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Pre- and Perinatal Risk for Attention-Deficit Hyperactivity Disorder: Does Neuropsychological Weakness Explain the Link?

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Abstract

Etiological investigations of attention-deficit hyperactivity disorder (ADHD) and disruptive behavior problems support multiple causal pathways, including involvement of pre- and perinatal risk factors. Because these risks occur early in life, well before observable ADHD and externalizing symptoms emerge, the relation between risk and symptoms may be mediated by neurodevelopmental effects that manifest later in neuropsychological functioning. However, potential dissociable effects of pre/perinatal risk elements on ADHD and familial confounds must also be considered to test alternative hypotheses. 498 youth aged 6–17 years (55.0% male) completed a multi-stage, multi-informant assessment including parent and teacher symptom reports and parent ratings of pre/perinatal health risk indicators. Youth completed a neuropsychological testing battery. Multiple mediation models examined direct effects of pre- and perinatal health risk on ADHD and other disruptive behavior disorder symptoms and indirect effects via neuropsychological functioning. Parental ADHD symptoms and externalizing status was covaried to control for potential familial effects. Effects of prenatal substance exposure on inattention were mediated by memory span and temporal processing deficits. Further, effects of perinatal health risk on inattention, hyperactivity-impulsivity, and ODD were mediated by deficits in response variability and temporal processing. Further, maternal health risks during pregnancy appeared to exert direct rather than indirect effects on outcomes. Results suggest that after controlling for familial relatedness of ADHD between parent and child, early developmental health risks may influence ADHD via effects on neuropsychological processes underpinning the disorder.

Keywords

attention deficit hyperactivity disorder; neuropsychological dysfunction; prenatal risk

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Attention-deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate and impairing difficulties with inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013). Etiological investigations of ADHD have implicated moderate to large genetic contributions (Knopik et al., 2005; Nikolas & Burt, 2010). Substantial evidence also supports multiple causal pathways involving interplay among genetic and environmental factors (Nigg, Nikolas, & Burt, 2010).

Due to their potential impact on brain development and subsequent neural function, pre- and perinatal health factors have been evaluated in relation to ADHD (Ernst, Moolchan, & Robinson, 2001; Gurevitz, Geva, Varon, & Leitner, 2014; Hofhuis, de Jongste, & Merkus, 2003). For example, low birth weight (LBW) robustly predicts ADHD symptoms (Langley, Holmans, van den Bree, & Thapar, 2007; Nigg & Breslau, 2007). Other relevant pre- and perinatal health risks include maternal stress during pregnancy (Bielas, Arck, Bruenahl, Walitza, & Grünblatt, 2014; Van den Bergh & Marcoen, 2004), prenatal substance use (Ernst et al., 2001; Nigg and Breslau, 2007), and perinatal complications (D'Onofrio et al., 2013). However, these risks are often correlated and, importantly, it is unclear whether critical effects on ADHD risk occur prenatally or perinatally (or both).

Despite the high co-occurrence of ADHD and other externalizing disorders, past research has hypothesized a potential dissociation of prenatal health risks and ADHD versus other externalizing disorders. Nigg and Breslau (2007) found that LBW specifically predicted ADHD symptoms (with prenatal tobacco exposure covaried), whereas prenatal tobacco exposure (with birth weight covaried) specifically predicted oppositional defiant disorder (ODD) and conduct disorder (CD) symptoms. Similarly, Langley et al. (2007) reported that prenatal tobacco exposure significantly predicted CD, apart from effects on hyperactivity-impulsivity, suggesting that prenatal tobacco exposure may relate to ADHD solely via its impact on externalizing behaviors. However, this work did not find a connection between LBW and ADHD, thus providing only limited support for potential dissociation of effects. Overall, the high degree of correlation among risk factors and mixed results regarding specificity of associations between individual risk factors and externalizing syndromes warrants further investigation.

Importantly, prior work examining pre- and perinatal health risk for ADHD has often failed to consider the impact of familial confounds, including the role of parental ADHD. Associations between pre- and perinatal risk and ADHD may partially reflect shared genes between parents and children (gene-environment correlation, rGE; Rice et al., 2010). For example, mothers with ADHD may be more likely to smoke during pregnancy (Zhu, Olsen, Liew, Niclasen, & Obel, 2014), leading to a spurious environmental association between prenatal tobacco exposure and ADHD that may in fact be due to rGE (Atlink et al., 2009; Thapar et al. 2009) or another genetically-mediated process. Thus, it remains critical for future work to consider the potential confounding role of familial factors.

Pre- and perinatal risk may exert effects via disruption of neurodevelopment, which then manifests in subsequent neuropsychological dysfunction in children with ADHD (Piper & Corbett, 2012). Deficits in both executive functions and non-executive processes have been

well-documented among youth with ADHD (Nikolas & Nigg, 2013; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Further, prenatal substance exposure and LBW influence neural functioning in brain regions purported to underlie ADHD symptoms (Ernst et al., 2001; Faraone & Biederman, 1998). For example, impulsive symptoms may stem from deficient reward processing underpinned by connections among orbitofrontal and striatal regions (Wilbertz et al., 2012), which appear to be affected by pre- and perinatal risk (Diwadkar et al., 2013; Derauf et al., 2012). Thus, pre- and perinatal health may indirectly influence risk for ADHD and other disruptive behavior disorders, such that early insults influence the development of cortico-striatal circuitry, resulting in neuropsychological dysfunction and subsequently increasing liability for ADHD and/or other disruptive behavior problems. Hatch, Healey, and Halperin (2014) recently demonstrated that primary neuropsychological functioning (defined as visuo-spatial perception and motor coordination) mediated associations between birth weight and ADHD symptoms. However, while innovative, this work did not consider potential differential effects of pre- and perinatal health risk on ADHD versus disruptive behavior disorders (Nigg & Breslau, 2007), other potentially relevant indicators of risk (e.g., teratogen exposure, complications during pregnancy and/or delivery, perinatal health), or familial confounds (i.e., potential impact of shared genetic and environmental factors).

The primary aim of the current study was to further develop recent work by Hatch, Healey, and Halperin (2014) by examining direct and indirect effects of multiple pre- and perinatal risk factors on ADHD and other disruptive behavior disorder symptoms via neuropsychological dysfunction within a multiple mediation framework. We predicted that pre and perinatal health risks would exert indirect effects on ADHD and other externalizing behaviors via their influence on neuropsychological functioning. Secondary aims to extend prior work included (1) statistical control for familial confounds, (2) incorporating comprehensive measures of pre- and perinatal health risks dissociating birth weight and teratogen exposure, (3) examining multiple measures of neuropsychological processes, and (4) differentiating effects on ADHD versus co-occurring disruptive behavior disorder outcomes.

METHOD

Participants

Participants were 498 children and adolescents ages 6 to 17 years ($M=10.8$, $SD=2.3$, 55.0% male). The sample, originally recruited to examine genetic and endophenotype effects for ADHD, included 205 sibling pairs and 88 singletons. Participants were recruited using mass mailings to parents in local school districts, public advertisements, and community outreach to local clinics to recruit a broad sample while avoiding potential biases inherent to purely clinic-referred samples. A multi-stage, multi-informant assessment procedure was used to identify cases and non-cases. 902 individual children from 762 families completed the stage 1 initial telephone screen, which evaluated potential rule-outs, including physical handicap, non-native English speaking, history of intellectual disability, autistic disorder, and prescription of long-active psychoactive medications (e.g., atomoxetine, bupropion). 724 individual children from 588 families were then invited to complete stage 2 diagnostic

assessment, which included parent and teacher ratings on the DSM-IV ADHD Rating Scale (DuPaul, Power, Anastopoulos, & Reid, 1998), and the Conners' Rating Scale – Revised Short Form (Conners, 1997). Parents completed the Kiddie Schedule for Affective Disorders and Schizophrenia-E (Puig-Antich & Ryan, 1986) for each child with a trained master's level clinical interviewer. A three-subtest version of the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) was administered to youth at this stage to estimate full scale IQ.

Clinical data were reviewed and a best estimate diagnostic procedure was implemented by a board-certified child psychiatrist and a licensed child clinical psychologist. Both professionals used a symptom count *or algorithm* from parent and teacher reports (i.e., symptom counted as present if endorsed by parent *or* teacher) as well as T-scores for both parent and teacher ratings on the Conners' Cognitive Problems or Hyperactivity Problems subscales (t-scores>60 considered clinically significant). Clinical decisions concerning ADHD, ADHD subtype, and comorbid diagnoses were made independently, using full DSM-IV-TR criteria. Agreement rates were acceptable for all ADHD subtype diagnoses ($\kappa > .88$) and all anxiety, mood, and disruptive behavior disorders occurring at a 5% or more base rate in the sample (all $\kappa > .70$).

Following the diagnostic assessment, youth were then invited to complete the stage 3 neuropsychological assessment, provided they were not identified for exclusion based on the following criteria. Youth were excluded if the diagnostic team identified intellectual disability (defined as full-scale IQ<75, n=3 excluded), head injury with a loss of consciousness (n=8 excluded), history of seizures as ascertained by parent report (n=5 excluded), or if youth met criteria on the KSADS-E for autism spectrum disorders (n=18 excluded), current major depressive episode (n=57 excluded), lifetime psychosis (n=5 excluded), or current substance abuse or dependence (n=5 excluded).

Of the 724 youth completing the diagnostic screen, 623 qualified for the follow-up neuropsychological testing visit. Of these, 498 youth from 295 families completed the stage 3 neuropsychological testing battery, on a separate day following the diagnostic visit (see below). There were no significant differences between those who participated in the stage 3 assessment (n=498) and those who elected not to return (n=125) in regard to sex, age, ADHD severity and income ($p > .26$). The final sample included 251 youth with ADHD and 213 non-ADHD youth. 34 youth had subthreshold or situational ADHD symptoms – these youth were excluded for group comparisons but included in all dimensional mediation analyses. 37.4 percent of participants who met criteria for ADHD were prescribed stimulant medication (consistent with expectations for community samples; Jensen et al., 2001). Youth currently taking stimulant medication completed a minimum washout period of 24 hours for short-acting preparations and 48 hours for long-acting preparations (range 24–152 hours, mean=58 hours) before completing neuropsychological testing, which occurred approximately 4 weeks after the diagnostic assessment (mean time between visits=4.2 weeks, $SD=3.2$). Eligible participants using longer-acting psychoactive prescription medications (including atomoxetine and guanfacine) were excluded (2%). Parents provided informed consent for themselves and their child; youth provided written assent. All procedures were approved by the Michigan State University Institutional Review Board.

Measures

Neuropsychological Functioning—The battery of tests employed was organized to capture multiple neuropsychological functions implicated in ADHD. A list of measures and their associated constructs are presented in Table 1. Tests measured working memory (Martinussen & Tannock, 2006), memory span, response inhibition (Barkley, 1997), processing speed, response variability (Karalunas et al., 2014), temporal processing (Noreika, Falter, & Rubia, 2013; Toplak & Tannock, 2005), and arousal (or activation; operationalized as signal detection sensitivity; Sergeant, 2005). All youth completed the same battery of tests, which were administered in a fixed order. Internal consistencies for each of the measures were adequate (α s ranging from .85 to .97, calculated based on non-ADHD participants only). Past research has established evidence of construct, convergent, and discriminant validity for several of the measures (Assesmany, McIntosh, Phelps, & Rizza, 2001; Delis, Kaplan, & Kramer, 2001; Logan, 1994; Martinussen & Tannock, 2006; Toplak & Tannock, 2005). Validity checks conducted for each measure indicated that invalid data were rare overall (less than 5% on any one task) and presence of invalid data was unrelated to ADHD diagnostic status, age, and sex (all p s > .15; see Nikolas & Nigg, 2013 for a detailed explanation of chosen measures and associated validity criteria).

ADHD and Comorbid Disruptive Behavior Problems—Parent and teacher ratings on the ADHD Rating Scale (DuPaul et al., 1998) constituted the main outcome measure. Parents and teachers rated the frequency of all 18 DSM ADHD symptoms on a 4-point Likert Scale (*never, sometimes, often, very often*). Notably, parents and teachers were instructed to rate their child's behavior off of medication, if they had observed such instances. Internal consistencies were adequate for ratings of inattention (parent α =.93; teacher α =.91) and hyperactivity-impulsivity (parent α =.90; teacher α =.88). Additionally, parent-reported ODD and CD symptoms were assessed with the KSADS-E (α =.87 ODD; α =.85 CD), whereas teachers rated these behaviors using a measure similar to the ADHD Rating Scale. Items rated by teachers as occurring "often" or "very often" were counted as symptoms (α =.86 ODD; α =.81 CD). To reduce the number of statistical tests required to achieve our aims while maximizing data collected from multiple informants, scores were averaged across informant for each symptom dimension (e.g., inattention, hyperactivity-impulsivity, ODD, and CD), based on recent work indicating that average composite scores best predicted ADHD diagnosis when compared to other methods of combining across informants (Martel, Schimmack, Nikolas, & Nigg, 2015). Standard scores were averaged across informant for inattention and hyperactivity-impulsivity. Because assessment ODD and CD symptoms relied on different measures for parents versus teachers, we first created z-scores within informant and then took the average of parent and teacher z-scores. Cross-informant correlations for these symptom dimensions ranged from r =.41 to r =.58. These average composites were retained as the four primary outcomes in subsequent mediation models.

Parental Psychopathology—Primary parents provided ratings regarding current ADHD symptoms for themselves and their child's other biological parent on the Barkley and Murphy (2006) Adult ADHD Rating Scale. Individuals rated the presence of each of the 18 DSM-items on a 4-point Likert scale (*never, sometimes, often, very often*). Internal

consistencies were adequate for both self-report (inattention $\alpha=.90$, hyperactivity-impulsivity $\alpha=.86$) and other reports (inattention $\alpha=.87$, hyperactivity-impulsivity $\alpha=.81$). A sum score was created for each parent, standardized, and then averaged to create an index of parental ADHD symptoms. Primary parents also indicated positive family history of other externalizing disorders as part of the developmental history questionnaire (see below). This included if the child's biological mother and/or father have had a confirmed or suspected diagnosis of alcoholism or other form of substance abuse/dependence, or a history of delinquency, conduct, or legal problems. Items were scored to determine parental externalizing disorder (yes/no) status. These variables were included as covariates in all analyses to account for associations between pre/perinatal health risk and child psychopathology potentially attributable to relatedness among families.

Pre- and Perinatal Risk Factors—A comprehensive developmental history questionnaire was completed for each youth by their primary caregiver ($n=454$ mothers, $n=44$ fathers) to assess three aspects of early child health—prenatal substance exposure, maternal health during pregnancy, and child perinatal health risk. This included several questions regarding the health and behavior of the mothers during pregnancy and delivery as well as questions regarding the health of the children during delivery and after birth. *Prenatal substance exposure* was assessed by having parents indicate whether mothers used tobacco, alcohol, and/or recreational drugs during pregnancy. *Maternal health during pregnancy* comprised questions assessing the presence of several illnesses during pregnancy, including toxemia, gestational diabetes, preeclampsia, placenta previa, high blood pressure, chronic infections, influenza, marked swelling of hands and feet, convulsions, frequent headaches, and/or abdominal pain. Parents also indicated any additional maternal health issues during pregnancy not covered on the questionnaire (most frequent responses including hyperemesis, spotting/bleeding, injuries/accidents) and reported the presence and frequency of additional exposures during pregnancy, including x-rays, prescription medications (most common prescription medications used were for asthma, allergies, and anxiety/depression), and presence of significant emotional stressors (e.g., frequent conflict with partner, divorce, loss of employment).

Labor and delivery characteristics were also assessed to gauge *perinatal health risks*. These included the gestational age at the time of delivery (number of weeks), the type of delivery (uncomplicated vaginal versus Caesarian or forceps), the length of labor (in hours), and the child's birth weight (in ounces). Further, the presence or absence of additional child health problems during delivery and immediately following birth were also assessed, including use of an incubator, heart and respiratory problems, jaundice, low Apgar score, meconium aspiration, and umbilical cord prolapse. Parents also indicated occurrence of any additional complication or health difficulty not included on the questionnaire (most common responses included infant temperature instability following birth, infections, and hernias). Parents also provided information regarding their age at each child's birth, given the robust association between parental age and pre and perinatal health risks (Cleary-Goldman et al., 2005; Najati & Gojatzadeh, 2010) as well as between parental age and ADHD (Chudal et al., 2015). Differences among ADHD and non-ADHD youth across all of the pre- and perinatal health indicators as well as in parental age at birth are presented in Table 2.

Data Reduction—Data reduction for all pre- and perinatal health indicators was accomplished via confirmatory factor analyses (CFA). Given that the health and family background questions concerning pre- and perinatal health were developed to assess three broad domains (i.e., prenatal substance exposure, maternal health during pregnancy, and perinatal health indicators), a three-factor model determined *a priori* was fitted to the data. Because several indicators were categorical or count variables and missingness was minimal (<1%), weighted least-squares with mean and variance adjustment estimation procedures (WLSMV) and theta parameterization were utilized (note – gestational age and birth weight were reversed scored so that all items had the same valence). Fit statistics indicated acceptable model fit of the three-factor model ($\chi^2=50.38$, $df=25$, CFI=.96, RMSEA=.046, [.027, .064]). Factor scores were then derived for each individual for each of the three factors using a regression-based approach. These scores were retained as predictors in all of the subsequent mediation analyses. Factor loadings and correlations between factors are depicted in Figure 1.

Neuropsychological factor scores from prior factor analytic work were also utilized (see Nikolas & Nigg, 2013, 2015). To create these factor scores, a series of confirmatory factor analyses were conducted, which included evaluation of models comprised of one through eight factors as well as several second-order factor models. The final second-order model provided a good fit to the data ($\chi^2=94.88$, $df=60$, CFI=.98, TLI=.98, RMSEA=.034). This model included seven lower-order factors labeled as response inhibition, working memory, memory span, speed, response variability, arousal, and temporal processing as well as one second-order factor termed cognitive control. This second-order factor was comprised of the inhibition, working memory, and memory span factors (see Table 1 for breakdown of how each measure loaded on each respective factor).

Data Analysis

Associations between outcome variables and predictor and mediating variables were examined via bivariate correlations. Tests of direct and indirect effects were based on methodology by Preacher and Hayes (2008) using full information maximum likelihood techniques to address missing data. A series of mediation models were examined that included (1) prenatal exposures, (2) maternal health risk factors, and (3) perinatal health risk factors as separate predictor variables. Composite scores for inattention, hyperactivity, ODD, and CD served as outcomes. The neuropsychological factor scores (Nikolas & Nigg, 2013) were examined simultaneously as statistical mediators of the association between pre- and perinatal health risk and each outcome. Both the total indirect effects and the point estimates for each pathway are estimated using this procedure. Sex, age, ethnicity, income, parental ADHD symptoms and externalizing disorder status, and maternal and paternal age at birth were included as covariates in all models. Missing data was generally low (<3.2%, with the exception of income, which was missing for 9.4% of the sample). Lastly, given the clustered nature of the sibling data, the CLUSTER option in MPlus was used to account for non-independence issues (Muthén & Muthén, 1998–2015). Further, delta method standard errors were computed, as bootstrapped confidence intervals could not be computed with clustered data.

RESULTS

Demographic and Descriptive Statistics

Results indicated that diagnostic procedures effectively discriminated the ADHD from the control group (see Table 2). Significant differences emerged in regard to child sex, age, income, and parental psychopathology; all were included as covariates in the models in addition to ethnicity, which was included due to indications of variation in ODD symptoms, CD symptoms, and birth weight by ethnicity. A higher proportion of youth in the ADHD group was exposed to tobacco prenatally and mothers of ADHD youth were more likely to have health problems or experience significant emotional stress during pregnancy relative to control mothers. Birth weight was also significantly lower among ADHD youth compared to their non-ADHD counterparts ($p=.002$, Cohen's $d=.28$). Additionally, statistically reliable group differences emerged across each of the pre- and perinatal health factor scores, such that youth with ADHD had higher scores on the prenatal substance exposure ($p=.02$; $d=.28$), maternal health risk ($p<.001$, $d=.38$), and perinatal health risk ($p=.001$, $d=.30$) factors. Maternal and paternal age at birth did not differ across groups ($ps>.48$), but maternal age at birth was significantly correlated with all three pre- and perinatal health factor scores, such that younger maternal age was associated with increased scores on prenatal substance exposure ($r=-.22$, $p=.02$) and older age was associated with increased scores on maternal health risk ($r=.16$, $p=.03$) and perinatal health risk ($r=.19$, $p=.01$).

Examination of bivariate correlations revealed small but significant associations between the pre- and perinatal health factor scores and symptom outcomes (see Table 3). As shown in prior work, neuropsychological functioning is also related to ADHD symptom scores as well as ratings of ODD and CD symptoms. Neuropsychological factors were moderately correlated with each other (rs ranging from .37–.61, all $p<.01$).

Primary Tests of Direct and Indirect Effects

Prenatal Substance Exposures—No direct effects of prenatal substance exposure were observed when predicting inattention ($\beta=.02$, $[-.03, .07]$, $p=.56$, total $R^2=.40$), hyperactivity-impulsivity ($\beta=.01$, $[-.05, .17]$, $p=.49$, total $R^2=.32$), ODD ($\beta=.03$, $[-.06, .12]$, $p=.62$, total $R^2=.19$), or CD ($\beta=.05$, $[-.01, .11]$, $p=.14$, total $R^2=.11$) after controlling for age, sex, ethnicity, income, parental psychopathology, and parental age at birth. However, a significant indirect effect emerged in predicting inattention, such that higher scores on prenatal substance exposure predicted increased inattention via its influence on neuropsychological performance ($\beta=.13$, $[-.04, .22]$, $p=.003$). Examination of the specific indirect pathways indicated that this effect was carried by the influence of prenatal exposures on both memory span deficits ($\beta=.07$, $[-.02, .12]$, $p=.022$) and temporal processing deficits ($\beta=.04$, $[-.01, .07]$, $p=.040$, see Figure 2).

Maternal Health During Pregnancy—In contrast to substance exposure, significant direct effects of maternal health risks during pregnancy emerged for inattention ($\beta=.16$, $[-.05, .27]$, $p=.014$, total $R^2=.38$), hyperactivity-impulsivity ($\beta=.12$, $[-.04, .20]$, $p=.011$, total $R^2=.33$), and ODD ($\beta=.15$, $[-.06, .24]$, $p=.005$, total $R^2=.20$). In all cases, higher scores on the maternal health risks during pregnancy factor was associated with increased symptom

scores, even after controlling for multiple confounds. The direct effect of maternal health risks during pregnancy on CD symptom scores was not significant ($\beta=.10$, $[-.005, .20]$, $p=.12$, total $R^2=.10$). No significant indirect pathways emerged in these models (see Figure 3).

Perinatal Health Risk—Direct effects of perinatal health risk were not significant in predicting inattention ($\beta=.03$, $[-.02, .08]$, $p=.59$, total $R^2=.40$), marginally significant in predicting both hyperactivity-impulsivity ($\beta=.08$, $[-.006, .15]$, $p=.08$, total $R^2=.33$) and ODD symptom scores ($\beta=.10$, $[-.01, .19]$, $p=.06$, total $R^2=.19$), and significant in predicting CD symptom scores ($\beta=.15$, $[-.04, .26]$, $p=.03$, total $R^2=.11$). For these three outcomes, increased perinatal health risk was associated with an increase in symptom scores, even when including multiple covariates. Additionally, significant indirect effects of perinatal health risk emerged in predicting both inattention ($\beta=.09$, $[-.02, .16]$, $p=.021$) and hyperactivity-impulsivity ($\beta=.12$, $[-.04, .20]$, $p<.001$). Examination of the specific indirect pathways indicated that in both models, perinatal health risk influenced ADHD outcomes via its influence on both response variability (inattention: $\beta=.06$, $[-.03, .09]$, $p=.018$; hyperactivity-impulsivity: $\beta=.07$, $[-.02, .12]$, $p<.001$) and temporal processing (inattention: $\beta=.04$, $[-.002, .08]$, $p=.035$; hyperactivity-impulsivity: $\beta=.04$, $[-.01, .07]$, $p=.007$). In both cases, increased perinatal health risk predicted deficits in both response variability and temporal processing, which, in turn, predicted increased ADHD symptom scores. Indirect effects of perinatal health risks on ODD symptoms ($\beta=.06$, $[-.009, .12]$, $p=.14$) and CD symptoms (inattention: $\beta=.05$, $[-.004, .09]$, $p=.13$) were not significant (see Figure 4).

Follow-Up Analyses

While our use of factor scores allowed us to aggregate across many highly correlated variables related to pre- and perinatal health, this method may also make it more difficult to compare findings from the current study to prior work focusing on indicators that have been specifically examined in relation to externalizing spectrum psychopathology, namely tobacco exposure during pregnancy and birth weight. Thus, we elected to re-run models examining these specific indicators as predictors rather than factor scores to facilitate comparisons with prior research.

Similar to findings using the exposures factor score, prenatal tobacco exposure did not exert a significant direct effect on inattention ($\beta=.05$, $[-.01, .11]$, $p=.19$, total $R^2=.40$), hyperactivity-impulsivity ($\beta=.03$, $[-.05, .11]$, $p=.56$, total $R^2=.32$), ODD symptom scores ($\beta=.04$, $[-.06, .14]$, $p=.19$, total $R^2=.20$), or CD symptom scores ($\beta=.02$, $[-.08, .12]$, $p=.76$, total $R^2=.11$). Prenatal tobacco exposure did, however, exert a significant indirect effect on inattention via neuropsychological functioning ($\beta=.08$, $[-.02, .14]$, $p=.020$). Examination of specific indirect effects revealed that tobacco exposure specifically influenced memory span deficits, which increased inattention scores (specific indirect effect: $\beta=.03$, $[-.005, .06]$, $p=.039$). Marginally significant indirect effects were also observed for ODD ($\beta=.04$, $[-.002, .07]$, $p=.08$) and CD symptom scores ($\beta=.04$, $[-.005, .07]$, $p=.060$).

Birth weight did not significantly predict either inattention ($\beta=.02$, $[-.06, .10]$, $p=.67$, total $R^2=.39$) or hyperactivity-impulsivity ($\beta=.02$, $[-.04, .08]$, $p=.72$, total $R^2=.33$), but was a marginally significant predictor of ODD symptom scores ($\beta=.10$, $[-.01, .19]$, $p=.06$, total $R^2=.11$).

20). Note, birth weight was inversed to facilitate comparison of interpretations. Birth weight did exert a significant direct effect on CD symptom scores ($\beta=.12$, [.03, .21], $p=.014$, total $R^2=.12$), such that lower birth weight was associated with increased CD symptoms. Significant indirect effects of birth weight via neuropsychological functioning were again observed for inattention ($\beta=.09$, [.02, .16], $p=.018$), hyperactivity-impulsivity, ($\beta=.10$, [.03, .17], $p=.006$), and ODD symptom scores ($\beta=.09$, [.02, .16], $p=.018$). In all cases, birth weight was associated with increased deficits in response variability, which predicted increased externalizing symptoms, as indexed by the significant specific indirect effects (inattention: $\beta=.05$, [.01, .09], $p=.031$; hyperactivity-impulsivity: $\beta=.07$, [.03, .11], $p=.026$; ODD: ($\beta=.03$, [.007, .06], $p=.044$). Birth weight did not exert significant indirect effects on CD symptom scores ($\beta=.04$, [-.04, .12], $p=.21$).

DISCUSSION

The current study evaluated direct and indirect effects of pre- and perinatal health risk factors on ADHD and other disruptive behavior disorder symptoms. Current analyses also accounted for potential familial confounds by covarying parental ADHD symptoms and externalizing disorder status. Results indicated that prenatal substance exposure did not appear to be directly associated with ADHD, ODD, or CD symptoms when these covariates were included. However, maternal health risks during pregnancy did exert significant (and marginally significant) direct effects on ADHD and other externalizing psychopathology (as did perinatal health risks on CD symptoms specifically). Our findings are consistent with recent work suggesting that associations between prenatal exposure and ADHD may be dependent upon shared genes between parents and children (Knopik et al., 2005; Skoglund et al., 2014; Thapar et al., 2009), but that other pre- and perinatal risk factors, such as birth weight, may play a causal role in ADHD (Pettersson et al., 2015).

Furthermore, several indirect effects also emerged. Prenatal substance exposure indirectly predicted increased inattention via neuropsychological functioning (memory span and temporal processing specifically), whereas perinatal health risk indirectly predicted increased inattention and hyperactivity-impulsivity via effects on response variability and temporal processing deficits. This is consistent with recent work suggesting that primary neuropsychological functions may account for the association between LBW and ADHD symptoms (Hatch, Healy, & Halperin, 2014) as well as one prior study demonstrating that motor coordination and motor speed mediated the association between birth weight and ADHD (Martel et al., 2007). Similarly, the current study also demonstrated some specificity in associations between early developmental risk and more basic cognitive processes, such as memory capacity, visuomotor coordination, and temporal processing. This may indicate that disruptions in early neural development may broadly impact several neural networks, which then give rise to higher-order cognitive processes (Aylward, 2014). Importantly, youth with ADHD have shown deficits in both lower and higher-order cognitive domains (Halperin & Shulz, 2006; Nikolas & Nigg, 2013). Thus, it may be that early developmental risk factors play an etiological role in ADHD and other externalizing psychopathology via effects on these more basic cognitive processes. However, more work in this area is needed, particularly within genetically-informed designs, to confirm this possibility.

An important implication of the present findings is that prenatal substance exposure and perinatal risk may independently predict ADHD and comorbid externalizing behaviors through somewhat similar (i.e., temporal processing) as well as via somewhat distinct mechanisms (i.e., one route involving memory span deficits and one involving response variability deficits). That is, while related, these early developmental risk factors may have partially separable effects on neurocognitive processes that underlie the development of ADHD and co-occurring externalizing disorders, rather than the double dissociation proposed in past work (Nigg & Breslau, 2007). Future work may benefit by linking these indirect effects to neural functioning, particularly in brain regions involved in primary neuropsychological processes (Russell et al., 2006). Further, current findings suggest that identifying and measuring multiple aspects of prenatal and early development is likely important for discerning their effects. Clinically, if such factors do indeed play a causal role in ADHD and co-occurring externalizing behaviors (directly or indirectly), improvement of maternal health during pregnancy and implementing safeguards that promote perinatal health in the infant may be important strategies in future efforts to prevent the development of psychopathology.

Results also highlight the importance of considering familial confounds in these associations. Controlling for parental ADHD symptoms and externalizing disorder status reduced the direct associations between prenatal substance exposure and ADHD and disruptive behavior disorder symptoms. That is, in addition to indirect effects on psychopathology via other intervening processes, such as neuropsychological functioning, future work would likely benefit by examining the interplay between these early neurodevelopmental insults and familial risk for psychopathology, including potential epigenetic effects (Nigg, 2012).

There are several limitations to the current work. First, current data were cross-sectional, precluding definitive conclusions regarding temporal ordering of variables. Future work should seek to collect data prospectively to verify the time course and order of these variables as well as evaluate the potential impacts of age and development on these associations (Nikolas & Nigg, 2015). However, the temporal primacy of indices of pre- and perinatal risk increases our confidence in the proposed pathways and findings. Second, the current study utilized categorical indicators of prenatal substance exposure. Although this was done because a large proportion of mothers reported not using any substances during pregnancy, future work should examine the frequency and intensity of substance exposure, and, if possible, examine such associations in a prospective manner. Third, only a selection of possibly relevant neuropsychological functions was included in current analyses; other domains such as delay aversion, temporal discounting, and decision-making may also be relevant (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Luman, Oosterlaan, Knol, & Sergeant, 2008). Fourth, the current study used parental ADHD and externalizing psychopathology as a proxy control for genetic relatedness. We acknowledge that this is potentially a limited method for controlling for genetic relatedness. Further, other parental factors (e.g., internalizing psychopathology) may also confound these associations. Examination of such associations using twin/adoption designs and with molecular genetic methodologies may enhance the ability of future work to understand the contributions of these risk factors and their interplay with genetic risk. Although the current sample

contained sibling pairs, examination of the impact of genetic relatedness via a sibling design was precluded due to lack of necessary statistical power. Lastly, although not within the scope of the current work, future research could benefit by examining how these early developmental risk factors impact the shared variance among ADHD and disruptive behavior disorder symptoms as well as the developmental progression of ADHD and externalizing symptoms.

In spite of these limitations, the current work demonstrated that pre- and perinatal health risk may influence ADHD and other disruptive behavior disorders via effects on neuropsychological functioning. Findings also point toward specific processes (i.e., memory span, response variability, temporal processing) as potential mechanisms for understanding how early risk factors influence the later development of child behavior problems.

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Figure 1. Three factor model of pre- and perinatal health indicators

Note. All loadings significant at $p < .01$. ** Indicates correlation significant at $p < .01$. Error terms are not included here to preserve figure clarity.

A. Inattention

B. Hyperactivity-impulsivity

C. ODD

D. CD

Figure 2. Direct and indirect effects of prenatal substance exposure on inattention, hyperactivity-impulsivity, ODD, and CD symptom scores

*Note, * $p < .05$, ** $p < .01$. Standardized parameter estimates reported for all pathways. Direct effect is presented to the left of the slash, whereas the sum of the indirect effect is presented to the right of the slash.*

A. Inattention

B. Hyperactivity-impulsivity

C. ODD

D. CD

Figure 3. Direct and indirect effects of maternal health risk during pregnancy on inattention, hyperactivity-impulsivity, ODD, and CD symptom scores

Note + $p < .10$, * $p < .05$, ** $p < .01$. Standardized parameter estimates reported for all pathways. Direct effect is presented to the left of the slash, whereas the sum of the indirect effect is presented to the right of the slash.

A. Inattention

B. Hyperactivity-impulsivity

C. ODD

D. CD

Figure 4. Direct and indirect effects of maternal health risk during pregnancy on inattention, hyperactivity-impulsivity, ODD, and CD symptom scores
Note + $p < .10$, * $p < .05$, ** $p < .01$. Standardized parameter estimates reported for all pathways. Direct effect is presented to the left of the slash, whereas the sum of the indirect effect is presented to the right of the slash.

Table 1

Neuropsychological tasks and measures, constructs, and factors

<i>Task & Measure</i>	<i>Construct</i>	<i>First order factor</i>
Spatial Span Forward Total Correct	Encoding, span	Memory span *
Spatial Span Backward Total Correct	Working memory	Working memory *
Digit Span Forward Total Correct	Encoding, span	Memory span *
Digit Span Backward Total Correct	Working memory	Working memory *
DKEFS Color-Word Color/Word Reading Time	Speeded naming	Processing speed
DKEFS Color-Word Inhibition Time	Interference control	Inhibition *
DKEFS Inhibition/Switching time	Switching speed	Inhibition *
DKEFS Trailmaking Number Sequencing Time	Sequencing speed	Processing speed
DKFES Trailmaking Number-Letter Sequencing Time	Switching speed	Working memory *
Stop Task Stop Signal Reaction Time	Response inhibition	Inhibition *
Stop Task Reaction Time Variability	Response time variability	Response variability
Continuous Performance Task d' -prime	Arousal/activation	Arousal
Tapping Task Visual 400-ms detrended SD	Time reproduction	Temporal processing
Tapping Task Auditory 400-ms detrended SD	Time reproduction	Temporal processing
Tapping Task Visual 1000-ms detrended SD	Time reproduction	Temporal processing
Tapping Task Auditory 1000-ms detrended SD	Time reproduction	Temporal processing

Note.

* Factor significantly loaded on 2nd order cognitive control factor (Nikolas & Nigg, 2013, 2015). DKEFS=Delis-Kaplan Executive Function System, SD=standard deviation.

Table 2

Descriptive and demographic statistics.

	Control	ADHD	<i>p</i> -value
N	213	251	
% Male	42.3	66.9	
Age (SD)	11.0 (2.4)	10.5 (2.3)	.021
% Caucasian	76.5	72.1	.64
Income ⁺ (SD)	79.0 (47.4)	64.5 (38.7)	.002
Inattention Symptoms (SD)	.74 (1.4)	7.2 (1.9)	<.001
Hyperactivity-Impulsivity Symptoms (SD)	.62 (1.2)	4.3 (2.9)	<.001
% ODD (lifetime)	14.1	41.6	<.001
% CD (lifetime)	0.5	8.4	<.001
% Parent with ADHD	17.4	31.1	<.001
% Parent with Externalizing Disorder	8.5	13.5	.083
% Tobacco Use During Pregnancy	14.9	22.7	.036
% Alcohol Use During Pregnancy	10.9	12.6	.59
% Drug Use During Pregnancy	3.6	5.0	.49
% Mothers with Illness During Pregnancy	33.7	46.2	.007
% Mothers with Severe Emotional Stress	18.8	31.5	<.001
% Mothers Exposed to X-Ray	3.8	3.2	.68
% Mothers Taking Prescription Medication	28.6	37.1	.098
% Born 36 Weeks Gestation or Less	12.9	18.6	.098
Length of labor (hours)	13.0 (12.3)	12.7 (26.4)	.90
Birth Weight (oz)	125.2 (23.3)	118.9 (23.5)	.006
% Children with Perinatal Difficulty	26.7	32.0	.23

Note.

⁺Income reported in thousands. Values denote means and standard deviations of key variables. CD = conduct disorder. ODD = oppositional defiant disorder.

Table 3

Correlations among pre and perinatal health risk, neuropsychological factors, and ADHD and externalizing behavior outcomes.

	Inattention	Hyperactivity	ODD	CD
Prenatal Exposures	.13 **	.07 ⁺	.09 *	.06
Maternal Health During Pregnancy	.16 **	.13 **	.17 **	.10 **
Perinatal Health Risks	.18 **	.17 **	.11 **	.15 **
Inhibition	.40 **	.41 **	.28 **	.18 **
Working Memory	.40 **	.38 **	.28 **	.25 **
Memory Span	.34 **	.32 **	.23 **	.16 **
Speed	.36 **	.38 **	.24 **	.20 **
Response Variability	.25 **	.28 **	.17 **	.12 **
Arousal	.25 **	.25 **	.12 **	.15 **
Temporal Processing	.30 **	.32 **	.17 **	.13 **

Note.

⁺ $p < .10$,

* $p < .05$,

** $p < .01$.

All variables scored such that higher scores reflects increased pre and perinatal problems, greater deficits in neuropsychological functioning, and increased symptomatology.