76) tapping into irritability and angry reactivity. It was derived from: (a) DISC ODD symptoms (e.g. “frequent temper loss”) and; (b) items from the AARS (e.g. “got into trouble because of my temper”) [11].
4. The *Low Concern Dimension* was comprised of 32 items (α=.85) tapping into remorselessness, lack of concern for others needs/feelings and, purposeful cruelty. It was derived from: (a) DISC symptoms (e.g. “done things to purposely annoy others); (b) YPI items (e.g. “don't feel guilty or regret wrongdoing to others”); (c) AARS items (e.g. “cheating to get even”); (d) items from the How I Think Questionnaire, which assess hostile attribution (e.g. “sometimes have to hurt someone if have a problem with them”) [5] and; (d) items from the Peer Experiences Questionnaire [49] (e.g. “mean teasing”).

This final item set was then included in a set of tau-equivalent confirmatory factor analyses [52], contrasting alternative models including from 1-4 dimensions. To maximize power to test the fit of these models, we included all youth who had EBFS dimensional data (n=238). Based on the results of these tau-equivalent analyses, the fit of the four-dimension model was superior to a one-dimensional model ($\Delta\chi^2$ (9, N=238) = 404.5, p < .001), a DSM-based two-dimension model ($\Delta\chi^2$ (7, N=238) = 326.7, p < .001), and a two-dimension model such

as that developed and validated by Frick [29] (differentiating general disruptive behavior from disruptive behavior including high scores on the Low Concern dimension) ($\Delta\chi^2$ (7, N=238) = 363.4, p < .001).

2.2.3 Parental responsive engagement—Mothers' and fathers' parenting was measured via youth report on the Network of Relationships Inventory (NRI) [30]. This measure of responsiveness differs from those used in prior studies because it assesses responsiveness (a) by questionnaire rather than observation; (b) during adolescence rather than early childhood and; (c) incorporates basic elements of contingent responsiveness together with the teen's felt experience of the parent-teen relationship (e.g. the teen's feeling of comfort in confiding in parent). As such, we termed this construct *responsive engagement*. The NRI is a 27-item questionnaire rated on a 5-point Likert-type scale (1=little/none to 5=the most) including both positive (e.g. “when you are feeling down or upset, how much do you depend on your (parent) to cheer things up”) and reverse-coded negative (e.g. “how often does (parent) point out your faults or put you down?”) items. We used the NRI total score as a more reliable measure of responsive engagement than individual subscales (as subscales are comprised of only 3 items each), and because we did not have *apriori* hypotheses about specific sub-dimensions of parenting as moderators. Reports of mothers' and fathers' responsive engagement were internally consistent and moderately correlated (r=.46).

2.2.4 Parental antisocial behavior—Mothers reported on their own antisocial behavior via the adult version of the Antisocial Behavior Checklist, which assesses frequency of antisocial behaviors during childhood and adulthood with 45 items (0=never to 3=often) [75]. Since the majority of respondents were mothers, paternal antisocial behavior was assessed with a measure of paternal antisocial behavior specifically validated for use by maternal report [14]. This 35-item paternal measure is derived from the rule-breaking, intrusive and aggression scales of the Achenbach adult-report instrument (0=not true to 2=very true or often true) [1]. Maternal and paternal antisocial behavior scores were moderately correlated (r=.24). To impute antisocial history scores for the 3% of mothers and 4% of fathers with missing data, an imputation model using the EM algorithm was employed (incorporating information from the four dimensional scores, exposure status, and the covariates).

2.2.5 Family adversity—A family adversity index was constructed to provide an aggregate score of sociodemographic risk factors robustly associated with both prenatal smoking and disruptive behavior [33,40,48,72]. Six risk factors were assessed by parental report as follows: (1) early maternal age at first birth (0 = ≥20, 1 = ≤19); (2) marital status (0=married; 1=not married); (3) poverty based on a low income:needs ratio (0=at or above the poverty threshold; 1=below the poverty threshold); (4-5) low parental education separately for mother and father (0= ≥high school education; 1= <high school education) and; (6) inadequate basic resources as defined by the bottom quartile on the Family Resources Scale [24]. This 30-item scale rates adequacy of resources (e.g. having enough food to eat, money to pay bills) on a 5-point Likert-type scale (ranging from 1=not at all adequate to 5=almost always adequate). These 6 risk factors were summed to create the family adversity index (range=0-5). Exposed youth were significantly more likely than non-exposed youth to have a high adversity index (≥ 3 risk factors) (20 vs. 6%, χ^2=8.86, p<.001).

3. Results

3.1.1 Analytic overview—We used multi-level repeated measures models to test for main effects of exposure on the dimensional scores. These models controlled for teen age, sex, maternal and paternal antisocial behavior, family adversity, and prenatal and current second-hand tobacco exposure. They also included appropriate terms to account for the inclusion of siblings in some families. Next, we tested whether effects of exposure differed by sex of teen. Finally, we expanded these models to test for the role of parenting in these pathways, including testing whether exposure effects were robust to control for parenting in the main effects models, and whether parenting moderated these pathways. In the interaction models, we also tested whether any moderated effects varied by sex of the teen. We did hypothesize specificity in prediction from the interaction. As such in the interaction models, our outcomes were the average disruptive behavior estimate (common variance reflecting the average effect over the four dimensions) in addition to the deviation from this average estimate for each specific dimension. All analyses were conducted using SAS version 9.2.

3.1.2 Association of exposure and disruptive behavior dimensions—As shown in Table 3, exposure significantly predicted the Noncompliance (β = .003, $p < .01$) and Aggression (β =.002, $p < .05$) dimensions. These differential associations were robust to adjustment for youth age and sex, maternal and paternal antisocial behavior and family adversity. In contrast, exposure was not significantly associated with Temper Loss or Low Concern for Others. The interaction between sex of teen and exposure was not significant (data not shown).

3.1.3 Interaction of exposure and parental responsive engagement—We first examined whether exposure effects were robust to control for parental responsive engagement. For these analyses, we included parenting variables as covariates in the regression models described above. Each model took into account the effect of responsive engagement by the other parent; maternal responsive engagement was controlled in paternal models and *vice versa*. In order to establish whether paternal responsive engagement effects were due to father presence in the home, paternal co-residence with the youth was also controlled in these models. Exposure remained a significant predictor of Noncompliance in these models (β =.003, $p < .01$) and of Aggression at the trend level (β =.002, $p < .06$). Maternal responsive engagement was not a significant predictor in these models. However, paternal responsive engagement predicted both Noncompliance (β =-.044, $p < .004$) and Aggression (β =-.034, $p < .006$). Separate models were then fitted for maternal and paternal responsive engagement to test for interaction effects (Table 4). The left-hand column of Table 4 shows the effect of exposure on the average estimate of disruptive behavior (common variance reflecting the average effect over the four dimensions), whereas the columns for each dimension show the unique effect or deviance of the specific dimensional estimate from this average estimate (i.e. specificity to the dimensions). *Maternal* responsive engagement did not moderate the effects of exposure on the average estimate of disruptive behavior or any of the specific dimensions. In contrast, a significant *paternal* responsive engagement x exposure interaction was demonstrated in prediction of the average estimate of disruptive behavior (β= -. 004, $p<.01$). As Figure 2 illustrates, at low levels of paternal responsive engagement, teens exposed to 10 and 20 cigarettes/day had significantly higher disruptive behavior scores than non-exposed teens ($p < .05$). In contrast, scores for non-exposed and moderately and heavily exposed youth did not differ significantly at high levels of paternal responsive engagement. Tests of a 3-way interaction with teen sex (exposure × responsive engagement × sex) were not significant (data not shown).

4. Discussion

In this study, we utilized enhanced precision of predictor (exposure) and outcome (disruptive behavior) to more precisely specify exposure-related patterns. This approach led to demonstration of differential association to specific disruptive behavior dimensions. We have also replicated and extended work on moderation of exposure-related patterns by demonstrating the interaction of *paternal* responsiveness and exposure in predicting disruptive behavior at adolescence. Finally, we have tested for sex differences in these patterns and have not found evidence of such in this adolescent sample.

Previous studies have typically utilized broad measures of disruptive behavior disorders or delinquency. Utilizing more narrowly defined dimensional measures in the present study, exposure was specifically associated with Aggression and Noncompliance but was not associated with Temper Loss or Low Concern for Others. The differential association of exposure to Aggression and Noncompliance but not Temper Loss is consistent with findings we previously observed in an early childhood sample [66]. The consistency of this pattern across two independent samples is particularly striking given that these studies focus on diverse developmental periods and employ distinctly different measurement methods. On the other hand, the absence of an association to the Temper Loss dimension is in contrast to several studies that have linked exposure to irritability and hyper-arousal in neonates and young infants [51,57,74]. However, the latter findings may represent a non-specific marker of immaturity in the first months of life [57] rather than a clinically sensitive and specific pattern of reactivity. The present pattern is also consistent with recent findings suggesting that irritability does not have predictive specificity for disruptive behavior [55].

To our knowledge, there is only one other study that has directly examined the association of exposure to behaviors reflecting Low Concern or related behaviors, such as callousness and psychopathy. Fowler et al. reported an association of exposure to psychopathy traits as assessed with the Hare Psychopathy Checklist in a sample of youth with ADHD [28]. However, importantly, multivariate analyses in this study indicated that exposure was associated specifically to impulsive/delinquent aspects of psychopathy (corresponding more to our Aggression/Noncompliance dimensions) rather than callous/remorselessness features (the latter being more akin to our Low Concern dimension). We have also previously demonstrated in the EBFS that exposure is not associated with impairments in fear recognition, an information processing deficit that underlies callous/psychopathic behavior[65].

This differential pattern (distinct associations to Aggression and Noncompliance but not Low Concern) is consistent with our hypotheses. These were based on a model articulated by Blair and colleagues suggesting distinct pathophysiologies underlying varying forms of disruptive behavior [17]. Of salience to the present findings is a pathway with *increased* basic threat circuitry responsiveness (particularly the amygdala) and/or dysfunctional emotional regulatory mechanisms [17]. The OFC plays a central role in this pathway and structural deficits in OFC have been linked to exposure [60]. The threat responsiveness system is particularly sensitive to early environmental disruptions [17], supporting the possibility that prenatal exposure may have deleterious effects via this mechanism. Heightened threat responsiveness is associated with reactive, impulsive aggression and related problems modulating behavior in social interactions. The alternate pathway of *decreased* responsiveness of systems engaged in basic emotional learning and decision-making (the amygdala and orbital frontal cortex) is associated with predatory behavior, callousness and psychopathy and is under considerable genetic influence [7].

Finding the association of exposure to Aggression and Noncompliance similar for boys and girls is not consistent with previous studies of adolescents, which have reported associations specifically for males [26,66,73]. Interestingly, however, the absence of sex differences is *consistent* with exposure-related patterns demonstrated in prior studies of early childhood [10, 32, 66]. This incongruence suggests that methods used in prior studies of older exposed youth may have obscured exposure-related patterns for females. That is, the reliance on outcome measures that measure categorical, broadly-defined disorders or extreme antisocial behaviors (such as criminal offending) in many adolescent studies may not capture typical manifestations in females as well as it does male manifestations [42]. Clearly, application of this multidimensional approach across samples and developmental periods is critical for establishing the replicability and generalizability of these findings.

While this level of behavioral specification is promising, a critical next step will be to test directly for increased threat responsiveness, and emotional regulatory impairments and their neural correlates as mechanisms of prenatal smoking effects. This will require studies that combine precise measurement of exposure with well-defined assessment of behavioral phenotypes and related brain-based measures of information-processing and neuroimaging.

While exposure differentially predicted these specific dimensions of disruptive behavior, the interaction of exposure and parenting predicted the average disruptive behavior score (common variance shared across the dimensions). Differential associations between exposure and narrow disruptive behavior dimensions were hypothesized due to the distinct neurobiologic mechanisms thought to underlie exposure effects as described above. However, we did not hypothesize interactions of parenting with particular dimensions. Although these dimensions account for unique variance they also have shared features that reflect their collective contribution to an overarching syndrome. This common variance is also an indicator of severity because it taps into underlying co-variation. We postulate that parents are likely to respond to this shared “gestalt” of behaviors rather than narrow component elements. This is supported via the differential findings reported in the two prior studies testing whether parental responsiveness moderates exposure effects. Specifically, an interaction was demonstrated in the study predicting broad-band disruptive behavior but not in the study in which prediction was to aggression alone [33, 69]. Protective effects are also often most marked in the face of more severe behaviors[50].

As our outcome and parenting data are cross-sectional, it is not possible to elucidate the direction of the interaction effect. Bidirectional effects in parenting and youth disruptive behavior have been repeatedly demonstrated [46]. Responsive parenting may serve as a buffer against the early behavioral effects of exposure that increase risk of disruptive behavior [71]. Youth with exposure-related disruptive behavior are also likely to evoke less responsive parenting. Longitudinal assessments of disruptive behavior and parenting are needed to parse these effects.

Whereas elevated levels of disruptive behavior were evident in moderately-and heavily-exposed youth compared to their non-exposed counterparts, exposed youth who had responsive fathers did not differ from non-exposed youth in levels of disruptive behavior. Since the majority of studies have demonstrated both parent and youth effects on these pathways [46], these findings certainly suggest the possibility that parental responsiveness exhibited more than a decade after the exposure may exert the same buffering effects as responsiveness in early life. A critical aspect of parental behaviors measured on the NRI is that they tap into adolescents' feelings that they can rely on the parent for help, support, understanding and problem-solving. For youth who are behaviorally vulnerable due to exposure-related tendencies to be reactive and resistant, this consistently available parenting style may promote the development of compensatory skills. To our knowledge, only one

previous study has examined the role of fathers in pathways from exposure to disruptive behavior. This study showed that father *absence* increased risk of delinquency for exposed youth [32]. It has been suggested that father absence may represent both a marker for a host of associated family risk processes and/or the loss of the protective effects of paternal socialization [41]. The present findings support the latter pathway, i.e. demonstrate that fathers' actual parenting behavior may exert a protective effect on youth behavioral risk, regardless of whether these fathers reside with the youth.

Demonstration of parental buffering during adolescence seems to counteract the notion that early childhood is a sensitive period for the exacerbation or amelioration of the behavioral effects of exposure. However, it is possible that the moderated effect of paternal responsiveness shown here does not reflect unique effects of parental behavior during adolescence but rather is a marker for continuities in parental responsiveness over time. Studies that examine the moderating role of parenting for exposed offspring across developmental periods are needed to test these alternative hypotheses [38].

Counter to our hypothesis, *maternal* responsiveness did not moderate exposure effects. It is conceivable that this unexpected pattern is a methodologic artifact. In particular, variations in maternal behavior may be better captured via the emphasis of direct observations on contingent sensitivity in moment-to-moment interactions than the broader emphasis on engaged parenting assessed by questionnaire measures. Alternatively, our findings may represent a true developmental effect in which maternal behavior moderates exposure effects in early life and paternal behavior does so in adolescence. In prior work, we have demonstrated that maternal responsiveness during infancy is uniquely protective against the negative effects of another environmental exposure (life stress) on disruptive behavior (relative to maternal responsiveness during adolescence) [63]. The moment-to-moment contingent shifting that characterizes sensitive maternal responsiveness during infancy may be particularly critical for scaffolding the development of early self-regulatory abilities. In contrast, constructive fathering has a more demanding element, which may be more crucial during adolescence. There is also evidence of transactional patterns by which youth problem behavior and parenting mutually influence each other [16]. Of particular salience to the present study is recent evidence that fathers *increase* their engagement with youth engaged in delinquent and other problem behaviors, whereas mothers do not [15,39]. Further, these paternal behaviors are associated with a concomitant decrease in youth problem behavior over time [15]. This suggests the possibility that fathers' parenting is uniquely protective during adolescence precisely because it is responsive to the types of behaviors that exposed teens are more likely to exhibit. Testing these hypotheses clearly requires longitudinal examination of prospectively ascertained exposed youth, with repeated and multi-method assessments of maternal and paternal responsiveness.

Strengths of the present study include prospective, multi-method assessment of exposure, multi-dimensional assessment of disruptive behavior phenotypes, robust control for key potential confounds and examination of the role of paternal and maternal behavior in exposure-related pathways. Limitations include the relatively small sample size and reliance on a single informant (youth) for assessment of disruptive behavior and parenting. In addition, our disruptive behavior dimensions were derived from secondary data analysis. This preliminary attempt at phenotypic specification is thus necessarily constrained by available data within the EBFS. Replication and extension in studies employing dimensions developed *apriori* will be an important avenue for future work to ensure thorough and comparable coverage across dimensions. Finally, although the present study indicates that the relation of exposure and disruptive behavior is robust to rigorous control for paternal and maternal antisocial behavior, recent studies utilizing within-family designs in large epidemiologic samples suggest that statistical control alone may be inadequate for assessing

the extent to which the co-variation of exposure and disruptive behavior is a marker for a passive gene-environment correlations [18]. Clearly, longitudinal studies that utilize genetically-sensitive designs combined with prospective, repeated measurement of exposure, the use of direct assessments of behavior and information-processing and careful measurement of intervening risk processes are needed. This type of translational approach, which considers the intersection of these multiple biologic and social influences on pathways to disruptive behavior in a nuanced and simultaneous manner, is critical to elucidating whether and how prenatal smoking exerts a teratologic effect on offspring behavior. The present findings advance this line of investigation via specification of exposure-related phenotypes that can serve as a basis for guiding hypothesis-driven testing of neural mechanisms. Whether driven by parent or youth behavior or both, the interaction of responsiveness and exposure also points to the potential benefits of implementing evidence-based preventive interventions focused on parenting [21] as a mechanism for reducing disruptive behavior in exposed offspring. As disruptive behavior trajectories in exposed offspring have been demonstrated in the first two years of life [67], experimental interventions to promote responsiveness in the parents of exposed infants have much promise for elucidating these pathways [45,59].

References

1. Achenbach, TM. Manual for the Young Adult Self-Report and Young Adult Behavior Checklist. University of Vermont Department of Psychiatry; Burlington: 1997.
2. Andershed, H.; Kerr, M.; Stattin, H.; Levander, S. Psychopathic traits in non-referred youths: A new assessment tool. In: Blaauw, E.; Sheridan, L., editors. Psychopaths: Current international perspectives. Elsevier; The Hague: 2002. p. 131-158.
3. Ashford J, Van Lier P, Timmermans M, Cuijpers P, Koot H. Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. J Am Acad Child Adolesc Psychiatry. 2008; 47:779–787. [PubMed: 18520960]
4. A.P. Association. Diagnostic and Statistical Manual of Mental Disorders-IV. Fourth. American Psychiatric Association; Washington, DC: 1994.
5. Barriga AQ, Gibbs JC. Measuring cognitive distortion in antisocial youth: Development and preliminary validation of the “How I Think” questionnaire. Agg Beh. 1996; 22:333–343.
6. Bennett D, Mohamed F, Carmody D, Bendersky M, Satel S, Khorrami M, Faro S, Lewis M. Response inhibition among early adolescents prenatally exposed to tobacco: An fMRI study. Neurotoxicol Teratol. 2009:1–8.
7. Blair, RJR.; Mitchell, DG.; Blair, K. The Psychopath: Emotion and the brain. Blackwell; Malden, MA: 2005.
8. Blair RJR. The roles of orbital frontal cortex in the modulation of antisocial behavior. Brain Cogn. 2004; 55:198–208. [PubMed: 15134853]
9. Blair RJR, Cipolotti L. Impaired social response reversal: A case of ‘acquired sociopathy’. Brain. 2000; 123:1122–1141. [PubMed: 10825352]
10. Brennan P. Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. Am J Psychiatry. 2002; 159:48–54. [PubMed: 11772689]
11. Burney D, Kromrey J. Initial development and score validation of the Adolescent Anger Rating Scale. Educational and Psychological Measurement. 2001; 61:446–460.
12. Burt S. Are there meaningful etiologic differences within antisocial behavior? Results of a meta-analysis. Clin Psychol Rev. 2009; 29:163–178. [PubMed: 19193479]
13. Carter S, Paterson J, Gao W, Iusitini L. Maternal smoking during pregnancy and behaviour problems in a birth cohort of 2-year-old Pacific children in New Zealand. Early Hum Dev. 2008; 84:59–66. [PubMed: 17499944]

14. Caspi A, Taylor A, Smart M, Jackson J, Tagami S, Moffitt T. Can women provide reliable information about their children's fathers? Cross-informant agreement about men's lifetime antisocial behaviour. J Child Psychol Psychiatry. 2001; 42:915–920. [PubMed: 11693586]
15. Coley R, Medeiros B. Reciprocal longitudinal betweens nonresident father involvement and adolescent delinquency. 2007
16. Coley R, Votruba-Drzal E, Schindler H. Trajectories of parenting processes and adolescent substance use: Reciprocal effects. J Abnorm Child Psychol. 2008; 36:613–625. [PubMed: 18288605]
17. Crowe S, Blair RJR. The development of antisocial behavior: What can we learn from functional neuroimaging studies. Dev Psychopathol. 2008; 20:1145–1160. [PubMed: 18838035]
18. D'Onofrio B, Van Hulle C, Waldman I, Rodgers J, Harden K, Rathouz P, Lahey B. Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds. Dev Psychopathol. 2008; 20:139–164. [PubMed: 18211732]
19. Day NL, Richardson GA, Goldschmidt L, Cornelius MD. Effects of prenatal tobacco exposure on preschoolers' behavior. J Dev Behav Pediatr. 2000; 21:180–188. [PubMed: 10883878]
20. Dempsey D, Jacob P, Benowitz N. Accelerated metabolism of nicotine and cotinine in pregnant smokers. J Pharmacol Exp Ther. 2002; 301:594–598. [PubMed: 11961061]
21. Dishion T, Shaw D, Connell A, Gardner F, Weaver C, Wilson M. The family check-up with high-risk indigent families: Preventing problem behavior by increasing parents' positive behavior support in early childhood. Child Dev. 2008; 79:1395–1414. [PubMed: 18826532]
22. Dukic V, Niessner M, Benowitz N, Hans S, Wakschlag L. Modeling the relationship of cotinine and self-reported measures of maternal smoking during pregnancy: A deterministic approach. Nicotine Tob Res. 2007; 9:453–466. [PubMed: 17454700]
23. Dukic V, Niessner M, Pickett K, Benowitz N, Wakschlag L. Calibrating self-reported measures of maternal smoking in pregnancy via bioassays using a Monte Carlo approach. Int J Environ Res Pub Hlth. 2009; 6:1744–1759.
24. Dunst C, Leet H. Measuring the adequacy of resources in households with young children. Child Care, Health and Development. 1987; 13:111–125.
25. U.S. Environmental Protection Agency. Respiratory health effects of passive smoking: Lung cancer and other disorders. United States Environmental Protection Agency; Washington D.C.: 1992.
26. Fergusson D. Prenatal smoking and antisocial behavior. Arch Gen Psychiatry. 1999; 56:223–224. [PubMed: 10078498]
27. Fergusson D, Woodward L, Horwood L. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. Arch Gen Psychiatry. 1998; 55:721–727. [PubMed: 9707383]
28. Fowler T, Langley K, Rice F, Whittinger N, Ross K, van Goozen S, Owen M, O'Donovan M, van den Bree M, Thapar A. Psychopathy traits in adolescents with childhood attention-deficit hyperactivity disorder. Brit J Psychiatry. 2009; 194:62–67. [PubMed: 19118328]
29. Frick P, White S. Research Review: The importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior. J Child Psychol, Psych. 2008; 49:359–375.
30. Furman W, Buhrmester D. Children's perceptions of the personal relationships in their social networks. Dev Psychol. 1985; 21:1016–1024.
31. Gatzke-Kopp LM, Beauchaine T. Direct and passive prenatal nicotine exposure and the development of externalizing psychopathology. Child Psychiatry Hum Dev. 2007; 38:255–269. [PubMed: 17520361]
32. Gibson CL, Tibbetts SG. A biosocial interaction in predicting early onset of offending. Psychol Rep. 2000; 86:509–18. [PubMed: 10840904]
33. Huijbregts S, Seguin J, Zelazo P. Interrelations between maternal smoking during pregnancy, birth weight and sociodemographic factors in the prediction of early cognitive abilities. Inf Child Dev. 2006; 15:593–607.
34. Huijbregts S, Seguin J, Zoccolillo M, Boivin M, Tremblay R. Associations of maternal prenatal smoking with early childhood physical aggression, hyperactivity – impulsivity and their co - occurrence. J Ab Child Psychol. 2007; 35:203–215.

35. Huijbregts S, Seguin J, Zoccolillo M, Boivin M, Tremblay R. Maternal prenatal smoking, parental antisocial behavior and early childhood physical aggression. Dev Psychopathol. 2008; 20:437–453. [PubMed: 18423088]
36. Hutchinson J, Pickett K, Green J, Wakschlag L. Smoking in pregnancy and disruptive behavior in 3-year-old boys and girls: An analysis of the UK Millennium Cohort Study. J Epidem Comm Hlth. 2010; 64:82–88.
37. Kahn R, Khoury M, Nichols T, Lanphear B. Role of Dopamine Transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. J Ped. 2003; 143:104–110.
38. Landry SH, Smith K, Swank P, Guttentag C. A responsive parenting intervention: The optimal timing across early childhood for impacting maternal behaviors and child outcomes. Dev Psychol. 2008; 44:1335–1353. [PubMed: 18793067]
39. Levine-Coley R, Votruba-Drzal E, Schindler H. Fathers' and mothers' parenting predicting and responding to adolescent sexual risk behaviors. Child Dev. 2009; 80:808–827. [PubMed: 19489905]
40. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch Gen Psychiatry. 2004; 61:836–43. [PubMed: 15289282]
41. Mendle J, Harden K, Turkheimer E, Van Hulle C, D'Onofrio B, Brooks-Gunn J, Rodgers J, Emery R, Lahey B. Associations between father absence and age of first sexual intercourse. Child Dev. 2009; 80:1463–1480. [PubMed: 19765012]
42. Moffitt T, Arseneault L, Jaffee S, Kim-Cohen J, Koenen K, Odgers C, Slutske W, Viding E. Research review: DSM-V Conduct Disorder: Research needs for an evidence base. J Child Psychol Psych. 2007:3–33.
43. Monuteaux M, Blacker D, Biederman J, Fitzmaurice G, Buka S. Maternal smoking during pregnancy and offspring overt and covert conduct problems: A longitudinal study. J Child Psychol Psych. 2006; 47:883–90.
44. Nigg J, Breslau N. Prenatal smoking exposure, low birth weight and disruptive behavior disorders. J Am Acad Child Adolesc Psych. 2007; 46:362–369.
45. O'Neal C, Miller Brotman L, Huang K, Gouley K, Kamboukos D, Calzada E, Pine D. Understanding relations among early family environment, cortisol response, and child aggression via a prevention experiment. Child Dev. 2010; 81:290–305. [PubMed: 20331668]
46. Pardini D. Novel insights into longstanding theories of bidirectional parent-child influences: Introduction to the special section. J Ab Child Psychol. 2008; 36:627–631.
47. Pickett K, Wood C, Abramson J, DeSouza L, Wakschlag L. Meaningful differences in maternal smoking behavior during pregnancy: Implications for infant behavioral vulnerability. J Epidemio and Comm Hlth. 2008; 62:318–324.
48. Pickett K, Wilkinson R, Wakschlag L. The psychosocial context of pregnancy smoking and quitting in the Millennium Cohort Study. J Epidem Comm Hlth. 2009; 63:474–480.
49. Prinstein MJ, Boergers J, Vernberg EM. Overt and relational aggression in adolescents: Social-psychological adjustment of aggressors and victims. J Clinic Child Psychol. 2001; 30:479–491.
50. Sameroff A. A unified theory of development: A dialectic integration of nature and nurture. Child Dev. 2010; 81:6–22. [PubMed: 20331651]
51. Schuetze P, Eiden R. The association between prenatal exposure to cigarettes and infant negative affect. Inf Beh Dev. 2007:387–398.
52. Graham J. Congeneric and (essentially) tau-equivalent estimates of score reliability: What they are and how to use them. Educational and Psychological Measurement. 2006; 66:930–944.
53. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry. 2000; 39:28–38. [PubMed: 10638065]
54. Stene-Larsen K, Borge A, Vollrath M. Maternal smoking in pregnancy and externalizing behavior in 18-month-old chldren: Results from a population-based prosepective study. J Am Acad Child Adolesc Psych. 2009; 48:283–289.

55. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. J Am Acad Child Adolesc Psych. 2009; 48:404–412.
56. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. J Child Psychol Psychiat. 2009; 50:216–223. [PubMed: 19166573]
57. Stroud L, Paster R, Papandonatos G, Niaura R, Salisbury A, Battle C, Lagasse L, Lester B. Maternal smoking during pregnancy and newborn neurobehavior: Effects at 10 to 27 Days. J Pediatr. 2009; 154:10–16. [PubMed: 18990408]
58. Tager I, Ngo L, Hanrahan J. Maternal smoking during pregnancy: Effects on lung function during the first 18 months of life. Am J Resp Crit Care Med. 1995; 152:977–983. [PubMed: 7663813]
59. Tolan P, Gorman-Smith D. What violence prevention research can tell us about developmental psychopathology. Dev Psychopathol. 2002; 14:713–729. [PubMed: 12549701]
60. Toro R, Leonard G, Lerner J, Lerner R, Perron M, Pike G, Richer L, Veillette S, Pausova Z, Paus T. Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. Neuropsychopharmacology. 2007:1–9. [PubMed: 17019409]
61. Tremblay R, Nagin D, Seguin J, Zoccolillo M, Zelazo P, Boivin M, Perusse D, Japel C. Physical aggression during early childhood: Trajectories and predictors. Pediatrics. 2004; 114:43–50.
62. van den Boom DC. Do first year intervention effects endure? Follow-up during toddlerhood of a sample of Dutch irritable infants. Child Dev. 1995; 66:1798–1816. [PubMed: 8556900]
63. Wakschlag L, Hans S. Relation of maternal responsiveness during infancy to the development of behavior problems in high risk youths. Dev Psychol. 1999; 37:569–579. [PubMed: 10082027]
64. Wakschlag L, Henry D, Tolan P, Carter A, Burns J, Briggs-Gowan M. Does a multidimensional approach to disruptive behavior have added value? Examination in early childhood. 2009 Submitted manuscript.
65. Wakschlag L, Kistner E, Pine D, Biesecker G, Pickett K, Skol A, Dukic V, Blair R, Leventhal B, Cox N, et al. Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. Mol Psychiatry. 2009 advance online.
66. Wakschlag L, Lahey B, Loeber R, Green S, Gordon R, Leventhal B. Maternal smoking during pregnancy and the risk of conduct disorder in boys. Arch Gen Psychiatry. 1997; 54:670–676. [PubMed: 9236551]
67. Wakschlag L, Leventhal B, Pine D, Pickett K, Carter A. Elucidating early mechanisms of developmental psychopathology: The case of prenatal smoking and disruptive behavior. Child Dev. 2006; 77:893–906. [PubMed: 16942496]
68. Wakschlag L, Pickett K, Kasza K, Loeber R. Is prenatal smoking associated with a developmental pattern of conduct problems in young boys? J Am Acad Child Adoles Psych. 2006; 45:461–467.
69. Wakschlag L, Pickett K, Cook E, Benowitz N, Leventhal B. Maternal smoking during pregnancy and severe antisocial behavior in offspring: A review. AJPH. 2002; 92:966–974.
70. Wakschlag L, Tolan P, Leventhal B. “Ain't misbehavin”: Towards a developmentally-specified nosology for preschool disruptive behavior. J Child Psychol Psychiat. 2010; 51:3–22. [PubMed: 19874427]
71. Wakschlag L, Hans SL. Maternal smoking during pregnancy and conduct problems in high-risk youth: a developmental framework. Dev Psychopathol. 2002; 14:351–69. [PubMed: 12030696]
72. Weaver K, Campbell R, Mermelstein R, Wakschlag L. Pregnancy smoking in context: The influence of multiple levels of stress. Nic Tob Res. 2008; 10:1065–1073.
73. Weissman MM, Warner V, Wickramaratne P, Kandel D. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. J Am Acad Child Adolesc Psychiatry. 1999; 38:892–899. [PubMed: 10405508]
74. Wiebe S, Espy K, Stoop C, Respass J, Stewart P, Jameson T, Gilbert D, Gilbert BO, Huggenvik J. Gene-environment interactions across development: Exploring DRD2 genotype and prenatal smoking effects on self-regulation. Dev Psych. 2009; 45:31–44.
75. Zucker, R.; Noll, R.; Ham, H.; Fitzgerald, H.; Sullivan, L. Assessing antisociality wtih the Antisocial Behavior Checklist: Reliability and validity studies. University of Michigan & Michigan State University; 1994.

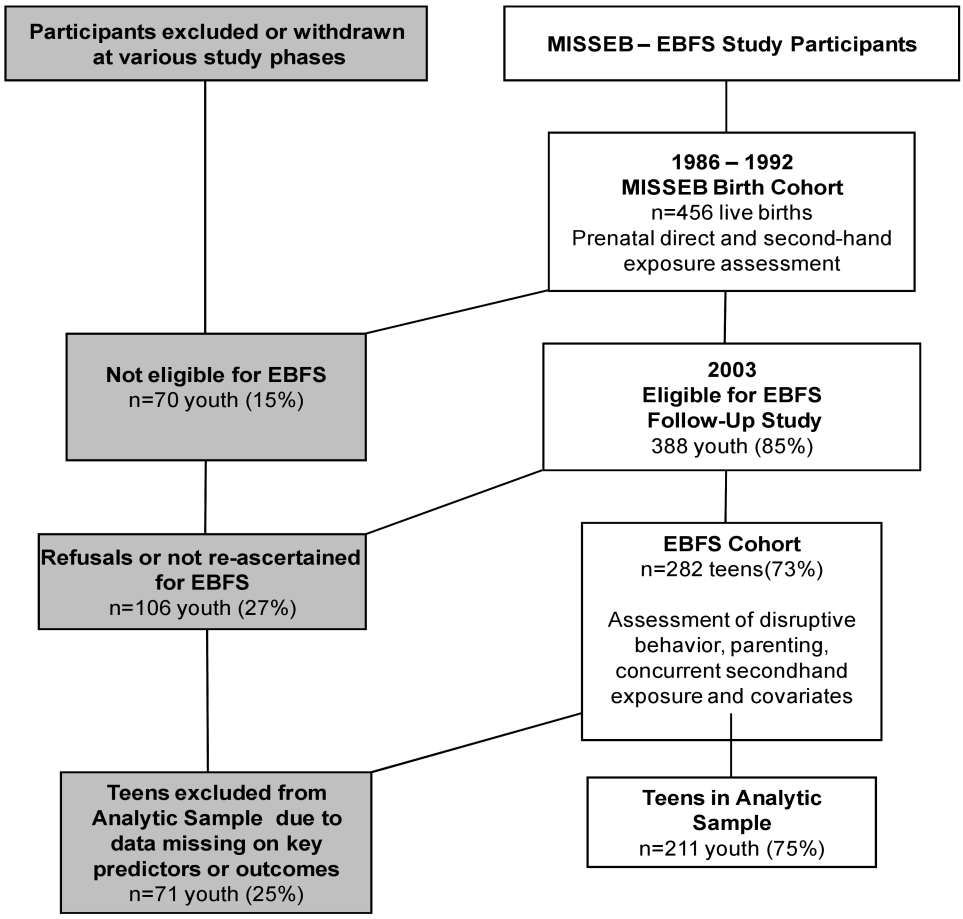

Figure 1. EBFS Study Timeline

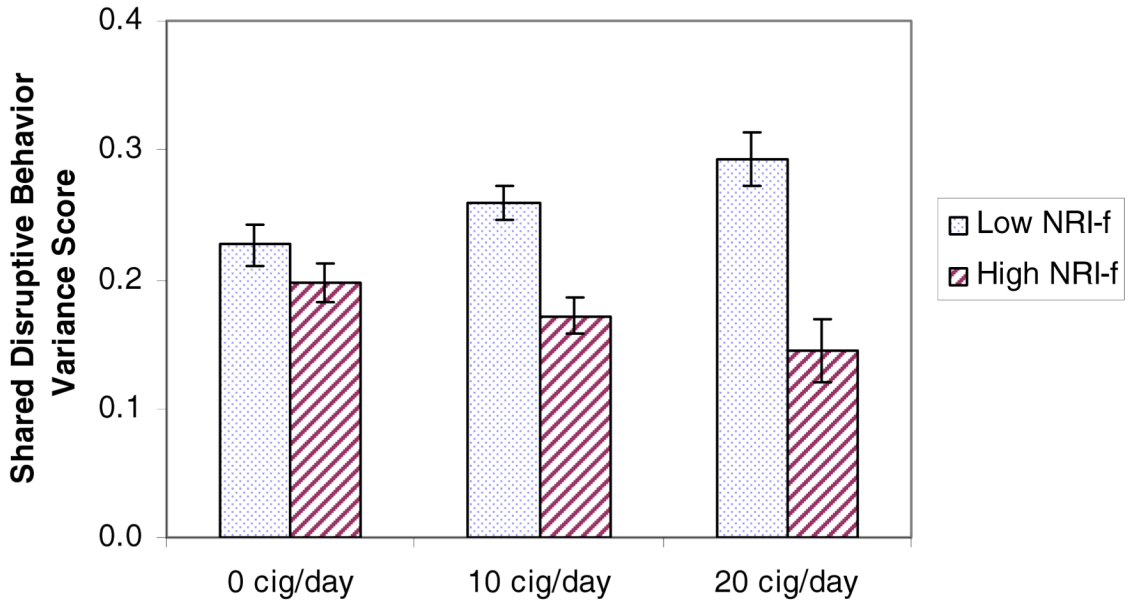

Figure 2. Interaction of Exposure & Paternal Responsive Engagement in Prediction of Shared Disruptive Behavior Variance

[a] For illustrative purposes, low paternal responsive engagement is graphed at 1 SD below the mean and high paternal responsive engagement is graphed at 1 SD above the mean.

[b]The minimum possible average estimate of disruptive behavior score is 0, and the maximum possible score is 1.

[c] At low levels of paternal responsive engagement, there were significant differences between average estimates of disruptive behavior for non-exposed youth vs. moderately and heavily exposed youth (10 cig/day vs 0 cig/day and 20 cig/day vs 0 cig/day) ($p < .05$). Comparisons across these exposure groups were not significant at high levels of paternal responsive engagement.

Table 1
East Boston Family Study Sample Characteristics and Descriptives (n = 211)

Variable	Not exposed (n = 108)	Exposed (n = 103)
Mean youth age (SD) at baseline (years)	14.9 (1.7)	14.9 (1.7)
% Female	56%	51%
Median household income	$50,001 - $75,000	$30,001 - $40,000 *
Living in Poverty (based on income:needs ratio)	8%	21% *
% inadequate family resources (based on bottom quartile score on the Family Resources index)	18%	30% *
Prenatal exposure to cigarettes		
Non-exposed, count (%)	108 (100%)	0 (0%)
Moderately exposed (<10 cig/day), count (%)		37 (36%)
Heavily exposed (≥ 10 cig/day), count (%)		66 (64%)
Household second-hand smoke exposure		
% exposed prenatally (not including active exposure)	40%	50%
% exposed at adolescence	31%	73% *
Mean parental age (SD) at baseline (years)	42.4 (6.0)	42.8 (5.0)
Young maternal early age at first birth (≤19)	22%	27%
Single parent	25%	34%
Father with less than high school education	10%	19%
Mother with less than high school education	6%	16% *

* Significant difference, $p < .05$

Table 2

Overview of Measures Comprising the Four Disruptive Behavior Dimensions

Measure	Alpha	Derived from	Assesses	# items
Aggression	0.83	Diagnostic Interview Schedule for Children (DISC-IV) [53]	Aggressive DBD symptoms	7
		Antisocial Behavior Checklist (ASBC) [75]	Aggressive delinquent acts	13
		Adolescent Anger Rating Scale (AARS) [11]	Reactive aggression	2
Noncompliance	0.92	Diagnostic Interview Schedule for Children (DISC-IV:C)	DBD noncompliant symptoms	17
		Antisocial Behavior Checklist (ASBC)	Rule breaking delinquency	23
		Youth Psychopathy Index (YPI) [2]	Psychopathic personality traits	1
		Adolescent Anger Rating Scale (AARS)	Rulebreaking when angry	1
Temper Loss	0.76	Diagnostic Interview Schedule for Children (DISC-IV:C)	ODD irritability symptoms	4
		Adolescent Anger Rating Scale (AARS)	Dysregulated angry reactivity	6
Low Concern for Others	0.85	Diagnostic Interview Schedule for Children (DISC-IV:C)	DBD low concern symptoms	7
		Youth Psychopathy Index (YPI)	Callous traits	15
		Adolescent Anger Rating Scale (AARS)	Acting cruelly when angry	2
		“How I Think” questionnaire (HIT) [5]	Hostile attribution	2
		Peer Experiences Questionnaire items (PPEQ) [49]	Nasty behavior with peers	5
		Antisocial Behavior Checklist (ASBC) [75]	Cruel delinquent behaviors	1

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Table 3

Differential Association of Exposure and Four Disruptive Behavior Dimensions [a] (n = 211)

	Temper loss		Noncompliance		Aggression		Low Concern	
	Estimate	**S.E.**	**Estimate**	**S.E.**	**Estimate**	**S.E.**	**Estimate**	**S.E.**
Intercept[b]	0.349**	(0.029)	0.136**	(0.020)	0.069**	(0.016)	0.155**	(0.014)
Teen age	0.030**	(0.009)	0.047**	(0.006)	0.029**	(0.005)	0.014**	(0.004)
Teen sex (0 = female, 1 = male)	0.029	(0.029)	0.026	(0.020)	0.067**	(0.016)	0.058**	(0.014)
Maternal antisocial behavior	0.002	(0.002)	0.002†	(0.001)	0.001	(0.001)	0.001	(0.001)
Paternal antisocial behavior	0.000	(0.001)	0.001	(0.001)	0.000	(0.001)	0.001	(0.000)
Family adversity index	0.007	(0.014)	-0.004	(0.010)	0.002	(0.008)	0.004	(0.007)
Current ETS exposure (1 = yes)	0.027	(0.032)	0.017	(0.022)	-0.009	(0.018)	0.012	(0.016)
Prenatal ETS exposure (1 = yes)	0.003	(0.032)	0.024	(0.022)	0.018	(0.018)	-0.001	(0.016)
Prenatal cigarette exposure (cig/d)	-0.001	(0.002)	0.003**	(0.001)	0.002*	(0.001)	0.000	(0.001)

† $p < .10$,

* $p < .05$,

** $p < .01$

[a] Multivariate regression with random intercepts for families, controlling for teen age and sex, maternal and paternal antisocial behavior, family adversity index, and prenatal and concurrent secondhand smoke exposure.

[b] Intercept represents estimated value of dimensional score for female at mean age, mean maternal and paternal antisocial behavior, with family adversity index, second-hand smoke exposure and prenatal cigarette exposure values of zero.

Table 4

Interaction of Exposure and Parental Responsive Engagement in Prediction of Youth Disruptive Behavior [a](n=211)

	Average Disruptive Behavior Estimate[b]		Deviation[c]							
			Temper loss		Noncompliance		Aggression		Low Concern	
	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.
Maternal Responsive Engagement X Exposure	0.001 **	(0.001)	0.000 *	(0.002)	0.001 **	(0.001)	0.000 *	(0.001)	-0.001	(0.001)
Paternal Responsive Engagement X Exposure	-0.004 **	(0.001)	-0.001 *	(0.001)	-0.002 †**	(0.001)	0.001 *	(0.001)	0.001	(0.001)

† $p < .10$,

* $p < .05$,

** $p < .01$

[a] Multivariate regressions with random intercepts for families, controlling for teen age and sex, maternal and paternal antisocial behavior, family adversity index, prenatal and concurrent secondhand exposure and whether the teen co-resided with mother and/or father. Maternal interaction model controlled for parental responsive engagement and vice versa. Full data from these models are available from the authors.

[b] The average estimate is the common variance in disruptive behavior across the four dimensional scores.

[c] Dimensional score estimates represent deviations from average estimate of disruptive behavior.