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Perinatal Problems and Psychiatric Comorbidity Among Children with ADHD

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Abstract

Objective—Among two large, independent samples of girls with attention-deficit/hyperactivity disorder (ADHD), we examined associations between specific (maternal gestational smoking and drug use, early labor, low birth weight, and infant breathing problems at birth) and cumulative prenatal and perinatal risk factors and psychiatric comorbidity during childhood.

Method—Data from the (a) Multimodal Treatment Study of Children with ADHD, a randomized clinical trial with 579 children aged 7 to 9.9 years with combined-type ADHD, and the (b) Berkeley Girls ADHD Longitudinal Sample, a naturalistic study of 140 girls with ADHD (93 combined-type and 47 inattentive-type) who were first seen when they were 6 to 12 years old, were analyzed separately. In each sample, perinatal risk factors were assessed retrospectively by maternal report, and current childhood psychiatric comorbidity was assessed using maternal report on the Diagnostic Interview Schedule for Children.

Results—Consistent findings across these two studies show that infant breathing problems, early labor, and total perinatal problems predicted childhood comorbid depression but not comorbid anxiety or externalizing disorders. These associations remained significant, in both samples, with control of family SES and maternal symptoms of ADHD and depression. Results attenuated slightly with control of the number of child comorbidities plus SES and maternal symptoms.

Conclusion—Accumulating evidence suggests that perinatal risk factors are important precursors of childhood psychiatric comorbidity and that the association between these risk factors and detrimental psychiatric outcomes cannot be explained by maternal psychiatric symptoms or SES during childhood.

Keywords

prenatal; perinatal; ADHD; comorbidity

Children with attention-deficit/hyperactivity disorder (ADHD) and comorbid internalizing or externalizing disorders demonstrate significant symptomatology and impairment (Angold, Costello, & Erkanli, 1999). Children with ADHD and depression have greater academic and social impairment, worse depressive episodes, and more suicidality and psychiatric hospitalizations than children with depression or ADHD alone (Biederman et al., 2008; Blackman, Ostrander, & Herman, 2005; Jensen, Shervette, Xenakis, & Richters, 1993). Children with ADHD and externalizing disorders have greater academic problems and

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worse behavioral outcomes than children with ADHD or externalizing problems alone (Angold et al., 1999; Biederman, Newcorn, & Sprich, 1991). Furthermore, comorbidities are common among children with ADHD. According to Biederman et al. (1991), 25% to 35% of children with ADHD have an anxiety disorder, 9% to 32% have a depressive disorder, and 35% to 50% have oppositional defiant or conduct disorder (see also Jensen, Martin, & Cantwell, 1997). Because over 9% of U.S. youth have received an ADHD diagnosis (Visser, Bitsko, Danielson, & Perou, 2010), several million children and adolescents have comorbid ADHD. Understanding and helping this large population is an important public health issue. Yet little is known about the etiology, treatment response, and prognosis of pure versus comorbid forms of ADHD (Jensen, 2003). We address etiology: why do some children with ADHD present with comorbidity?

We examine whether certain early prenatal and perinatal adversities predict childhood psychiatric comorbidity. Because most known environmental risk factors for ADHD occur in utero or very early in life (Mill & Petronis, 2008), we speculate that comorbidity will be associated with similar experiences. In other words, unlike childhood mental illnesses including conduct or oppositional defiant disorder, the environmental factors implicated in ADHD are pre- and perinatal, which provides a rationale for our hypotheses. We are guided by the biological programming approach, whereby experiences very early in life produce changes in the structure and function of the brain that produce adaptations over time (Rutter, O'Connor, et al., 2004; Swanson & Wadhwa, 2008). Hypotheses concerning both plasticity and pathology emerge from this approach (Swanson & Wadhwa, 2008). Our question involves pathology: Do certain prenatal and perinatal disadvantages predict long term detrimental outcomes, in this case, psychiatric comorbidity? For simplicity, we subsequently use the term perinatal (not prenatal), even though these developmental periods are distinct and uniquely significant. We test only a subset of relevant prenatal and perinatal factors.

Dozens of studies document positive associations between gestational smoking (e.g., Indredavik, Brubakk, Romundstad, & Vik, 2007; Mick, Biederman, Faraone, Sayer & Kleinman, 2002; Milberger, Biederman, Faraone, & Chen, 1996), low birth weight (e.g., Indredavik et al., 2004; Lahti et al., 2006; Nigg & Breslau, 2007), or premature birth (e.g., Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Lou, 1996) and child ADHD symptoms or diagnoses. Additionally, gestational smoking has been linked to later conduct problems (e.g., Fergusson, Woodward, & Horwood, 1998; Huizink & Mulder, 2006; Weissman, Warner, Wickramaratne, & Kandel 1999), and low birth weight is associated with later depression or anxiety (Bohnert & Breslau, 2008; Indredavik et al., 2004; Nomura, Brooks-Gunn, Davey, Ham, & Fifer, 2007; Wals et al., 2003) and disruptive behavior (Bohnert & Breslau, 2008). Children exposed in utero to alcohol or recreational drugs are at increased risk for later ADHD diagnoses or symptoms (Leech, Richardson, Goldschmidt, & Day, 1999; Huizink & Mulder, 2006; Mick et al., 2002; Williams & Ross, 2007) and are more likely to be disruptive and aggressive (Huizink & Mulder, 2006; Roebuck, Mattson & Riley, 1999). Perinatal hypoxia also increases risk for ADHD (Lou, 1996); hypoxia may be a final common pathway through prematurity and gestational smoke exert their effects.

Positive associations between perinatal risk factors and childhood psychiatric comorbidity also exist. Bos-Veneman, Kuin, Minderaa, and Hoekstra (2010a) and Pringsheim, Sandor, Lang, Shah, and O'Connor (2009) found ADHD plus tics to be related to gestational smoking, low birthweight, and/or infant breathing problems, but Motlagh et al. (2010) did not find heavy gestational smoking to be related to this comorbidity. Arnold et al. (2005) found comorbid conduct disorder to be associated with gestational smoking among some of the participants with ADHD examined herein. In addition, Bos-Veneman, Minderaa, and Hoestra (2010b) found delivery complications to predict internalizing symptoms among

certain children with tic disorders; Mathews et al. (2006) and Geller et al. (2008) found gestational smoking and infant jaundice to predict comorbidity between OCD and tics.

Most analyses have been variable-based, but we expand the literature by conducting person-based analyses concerning comorbidity. We also investigate whether various perinatal risks predict a particular comorbidity (equifinality) or a specific risk factor predicts various comorbidities (multifinality). Fergusson et al. (1998) found that gestational smoking predicted conduct problems but not anxiety or depression, yet evidence is far from definitive.

Linkages between perinatal risk factors and psychiatric comorbidities may be artifactual. In particular, links between gestational smoking and ADHD may be due to maternal ADHD or conduct problems, with genetic mediation explaining part of the linkage (Thapar et al., 2009). When maternal psychiatric symptoms are controlled, perinatal risk factors still account for significant variance in child psychiatric problems (Indredavik, 2004; Mick et al., 2002 Milberger et al., 1996; Wals et al., 2003; Weissman et al., 1999). When socioeconomic status is controlled, significant associations often remain between perinatal adversities and later psychiatric problems (e.g., Biederman, Monuteaux, Faraone, & Mick, 2009; Fergusson et al., 1998; Indredavik, 2004; Mick et al., 2002, Milberger et al., 1996; Weissman et al., 1999; but see Nigg & Breslau, 2007). We control for these key potential confounders.

In sum, we aim to extend the evidentiary base for the biological programming approach to understanding childhood psychiatric comorbidity by using person-based analyses to examine associations between (a) perinatal risk factors (gestational smoking and drug exposure, early labor, infant low birth weight and breathing problems) and (b) psychiatric comorbidities (depression, anxiety, and externalizing) among children with ADHD. We test risk factors specifically and cumulatively, analyze potential confounders, and examine associations in two independent samples.

Method

Participants

To guard against chance or sample-specific findings, we tested associations in two large and independent samples of children with ADHD. The first is the Multimodal Treatment Study of Children with ADHD (MTA), a randomized clinical trial with 579 children aged 7 to 9 years with combined-type ADHD. Eighty percent are male; 61% are white. Families were predominantly middle (41%) or upper middle class (36%), with 19% receiving public assistance. Children were recruited in the mid-1990s at six sites in the U.S. and Canada from mental health settings, pediatricians, advertisements, and schools. A rigorous multi-gated screening and diagnostic procedure was employed. ADHD diagnosis was determined using parent report on the Diagnostic Interview Schedule for Children 3.0, supplemented with up to two symptoms identified by teachers. For detail, see MTA Cooperative Group (1999). Six MTA girls participated in the BGALS, described below; they were omitted from the MTA analyses, yielding a total N of 573.

The second was the Berkeley Girls ADHD Longitudinal Sample (BGALS), a naturalistic study of 140 girls from the San Francisco area. All had ADHD (93 combined-type and 47 inattentive-type) and were first seen in 1997 to 1999 when they were 6 to 12 years old (Hinshaw, 2002). Fifty-six percent were Caucasian. Families ranged widely in terms of socioeconomic status, with 15% receiving public assistance. Recruitment and diagnostic procedures were highly similar to those of the MTA, except the Diagnostic Interview Schedule for Children 4.0 was used. See Hinshaw (2002) for detailed information about recruitment and selection.

Measures

Psychiatric comorbidities—Comorbidities were established via the DISC and the Children's Depression Inventory (CDI, Kovacs, 1992). In the MTA, the presence of an anxiety disorder (agoraphobia, overanxious, avoidant, separation, social phobia, obsessive compulsive, or panic) or externalizing disorder (oppositional defiant, conduct) was established using current parent-report on the DISC 3.0. Depressive disorders (major depression or dysthymia) were established using parent-report on the DISC 3.0 or a child-reported CDI total of at least 20. In the BGALS, the presence of an externalizing disorder was established using past-year or past-month parent report on the DISC 4.0. Anxiety disorders were determined using youth or parent report on the DISC 4.0. Depressive disorders were determined using youth- or parent-report on the DISC 4.0 or a child-reported CDI score of 20 or above.

Risk factors—Perinatal problems were assessed during childhood using retrospective report. Mothers were asked whether the following problems occurred: mother smoked cigarettes while pregnant, mother used recreational drugs while pregnant (BGALS) or infant was born drug addicted (MTA), mother experienced early labor, or infant had trouble breathing at birth. Low birthweight was defined as less than 2500g. Although small, the literature concerning retrospective report of perinatal events consistently supports the validity and reliability of this measurement strategy (Pickett, Kasza, Biesecker, Wright, & Wakschlag, 2009; Reich, Todd, Joyner, Neuman, & Heath, 2003), even 22 years later (Buka, Goldstein, Spartos, & Tsuang, 2004). In fact, Hannigan et al. (2010) and Ernhart, Morrow-Tlucak, Sokol, and Martier (1988) show that long term recall of drinking during pregnancy was more accurate than antenatal report.

Covariates—In both samples, socioeconomic status (SES) was calculated using family income and mother's education. Pre-tax income was measured on a 9-point scale and education level was measured using a 6-point scale. Scores were standardized and averaged to create our SES covariate. Maternal self-reported symptoms were indexed using (a) the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and (b) the Wender Utah Rating Scale (Ward, Wender, & Reimherr, 1993), designed to assess ADHD symptoms in adults.

Data Analytic Plan

First, children were grouped as having a depressive disorder or not, an anxiety disorder or not, or an externalizing disorder or not. We also computed the total number of comorbidities for each child (0-3) as a covariate. We then conducted 15 X^2 tests within each dataset examining associations between five specific perinatal problems and each type of comorbidity, as well as three *t*-tests within each dataset examining associations between total number of perinatal problems and each comorbidity. In each *t*-test we compared children with a particular comorbidity to all other children, including children with other comorbidities. This conservative comparison strategy better informed our question about the specificity of prediction. When significant associations were found in *both* datasets, we repeated analyses controlling for SES and maternal symptoms of ADHD and depression, and then controlling for number of child comorbidities. Because of a small cell size in the BGALS sample, we did not compare children with ADHD only, ADHD/only depression, and ADHD/any other comorbidity. However, as noted in the Discussion, we did so using MTA data. Finally, we re-tested significant associations controlling for other significant individual perinatal risk factors. We attempted to reduce Type I error rate by interpreting as significant only those findings that were significant at $p < .05$ in *both* samples.

Results

Rates of comorbidities in the MTA were as follows: of the 573 with ADHD, 102 (18%) had a depressive diagnosis, 220 (39%) had an anxiety diagnosis, and 310 (54%) had an externalizing diagnosis. In the BGALS sample, of the 140 with ADHD, 24 (17%) had a depressive diagnosis, 48 (34%) an anxiety diagnosis, and 91 (65%) an externalizing diagnosis. These rates do not account for multiple comorbidities. The following associations (all $p = .000$) among perinatal disadvantages were found in both the MTA and BGALS samples: infant breathing problems and early labor ($X^2 = 15.8$, $X^2 = 30.2$, respectively), infant breathing problems and low birth weight ($X^2 = 25.2$, $X^2 = 23.7$, respectively), gestational drug use and smoking ($X^2 = 19.1$, $X^2 = 42.7$, respectively), early labor and low birth weight ($X^2 = 48.3$, $X^2 = 20.9$, respectively).

As seen in Table 1, infant breathing problems (MTA $X^2 = 8.7$, $p = .003$; OR = 2.6, 95% CI = 1.3 to 5.3; BGALS $X^2 = 10.4$, $p = .001$, OR = 5.6, 95% CI =1.8 to 17.5) and mother's early labor (MTA $X^2 = 6.4$; $p = .011$; OR = 2.1, 95% CI = 1.2 to 3.6; BGALS $X^2 = 4.6$, $p = .031$, OR = 3.3, 95% CI = 1.1 to 10.3) were both associated with depressive comorbidity, but not with anxiety or externalizing comorbidity, in both samples. As seen in Table 2, cumulative perinatal problems were associated with depressive comorbidity (MTA $t = -2.9$, $p = .004$, $d = .35$; BGALS $t = -2.6$, $p = .015$, $d = .91$), but not with anxiety or externalizing comorbidity, in both samples. No perinatal problems, specifically or cumulatively, were related to anxiety or externalizing comorbidity in both samples.

Using six logistic regressions we tested whether the relations between infant breathing problems, early labor, and total perinatal problems were associated with comorbid depression, controlling for SES and maternal ADHD and depressive symptoms. In both samples, associations remained significant for infant breathing problems (MTA Wald = 7.6, $p = .006$, OR = 2.9; BGALS Wald = 8.8, $p = .003$, OR = 6.0), early labor (MTA Wald = 7.1, $p = .008$, OR = 2.1; BGALS Wald = 4.8, $p = .028$, OR = 3.7), and total perinatal problems (MTA Wald = 8.3, $p = .004$, $d = .34$; BGALS Wald = 12.1, $p = .001$, $d = .94$). Results attenuated slightly when we controlled for the number of child psychiatric comorbidities in addition to SES and maternal symptoms (for early labor MTA Wald = 3.2, $p = .075$; BGALS Wald = 1.3, $p = .225$; for total perinatal problems MTA Wald = 3.9, $p = .050$; BGALS Wald =4.1, $p = .043$; for breathing problems MTA Wald = 3.1, $p = .080$; BGALS Wald =6.8, $p = .009$). Finally, we tested whether infant breathing problems was associated with depressive comorbidity controlling for early labor, and vice-versa. We did not control for SES and maternal psychiatric symptoms in order to conduct a more interpretable comparison of the two predictors. Infant breathing problems predicted depressive comorbidity controlling for early labor (MTA Wald = 4.5, $p = .034$; BGALS Wald = 5.0, $p = .025$), but early labor did not, above and beyond infant breathing problems (MTA Wald = 3.8, $p = .052$; BGALS Wald = 1.3, $p = .258$).

Discussion

Consistent findings across these two large studies of children with ADHD show that infant breathing problems and total perinatal problems predicted childhood comorbid depression, but did not predict comorbid anxiety or externalizing disorders. Three of the four effect sizes were medium or large; one was small to medium. These associations remained significant, in both samples, when controlling for SES and maternal symptoms of ADHD and depression. Early labor was also specifically associated with comorbid depression, and this association survived control for SES and maternal psychiatric symptoms. However, early labor was not predictive once infant breathing problems were controlled (infant breathing problems was still predictive once early labor was considered). When the total number of

comorbidities was also controlled, in five of six instances relations between perinatal problems and childhood depressive comorbidity remained at least marginally significant.

In general, our findings are consistent with previous literature. Perinatal problems are associated with increased risk for childhood psychiatric problems, occurring alone and in combination, and this association is not due to SES or maternal psychiatric symptoms. Regarding the biological programming hypothesis, our results support the notion that experiences very early in life produce adaptations, presumably neurological, that may be detrimental in the longer term. Additionally, our results suggest equifinality because across samples a single outcome, depression, was significantly predicted. However, most of the depressed children had another comorbidity (76% in the MTA sample; 81% in the BGALS sample) and controlling for number of comorbidities slightly reduced the associations between perinatal disadvantages and comorbidity. Furthermore, among MTA participants the largest associations with infant breathing problems and total perinatal problems were found for the children with ADHD and only depression, although both comorbidity groups (only depression or any) were significantly different from the non-comorbid group. Thus, findings are also modestly consistent with literature suggesting that particular risk factors often lead to diverse outcomes, or multifinality, (e.g., low birthweight predicts ADHD, externalizing, and internalizing symptoms [Bhutta et al., 2002; Indredavik et al., 2004; Nomura et al., 2007)]). The perinatal factors investigated to date may be proxies for a fundamental mechanism, such as oxygen deprivation, that if measured directly might clarify whether pathways between perinatal problems and psychiatric outcomes are multifinal or equifinal.

Of course, limitations of this research exist. Risk factors measurement was brief. Outcome was assessed at a single time; associations with perinatal disadvantages may be different earlier or later in development. Although most of our comorbid cells were sizable, only 24 girls in the BGALS had ADHD and depression. We did not test associations among our comparison participants because of small cell sizes. This would have illuminated whether associations were specific to children with ADHD. Some potentially important confounders, such as postnatal smoking, were not tested. Although an argument could be made that we risked a large Type I error rate, we ignored the six findings that were significant in only one sample, thus reducing the likelihood that results we did interpret were due to Type I error. Furthermore, because we interpreted only findings that were significant in both samples, we cannot comment on possibly important sex-specific findings. The MTA was comprised primarily of boys (80%) and the two associations found only in the MTA (between maternal drug use and child externalizing comorbidity, and between child low birth weight and depressive comorbidity) may be important for boys. The four associations found only in the all-female BGALS sample (maternal drug use and smoking predicted both child comorbid depression and anxiety) may be important for girls; however in post hoc analysis using only the MTA girls, these associations were not significant.

In conclusion, comorbidity between ADHD and depression appears to be uniquely associated with perinatal disadvantages, both specifically and cumulatively, with moderate to large effects. The associations cannot be explained by maternal psychiatric symptoms or SES during childhood. Helping pregnant women avoid controllable perinatal risks might translate into less psychiatric comorbidity among their children. In addition to attempted replication of these results, future research should test associations between perinatal risk factors and psychiatric outcomes at later points in development and among samples of children with and without psychiatric diagnoses in order to determine the degree to which findings generalize or are specific to certain populations. Important subsequent questions also involve the mechanisms by which these very early insults, especially the effects of oxygen reduction, affect psychiatric outcome.

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Table 1

Relations between specific perinatal problems and comorbidity with ADHD during childhood

	No dep vs. comorbid dep 105 in MTA, 24 in BGALS			No anx vs. comorbid anx 224 in MTA, 48 in BGALS			No ext vs. comorbid ext 314 in MTA, 91 in BGALS		
	% of no dep / % of dep	*p*	OR [95% CI]	% of no anx / % of anx	*p*	OR [95% CI]	% of no ext / % of ext	*p*	OR [95% CI]
Infant drug exposed/addicted									
MTA	3 / 4	.434	1.4 [0.5-4.4]	2 / 4	.360	1.6 [0.6-4.3]	0 / 5	.001	13.2 [1.7-100.8]
BGALS	5 / 25	.003	6.0 [1.6-22.1]	5 / 16	.028	3.9 [1.1-14.2]	6 / 9	.525	1.6 [0.4-6.2]
Gestational smoking									
MTA	24 / 23	.982	1.0 [0.6-1.7]	23 / 26	.459	1.2 [0.8-1.7]	22 / 25	.543	1.1 [0.8-1.7]
BGALS	18 / 44	.012	3.7 [1.3-10.5]	12 / 32	.044	2.4 [1.0-5.7]	14 / 25	.152	2.1 [0.8-5.6]
Infant breathing problems									
MTA	5 / 14	.003	2.6 [1.3-5.3]	6 / 8	.496	1.3 [0.6-2.5]	5 / 9	.077	1.9 [.9-3.8]
BGALS	8 / 33	.001	5.6 [1.8-17.5]	14 / 9	.401	0.6 [0.2-2.0]	9 / 14	.354	1.8 [0.5-5.8]
Low birth weight									
MTA	5 / 12	.003	2.8 [1.3-5.8]	6 / 7	.603	1.3 [0.6-2.5]	6 / 6	.766	1.1 [0.5-2.3]
BGALS	9 / 20	.129	2.6 [0.7-9.6]	20 / 18	.754	0.8 [0.3-2.4]	21 / 18	.118	3.3 [0.7-15.5]
Early labor									
MTA	14 / 25	.011	2.1 [1.2-3.6]	15 / 18	.313	1.3 [0.8-2.0]	16 / 15	.890	1.0 [0.6-1.5]
BGALS	11 / 29	.031	3.3 [1.1-10.3]	11 / 19	.260	1.8 [0.6-5.1]	11 / 16	.491	1.5 [0.5-4.5]

Note. Dep = depression, anx = anxiety, ext = externalizing. MTA = Multimodal Treatment Study of Children with ADHD, BGALS = Berkeley Girls ADHD Longitudinal Sample. MTA *N* = 579; BGALS *N* = 140.

Table 2

Relations between cumulative perinatal problems and comorbidity with ADHD during childhood

	No dep vs. comorbid dep 100 in MTA, 23 in BGALS				No anx vs. comorbid anx 213 in MTA, 47 in BGALS				No ext vs. comorbid ext 302 in MTA, 87 in BGALS			
	***M* (*SD*)**	***M* (*SD*)**	***p***	***d***	***M* (*SD*)**	***M* (*SD*)**	***p***	***d***	***M* (*SD*)**	***M* (*SD*)**	***p***	***d***
MTA	0.48 (.73)	0.74 (.84)	.004	.35	.50 (.73)	.58 (.81)	.201	.11	.47 (.69)	.56 (.80)	.159	.12
BGALS	0.47 (.76)	1.36(1.56)	.015	.91	.53 (.92)	.79 (1.08)	.144	.16	.42 (.77)	.72 (1.07)	.057	.30

Note. Dep = depression, anx = anxiety, ext = externalizing. MTA = Multimodal Treatment Study of Children with ADHD, BGALS = Berkeley Girls ADHD Longitudinal Sample. MTA *N* = 579; BGALS *N* = 140.