

Neonatal Head Ultrasound Abnormalities in Preterm Infants and Adolescent Psychiatric Disorders

Agnes H. Whitaker, MD; Judith F. Feldman, PhD; John M. Lorenz, MD; Fiona McNicholas, MD; Prudence W. Fisher, PhD; Sa Shen, PhD; Jennifer Pinto-Martin, PhD; David Shaffer, MD; Nigel Paneth, MD, MPH

Context: Infants born prematurely are at risk for a perinatal encephalopathy characterized by white and gray matter injuries that affect subsequent cortical development and neural connectivity and potentially increase risk for later psychiatric disorder.

Objective: To determine the relation of perinatal brain injury, as detected by neonatal head ultrasound, to psychiatric disorders in adolescents who were born prematurely.

Design: Prospective cohort.

Setting: Community.

Participants: Adolescent survivors of a population-based low-birth-weight (<2000 g; 96% preterm; born 1984-1987) cohort (n=1105) screened as neonates with serial head ultrasounds. Neonatal head ultrasound abnormalities were categorized as either (1) germinal matrix and/or intraventricular hemorrhage or (2) parenchymal lesions and/or ventricular enlargement. Of 862 eligible survivors, 628 (72.9%) were assessed at age 16 years. The sample consisted of 458 nondisabled survivors assessed in person.

Main Outcome Measure: Adolescent current and lifetime psychiatric disorders assessed with parent re-

port on the Diagnostic Interview Schedule for Children-IV.

Results: Compared with no abnormality, germinal matrix/intraventricular hemorrhage increased risk for current major depressive disorder (odds ratio, 2.7; 95% confidence interval, 1.0-6.8) and obsessive-compulsive disorder (9.5; 3.0-30.1). Parenchymal lesions/ventricular enlargement increased risk for current attention-deficit/hyperactivity disorder-inattentive type (odds ratio, 7.6; 95% confidence interval, 2.0-26.5), tic disorders (8.4; 2.4-29.6), and obsessive-compulsive disorder (7.6; 1.39-42.0). Parenchymal lesions/ventricular enlargement were not related to lifetime attention-deficit/hyperactivity disorder-inattentive type, but all other relations were similar for lifetime disorders. Control for other early risk factors did not alter these relations. Most of these relations persisted with control for concurrent cognitive or motor problems.

Conclusion: In preterm infants, 2 distinct types of perinatal brain injury detectable with neonatal head ultrasound selectively increase risk in adolescence for psychiatric disorders in which dysfunction of subcortical-cortical circuits has been implicated.

Arch Gen Psychiatry. 2011;68(7):742-752

Author Affiliations: Division of Child and Adolescent Psychiatry, Department of Psychiatry (Drs Whitaker, Feldman, Fisher, Shen, and Shaffer), and Division of Neonatology, Department of Pediatrics (Dr Lorenz), Columbia University Medical Center, and New York State Psychiatric Institute (Drs Whitaker, Feldman, Fisher, Shen, and Shaffer), New York, New York; University Hospital Dublin, Dublin, Ireland (Dr McNicholas); University of Pennsylvania, School of Nursing, Philadelphia (Dr Pinto-Martin); and Michigan State University, College of Human Medicine, East Lansing (Dr Paneth).

THE CONCEPT THAT PERINATAL brain injury influences risk for later psychiatric disorder has been invoked in neurodevelopmental discussions of psychiatric disorders for more than 5 decades.¹⁻⁵ To date, however, studies having the prospective design, sample size, and brain imaging technique suitable for testing this concept have been rare.⁴ Infants born prematurely (at <37 weeks' gestational age [GA]) constitute a large and growing subgroup of the population for whom this concept, if correct, has direct relevance.

Preterm infants, especially those born very preterm (<32 weeks' GA), are at high risk for perinatal brain injury because of zone-specific vascular and cellular vulnerabilities of the laminar fetal brain be-

tween 24 and 36 weeks GA.^{6,7} As reviewed by others,^{7,8} neuropathologic studies of preterm infants who died soon after birth have found that the anatomic sites most commonly injured are (1) the germinal matrix (GM), a transient fetal brain structure that proliferates cellular precursors, (2) the cerebellum, (3) immature white matter (WM), and (4) subcortical gray matter nuclei, including the basal ganglia and thalami. Although neuronal migration to the cortical mantle is nearly complete at birth in preterm infants, the neurons are largely unconnected, cortical tissue is minimal, and primary cortical lesions are described infrequently.⁹ A secondary effect of subcortical gray matter and WM injury on cortical development by term age in preterm infants, however, is supported by (1) neuropathologic

findings of cortical neuronal abnormalities,^{8,10-12} (2) structural magnetic resonance imaging (MRI) evidence of reduced cortical volumes,^{13,14} and (3) functional connectivity MRI evidence of impaired neural network development.¹⁵ Other neuroimaging evidence of impaired connectivity in preterm survivors has been reviewed recently by Ment et al.¹⁶ Considering the neuropathologic and brain imaging evidence, Volpe^{7,17} proposed the term *encephalopathy of prematurity* to describe “a complex amalgam of primary destructive disease and secondary maturational and trophic influences”^{7(p111)} that affects neurodevelopmental outcomes. The consequences of the encephalopathy of prematurity have been studied most intensively with respect to motor and cognitive outcomes but may also have relevance for psychiatric disorders.

Although MRI is an invaluable tool for investigating the encephalopathy of prematurity,^{14,16,18} the most common method of screening preterm infants for perinatal brain injury in the clinical setting is neonatal head ultrasound (HUS) directed through the anterior fontanelle.^{19,20} This imaging technique can detect 2 early components of encephalopathy of prematurity: hemorrhagic injury to the GM and focal necrotic/ischemic injury to WM. Both types are of particular interest to psychiatry because they might be expected to disrupt normal brain development during the third trimester,²¹⁻²³ including the development of subcortical-cortical circuits that have been implicated in neurodevelopmental psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), tic disorders (TD), obsessive-compulsive disorder (OCD), major depression, and schizophrenia.²⁴

The GM (also called the ventricular zone) is located between the ventricular wall and the periventricular zone. Past 27 weeks' GA, the GM proliferates predominantly glial precursors. The glial precursors become pre-oligodendrocytes and astrocytes.^{25,26} The astrocytes migrate to the immature WM, where they assist in myelination, and to the outer layer of the cortex, where they play a role in cortical organization.^{27,28} Because of its immature vasculature, the GM is vulnerable to hemorrhage that may extend into the ventricle.²⁹ Early enlargement of the lateral ventricle due to the presence of intraventricular blood, while sometimes catastrophic, is usually transient; lateral ventricular enlargement (VE) that persists to term is often a marker of injury to WM.³⁰ Head ultrasound-detectable GM and/or intraventricular hemorrhage (GM/IVH) without persistent ventricular dilatation occurs in at least 25% of infants of less than 32 weeks' GA and is typically diagnosable with HUS by 72 hours of age.³¹ Although GM/IVH has been associated with lower cortical volumes at term^{32,33} and transient neuropsychological deficits in infancy,^{34,35} relatively short-term follow-up studies have not found it to be a predictor of major cognitive or motor disability or impairments in childhood.³⁶⁻⁴⁰ This relative absence of effect may reflect repair and recovery.^{41,42} Inder,⁴³ however, has warned that follow-up times may have been too short, or the measures used too insensitive, to detect an effect of GM/IVH.

The immature WM (also called the brain parenchyma or intermediate zone) is located between the subventricular zone and the cortical subplate. The paren-

chyma contains pre-oligodendrocytes and astrocytes as well as afferent and efferent fibers.^{25,26} Between 24 and 37 weeks' GA, the pre-oligodendrocytes are vulnerable to injury from reactive oxygen species, particularly hydroxyl radicals, generated during infection and ischemia.^{44,45} Hemorrhagic infarcts and necrotic foci, including the lesions often referred to as periventricular leukomalacia,⁴⁶ appear on HUS as echodense and echolucent parenchymal lesions (PL), respectively. Persistent, but not progressive, HUS-identified VE is associated on post mortem with all types of PL and often reflects loss of WM volume (hydrocephalus ex vacuo).^{30,31} Neonatal HUS-detectable injury to immature WM as PL/VE occurs in up to 10% of preterm infants and is reflected on HUS typically within 1 week but may be evident as far out as 3 weeks.³¹ Neonatal PL/VE is associated on post mortem with neuronal injury to basal ganglia and thalami; the neuronal injury is thought to be due to the same excitotoxic factors that cause injury to the immature WM.^{8,11,47} On MRI, PL/VE is associated with reduced subcortical gray matter volumes^{14,48-50} and reduced cortical volumes¹³ at term age. Parenchymal lesions/VE is an important predictor of major cognitive and motor disability,¹⁹ as well as cognitive impairment and motor problems, as far out as adolescence.^{39,51}

The present report on the psychiatric sequelae of ultrasound-detected GM/IVH and PL/VE is based on the adolescent follow-up of the Neonatal Brain Hemorrhage Study (NBHS) cohort. The NBHS cohort is the largest low-birth-weight (<2000 g, 96% preterm) cohort to be systematically screened neonatally with serial HUS for GM/IVH and PL/VE³¹ and followed up longitudinally into adolescence. Among the cohort survivors who did not have major motor or cognitive disability, PL/VE but not GM/IVH predicted increased risk for suboptimal motor and cognitive performance that was evident by age 6 years^{38,40} and still present at adolescence.³⁹ At the 6-year follow-up of the NBHS cohort, neonatal PL/VE predicted ADHD and TD, whereas uncomplicated GM/IVH was unrelated to any psychiatric disorder.⁵¹ In our report on psychiatric disorders at age 6, we suggested that with longer-term follow-up, a relation to later-onset disorders might emerge not only for PL/VE but also for GM/IVH.

Three questions are addressed in this report from the adolescent follow-up of the NBHS cohort. First, are neonatal HUS-detected GM/IVH or PL/VE related to current and lifetime psychiatric disorders by age 16 years? Second, if there are any such relations, do they withstand control for other potentially explanatory early biological and social risk factors? Third, do any such relations withstand control for concurrent cognitive and motor performance?

METHODS

BIRTH COHORT

Adolescent participants belong to the NBHS birth cohort.^{31,52} The NBHS study prospectively enrolled 1105 consecutive infants with birth weights less than 2000 g who were born in, or admitted to, 3 New Jersey hospitals from September 1, 1984, through June 30, 1987. These 3 hospitals cared for 85% of in-

Table 1. Neonatal Head Ultrasound Abnormalities

Term	Definition
Germinal matrix hemorrhage (GMH)	A focal echodensity, on ≥ 1 scan, in the thalamocaudate groove, sometimes extending to the head of the caudate nucleus, just lateral to the frontal horns of the lateral ventricles.
Intraventricular hemorrhage (IVH)	An echodense focus or foci, on ≥ 1 scan, within the lateral, third, or fourth ventricles separate from, and at least as echodense as, the choroid plexus. Also diagnosed when irregularity of the choroid plexus margin indicated adherent intraventricular blood.
Parenchymal lesions (PL)	Focal or confluent echodense and/or echolucent areas, on at least 1 scan, in the parenchyma, replacing the normal pattern of alternating or interlaced gracile echogenic or echopoor lines.
Ventricular enlargement (VE)	At least moderate enlargement of at least one lateral ventricle, as read by the radiologist on the final scan obtained.

fants with birth weights from 501 to 2000 g and 90% of those with birth weights of 1500 g or less in 3 New Jersey counties. These counties were somewhat more affluent than the nation as a whole; 26% of the sample was black, but Hispanic and other minorities were uncommon.³¹ All enrolled families were English speaking. All but 17 infants in the cohort were successfully entered into a protocol that screened for neonatal brain injury at 24 hours, 72 hours, and 7 days of life. (See eAppendix for description of HUS procedures; <http://www.archgenpsychiatry.com>) Of the 17 infants missing HUS, 14 had died before 12 hours.³¹ Approximately half of the cohort also had later ultrasounds, most commonly just before discharge.³²

AGE 16 FOLLOW-UP

At the 16-year follow-up, 212 (19.2%) of the original birth cohort were known to have died and 31 (2.8%) were adopted or in foster care, leaving 862 enrollees potentially eligible for follow-up. Of eligible enrollees, 628 (72.9%) participated in the adolescent follow-up, 83 (9.6%) refused, and 151 (17.5%) could not be located, 68 (45.0%) of whom had been lost to follow-up since hospital discharge.

Thirty-three participants with severe disability (IQ <55 and/or disabling cerebral palsy) are excluded from this report. Of the 595 participants who were not disabled, 474 (79.7%) were assessed on home visits and 121 (20.3%) by telephone. Participants assessed by telephone were not evaluated for psychiatric diagnoses; although slightly older, on average, than those assessed at home, they did not differ in any other respect, including frequency of behavior problems. Time constraints precluded a psychiatric interview for 16 participants seen at home, leaving 458 adolescents in the sample.

PROCEDURES

The New York State Psychiatric Institute Institutional Review Board approved this follow-up study; informed consent by parents or legal guardians, and assent, as appropriate, from the adolescents, was obtained before participation. During the home assessment, the primary caretaker was interviewed regarding the adolescent; the interviewers were masked to neonatal history, including HUS findings, apart from low-birth-weight status. Parents were masked to the study hypotheses although not to their child's neonatal history.

PREDICTORS

Neonatal HUS abnormalities are defined in **Table 1**. Head ultrasound abnormalities were categorized as follows: (1) NA, no abnormality; (2) GM/IVH, GM or IVH without either PL or VE;

(3) PL/VE, PL and/or VE with or without GM/IVH. This categorization differs from the widely used Papile system, which rates severity of intracerebral hemorrhage on the basis of computed tomography.⁵³ The present system is more consistent with lesions observed post mortem^{31,54} and has been used in follow-up studies of the Neonatal Brain Hemorrhage Study cohort^{37-40,55} and other contemporary cohorts.^{56,57} Other early risk factors (non-HUS prenatal, perinatal, and neonatal risk factors) that were of a priori theoretical importance or have been shown to be indicators of risk are listed in **Table 2** and defined in eTable 1.

OUTCOMES BY ADOLESCENCE

Parent-reported psychiatric disorders by age 16 years were assessed with the parent report version of the Diagnostic Interview Schedule for Children-IV (DISC-IVP).⁵⁸ The DISC-IVP is a structured, computer-assisted, psychiatric diagnostic interview that assesses current (past year) and lifetime mental disorders, as defined in the DSM-IV^{59,60} for 26 current and lifetime disorders, not including the pervasive developmental disorders (**Table 3**; footnotes explain the definitions of diagnoses). Adolescents were not interviewed using the youth version of this instrument because cognitive testing was a higher priority; time considerations precluded doing both.

STATISTICAL ANALYSIS

Current and lifetime prevalence rates for each psychiatric disorder and for groups of disorders were calculated by dividing the number of positive cases by the number of cases assessed. The relation of HUS status to each disorder (or to a group of disorders) was examined by means of a priori contrasts using logistic regression. Head ultrasound was represented by 2 dummy variables, each encoding the comparison of those with no HUS abnormality to 1 of the 2 HUS abnormality groups (GM/IVH or PL/VE). Disorders with a prevalence of at least 15 cases (approximately 3% of the sample) at the threshold level (or, failing that, at the level of threshold plus subthreshold) on the DISC-IVP were examined in relation to HUS. Current subthreshold diagnoses are considered comparable to a DSM-IV diagnosis of "not otherwise specified" for a given disorder. Subthreshold levels were included to allow relations of rare but important psychiatric disorders to be tested. Relations of HUS status to groups of disorders were reported when there was an insufficient number of cases for analysis of any specific disorder within the group but a sufficient number for the group as a whole. The 2 HUS dummy variables were the sole risk factors for the unadjusted relations.

For adjusted relations, selected other early risk factors from Table 2 were included in the model as well. Variables ex-

Table 2. Risk Exposure for Preterm/LBW Nondisabled Adolescents in Sample vs Other Eligible Adolescents

Risk Factor	In Sample ^{a,b} (n = 458)	Other Eligible ^{b,c} (n = 371)	t_{df}/χ^2_{df}	P Value
Head ultrasound abnormality				
No abnormality	80.3	80.1	$\chi^2_2 = 0.87$.65
Germinal matrix/intraventricular hemorrhage	15.1	14.0		
Parenchymal lesion/ventricular enlargement	4.6	5.9		
Maternal social risk	42.9	57.8	$\chi^2_1 = 18.28$	<.001
Male sex	51.7	48.2	$\chi^2_1 = 1.00$.32
Birth weight, mean (SD), g	1482 (354)	1501 (355)	$t_{627} = 0.78$.44
1500-1999	53.5	54.7	$\chi^2_2 = 0.13$.94
1000-1499	34.7	34.0		
<1000	11.8	11.3		
Gestational age, completed wk, mean (SD)	31.2 (3.1)	31.3 (3.2)	$t_{627} = 0.19$.85
>36	3.7	4.6	$\chi^2_3 = 0.64$.89
34-36	19.9	18.3		
32-33	24.0	24.3		
<32	52.4	52.8		
Fetal growth ratio	0.8	0.9	$t_{627} = 0.93$.35
Small for gestational age	32.5	33.4	$\chi^2_1 = 0.74$.79
Multiple birth	29.7	21.0	$\chi^2_1 = 8.04$	<.001
Maternal smoking in pregnancy ^d				
No. of cigarettes/d, mean (SD)	3.8 (7.2)	3.8 (6.7)	$t_{698} = 0.09$.93
None	68.6	64.2	$\chi^2_2 = 3.93$.14
≤½ pack	19.0	25.1		
>½ pack	12.5	10.7		
Maternal drinking of alcohol in pregnancy ^d				
None	47.5	59.1	$\chi^2_2 = 10.82$	<.01
<7 drinks/wk and <3 drinks/occasion	49.1	36.5		
≥7 drinks/wk or ≥3 drinks/occasion	3.4	4.4		
Maternal hypertension				
None	70.5	72.3	$\chi^2_2 = 0.22$.90
Preexisting hypertension	4.4	3.6		
PIH or preeclampsia	25.1	24.1		
Active labor	58.9	61.6	$\chi^2_1 = 0.57$.45
Nonvertex presentation	31.5	32.5	$\chi^2_1 = 0.09$.77
Low Apgar score	10.5	8.5	$\chi^2_1 = 0.97$.33
Small head circumference at birth	33.7	33.0	$\chi^2_1 = 0.05$.83
Base excess, mean (SD), mEq/L ^c	-4.7 (4.2)	-4.6 (3.6)	$t_{629} = 0.26$.79
Thyroxine level, mean (SD), z score	-1.4 (1.0)	-1.5 (1.1)	$t_{789} = -0.30$.13
Hypocapnia exposure ^e	24.5	24.6	$\chi^2_1 = 0.00$.99
Hyperoxia exposure ^e	36.9	31.9	$\chi^2_1 = 2.15$.14
Systolic hypotension ^f	34.5	34.0	$\chi^2_1 = 0.03$.87
Diastolic hypotension ^f	23.0	23.1	$\chi^2_1 = 0.00$.96
Peak bilirubin, first 8 d, mean (SD), mg/dL	9.2 (2.7)	9.1 (2.5)	$t_{768} = -0.26$.80
Neonatal infection	31.4	26.1	$\chi^2_1 = 2.79$.10
Prolonged ventilation	11.4	9.7	$\chi^2_1 = 0.59$.44

Abbreviations: LBW, low birth weight; PIH, pregnancy-induced hypertension.

SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.104.

^aPreterm/LBW nondisabled adolescents assessed with the parent report on the Diagnostic Interview Schedule for Children-IV (DISC-IVP).

^bData are given as percentage of participants unless otherwise indicated.

^cPreterm/LBW adolescents who were lost to follow-up (n = 151), refused (n = 83), assessed by phone (n = 121), or assessed at home but without DISC-IVP data (n = 16).

^dThe 3 categories were entered into regressions as a single variable, coded 0, 1, and 2, respectively.

^eHighest 2 quintiles of time-weighted exposure; obtained only when clinically indicated (n = 387 for those in sample and n = 313 for other eligible adolescents).

^fAny day(s) with hypotension.

cluded from the regression were (1) those too asymmetrically distributed, having very few positive cases (neonatal seizures, placenta previa, placental abruption, and chorioamnionitis); (2) those unrelated to any of the diagnoses of interest (maternal hypertension, low Apgar score, small head circumference at birth, peak bilirubin level during the first postnatal week, and neonatal infection), and (3) the variable of lesser theoretical importance of a redundant or highly correlated pair that posed a risk of multicollinearity (birth weight, which is redundant with GA when small-for-GA is also included, and diastolic blood pressure, which was highly correlated with systolic blood pres-

sure, $r > 0.70$). All analyses were conducted using SPSS software (Chicago, Illinois)⁶¹; statistical tests were considered significant at the .05 level.

To conserve cases and power in the regressions, missing values were replaced using an expectation maximization algorithm with 200 iterations.⁶² Only 6 non-HUS risk factors had more than 10% missing. Preliminary analyses using dummy-coded missing value indicators for these 6 measures had shown that none of the missing value indicators was related to any outcome of interest. Altogether, only 3.9% of the predictor values were missing.

Table 3. Prevalence of DISC-IVP DSM-IV Disorders in 458 Nondisabled Preterm/LBW Adolescents^a

Disorder Group/Specific Disorder	No. (%) of Participants			
	Current Cases ^b		Lifetime Cases ^c	
	Threshold ^d	Threshold Plus Subthreshold ^e	Threshold ^d	Lifetime Threshold, Plus Current Subthreshold ^e
Attention-deficit/hyperactivity disorder-any-unmodified-refined ^f	25 (5.5)	89 (19.4)	57 (12.4)	105 (22.9)
Inattentive type-refined	17 (3.7)	69 (15.1)	49 (10.7)	89 (19.4)
Hyperactivity type-refined	0	4 (0.9)	22 (4.8)	26 (5.7)
Combined type-refined	8 (1.7)	16 (3.5)	No items	No items
Any disruptive disorder ^g	42 (9.2)	130 (28.4)	52 (11.4)	135 (29.5)
Oppositional defiant disorder	41 (9.0)	126 (27.5)	49 (10.7)	130 (28.4)
Conduct disorder	6 (1.3)	16 (3.5)	9 (2.0)	18 (3.9)
Any anxiety disorder ^g	43 (9.4)	73 (15.9)	69 (15.1)	91 (19.9)
Generalized anxiety disorder	4 (0.9)	13 (2.8)	17 (3.7)	25 (5.5)
Separation anxiety disorder	4 (0.9)	14 (3.1)	12 (2.6)	20 (4.4)
Social phobia	14 (3.1)	28 (6.1)	20 (4.4)	31 (6.8)
Specific phobia	22 (4.8)	28 (6.1)	31 (6.8)	36 (7.9)
Posttraumatic stress disorder	1 (0.2)	4 (0.9)	No items	No items
Panic disorder without agoraphobia	1 (0.2)	8 (1.7)	2 (0.4)	9 (2.0)
Panic disorder with agoraphobia	0	0	0	0
Agoraphobia without panic disorder	0	0	0	0
Selective mutism	1 (0.2)	2 (0.4)	2 (0.4)	3 (0.7)
Any mood disorder ^g	8 (1.7)	28 (6.1)	13 (2.8)	34 (7.4)
Major depression	4 (0.9)	22 (4.8)	12 (2.6)	29 (6.3)
Dysthymic disorder	3 (0.7)	12 (2.6)	No items	No items
Mania	1 (0.2)	5 (1.1)	1 (0.2)	5 (1.1)
Hypomania	0	No items	No items	No items
Any elimination disorder ^h	1 (0.2)	4 (0.9)	48 (10.5)	49 (10.7)
Nocturnal enuresis	1 (0.2)	4 (0.9)	40 (8.7)	41 (9.0)
Diurnal enuresis	0	0	1 (0.2)	1 (0.2)
Encopresis	0	0	9 (2.0)	9 (2.0)
Any tic disorder ^h	17 (3.7)	26 (5.7)	24 (5.2)	33 (7.2)
Transient tic disorder	5 (1.1)	No items	No items	No items
Motor/vocal tic disorder	11 (2.4)	No items	No items	No items
Tourette syndrome	1 (0.2)	No items	No items	No items
Other disorders ^h				
Pica	0	0	2 (0.4)	2 (0.4)
Obsessive-compulsive disorder	2 (0.4)	15 (3.2)	2 (0.4)	15 (3.2)
Trichotillomania	0	0	0	0
Any eating disorder	0	7 (1.5)	3 (0.7)	9 (2.0)
Schizophrenia	0	3 (0.7)	0	3 (0.7)
Any substance abuse/dependence	5 (1.1)	7 (1.5)	5 (1.1)	7 (1.5)
Any disorder	104 (22.7)	219 (47.8)	169 (36.9)	239 (52.2)
Multiple disorders	36 (7.9)	95 (20.7)	74 (16.2)	121 (26.4)

Abbreviations: DISC-IVP, parent report version of the Diagnostic Interview Schedule for Children-IV; LBW, low-birth-weight.

^aBoldface indicates percentages for current and lifetime disorders qualifying for further analysis (threshold $\geq 3\%$ or, failing that, threshold + subthreshold $\geq 3\%$).

^bThe DISC-IVP leaves the definition of caseness up to the investigator; here, caseness is defined by meeting the symptom criterion for a disorder (as defined for threshold and subthreshold levels; see footnotes *d* and *e*) with or without impairment. (See footnotes *f*, *g*, and *h*.) "Current" refers to symptoms present in the past year.

^cCaseness is defined per footnote *b*. "Lifetime" refers to symptoms present from age 5 years on for most disorders (age 4 years for pica and encopresis).

^dThe threshold symptom criterion requires the full count of symptoms stipulated for a given disorder to be present.

^eThe subthreshold symptom criterion requires at least half, but not all, of the symptoms stipulated for a given disorder to be present.

^fCurrent attention-deficit/hyperactivity disorder cases are defined per *DSM-IV-TR*, requiring the DISC-IVP impairment B criterion (intermediate to severe impairment in ≥ 2 domains) and onset of symptoms that caused impairment before 7 years of age as well as the relevant symptom criterion.

^gFor disruptive, anxiety, and mood disorders, cases are defined using the DISC-IVP impairment A criterion (intermediate to severe impairment in ≥ 1 domain), as well as the relevant symptom criterion.

^hFor elimination disorders, tic disorders, and other disorders, cases are defined using only the relevant symptom criterion, with no impairment required. The behaviors involved in these disorders were considered of sufficient clinical concern to define caseness irrespective of impairment.

RESULTS

SAMPLE DESCRIPTION

As shown in Table 2, the mean age at follow-up was 15.9 years (range, 15.3-18.8 years). Consistent with most lon-

gitudinal studies, those in the study sample were born at lower social risk than those eligible but not in the sample, particularly those lost to follow-up (75.5% of whom had ≥ 1 social risk factors). Of the medical risk factors, the 2 groups differed significantly only in respect to multiple births and moderate maternal prenatal

Table 4. Rates for Selected DSM-IV Disorders^a by Neonatal Head Ultrasound Status in 458 Nondisabled Preterm/LBW Adolescents

Disorder	Current			Lifetime		
	NA (n = 368)	GM/IVH (n = 69)	PL/VE (n = 21)	NA (n = 368)	GM/IVH (n = 69)	PL/VE (n = 21)
Attention-deficit/hyperactivity disorder						
Inattentive type	3.0	2.9	19.0 ^b	10.3	8.7	23.8
Hyperactive type	Unavailable ^c	Unavailable ^c	Unavailable ^c	4.1	7.2	9.5
Combined type	3.3	4.3	4.8	Unavailable ^c	Unavailable ^c	Unavailable ^c
Oppositional defiant disorder	9.3	8.7	4.8	11.1	8.7	9.5
Conduct disorder	3.3	2.9	9.5	3.5	4.3	9.5
Generalized anxiety disorder	Unavailable ^c	Unavailable ^c	Unavailable ^c	3.5	5.8	0.0
Separation anxiety disorder	2.4	5.8	4.8	3.8	7.2	4.8
Social phobia	3.5	1.4	0.0	4.9	1.4	4.8
Specific phobia	4.6	4.3	9.5	6.8	5.8	9.5
Major depression	4.1	10.1 ^d	0.0	5.2	13.0 ^d	4.8
Nocturnal enuresis	Unavailable ^c	Unavailable ^c	Unavailable ^c	7.6	13.0	14.3
Any tic disorder	2.7	4.3	19.0 ^b	4.7	4.5	20.0 ^e
Obsessive-compulsive disorder	1.4	11.6 ^b	9.5 ^d	1.4	11.6 ^b	9.5 ^d

Abbreviations: GM, germinal matrix; IVH, intraventricular hemorrhage; LBW, low birth weight; NA, no head ultrasound abnormalities; PL, parenchymal lesions; VE, ventricular enlargement.

^aData are given as percentages. Disorders having 15 or more cases (3% of the full sample) at the threshold level, or failing that, at the threshold plus subthreshold level (Table 3).

^bGreater than NA; $P \leq .001$.

^cDisorder not defined or fewer than 15 cases in the full sample.

^dGreater than NA; $P \leq .05$.

^eGreater than NA; $P \leq .01$.

alcohol consumption, both more common in the study group. Of the 458 adolescents in the study sample, the overwhelming majority had been born prematurely (most extremely to moderately so). Based on age 16 motor and cognitive assessments described in detail elsewhere,³⁹ 14.6% of study participants scored in the top 2% on a standardized test of motor problems; 3.9% had full-scale IQ score in the range 55 to 69, 13.5% in the range 70 to 84, and 82.5% had scores of 85 or greater.

DESCRIPTIVE EPIDEMIOLOGY

Current Disorders

At the threshold level (Table 3, second column), 4 specific psychiatric disorders had sufficient prevalence ($\geq 3.0\%$) to be considered further. In decreasing order of prevalence, these were oppositional defiant disorder, specific phobia, ADHD–inattentive type, and social phobia. The group of TD had a sufficient prevalence to be considered further, although none of the specific disorders within this group did.

When subthreshold levels of disorder were counted along with threshold levels (Table 3, third column), an additional 5 specific disorders had a prevalence of at least 3.0%: major depression, ADHD–combined type, conduct disorder, OCD, and separation anxiety disorder.

Lifetime Disorders

As expected, prevalence rates were greater for most individual disorders and for disorders overall when criteria for lifetime diagnoses at the threshold level were applied (Table 3, fourth column). For some disorders (eg, OCD), however, there were no additional cases. At the

threshold level, 6 specific lifetime disorders had a prevalence of at least 3%: in decreasing order of frequency, these were oppositional defiant disorder, ADHD–inattentive type, nocturnal enuresis, specific phobia, ADHD–hyperactive type, social phobia, and generalized anxiety disorder. The group of lifetime TD had sufficient prevalence to be considered further, although none of the specific disorders within this group did. When current subthreshold diagnoses were added to the lifetime threshold diagnoses (Table 3, fifth column), 2 additional specific disorders (major depressive disorder [MDD] and separation anxiety disorder) met the prevalence criterion.

RELATION OF NEONATAL HUS STATUS TO PSYCHIATRIC DISORDERS

For those disorders with a prevalence qualifying for further analysis, the rates by neonatal HUS category are presented in **Table 4**. For disorders that did not qualify for further analysis, the number of adolescents with each disorder is provided in eTable 2 by HUS status. Germinal matrix and/or intraventricular hemorrhage was related significantly, without adjustment for other early risk factors, to current and lifetime MDD and OCD (**Table 5**). After adjustment, the significant relation of GM/IVH to lifetime MDD persisted, whereas that to current MDD did not. The significant relation to current and lifetime OCD also persisted. Overall, PL/VE was related significantly to ADHD–Inattentive Type, any TD, and OCD. Unadjusted for other early risk factors, PL/VE was related significantly to current (but not lifetime) ADHD–inattentive type, current and lifetime TD, and current and lifetime OCD. (As previously noted, all lifetime cases of OCD were also current.) After adjustment, the significant relation of PL/VE to current ADHD–inattentive type,

Table 5. Unadjusted and Adjusted^a Relations of Head Ultrasound Abnormalities to Current and Lifetime Psychiatric Disorders

Psychiatric Disorders	Odds Ratio (95% Confidence Interval)			
	Unadjusted		Adjusted ^a	
	GM/IVH	PL/VE	GM/IVH	PL/VE
Current				
ADHD–inattentive type	0.97 (0.21-4.47)	7.64 ^b (2.20-24.48)	1.01 (0.19-5.44)	6.83 ^c (1.26-36.91)
Major depression	2.66 ^c (1.04-6.78)	No cases ^d	2.23 (0.80-6.24)	No cases ^d
Tic disorders	1.63 (0.44-6.07)	8.42 ^e (2.40-29.62)	1.89 (0.42-8.57)	9.77 ^c (1.69-56.47)
Obsessive-compulsive disorder	9.52 ^b (3.02-30.06)	7.64 ^c (1.39-41.98)	11.85 ^b (3.22-43.62)	15.32 ^c (1.82-128.74)
Lifetime				
ADHD–inattentive type	0.83 (0.34-2.04)	2.71 (0.94-7.82)	0.64 (0.24-1.74)	1.13 (0.31-4.10)
Major depression	2.76 ^c (1.19-6.38)	No cases ^d	2.59 ^c (1.02-6.58)	No cases ^d
Tic disorders	0.95 (0.27-3.34)	5.07 ^e (1.53-16.82)	0.85 (0.21-3.51)	5.02 ^c (1.05-23.92)
Obsessive-compulsive disorder	9.52 ^b (3.05-30.06)	7.64 ^c (1.39-41.98)	11.85 ^b (3.22-43.62)	15.32 ^c (1.82-128.74)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; GM/IVH, germinal matrix and/or intraventricular hemorrhage without either parenchymal lesions or ventricular enlargement; PL/VE, parenchymal lesions and/or ventricular enlargement with or without GM/IVH.

^aAdjusted for selected risk factors from Table 2, namely, the presence/absence of maternal social risk at birth, sex, completed weeks of gestation, fetal growth ratio, whether the participant was a member of a set of multiples at birth, maternal smoking during pregnancy, maternal drinking during pregnancy, presence/absence of active labor, nonvertex birth presentation, base excess from the first postnatal blood gas, thyroid status, hypocalcemia, hyperoxia, systolic hypotension, and the presence/absence of prolonged ventilation. (See eTable 1 for definitions.)

^b $P \leq .001$.

^c $P \leq .05$.

^dThere were no cases of PL/VE having this disorder.

^e $P \leq .01$.

Table 6. Current Diagnoses Related to Head Ultrasound Status Regressed on Head Ultrasound Controlling for WASI-FSIQ and Riley Motor Problems Inventory Scores

Psychiatric Disorders	Odds Ratio (95% Confidence Interval) ^a			
	Controlling for FSIQ		Controlling for Motor Problems	
	GM/IVH	PL/VE	GM/IVH	PL/VE
ADHD–inattentive type	0.86 (0.18-3.99)	5.04 (1.36-18.65) ^a	0.99 (0.21-4.62)	5.43 (1.32-22.40) ^a
Major depression	0.43 (0.16-1.11)	No cases ^b	0.40 (0.15-1.05)	No cases ^b
Tic disorders	1.54 (0.41-5.78)	7.01 (1.88-28.14) ^c	1.45 (0.38-5.48)	4.38 (1.05-18.23) ^a
Obsessive-compulsive disorder	8.68 (2.72-27.69) ^d	4.78 (0.83-28.10)	10.91 (3.13-37.99) ^d	3.58 (0.50-25.94)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FSIQ, full-scale IQ; GM/IVH, germinal matrix and/or intraventricular hemorrhage without either parenchymal lesions or ventricular enlargement; PL/VE, parenchymal lesions and/or ventricular enlargement with or without GM/IVH; WASI, Wechsler Abbreviated Scale of Intelligence.

^a $P < .05$.

^bThere were no cases of this disorder with PL/VE.

^c $P < .01$.

^d $P < .001$.

current and lifetime TD, and to current and lifetime OCD, persisted. In the adjusted analyses, several other early risk factors had significant independent relations to current and lifetime disorders that were predicted by PL/VE and/or uncomplicated GM/IVH (eTable 3, A and B).

Because both cognitive and motor performance are also affected by HUS,³⁸⁻⁴⁰ additional regression analyses were run for current disorders having a relation to HUS adjusting for Wechsler Abbreviated Scale of Intelligence Full-Scale IQ³⁹ and, separately, for the total problems score of the Riley Motor Problems Inventory,⁶³ both obtained at age 16. With control for IQ, all previously significant relations persisted except for that of GM/IVH to MDD and PL/VE to OCD (**Table 6**). With control for motor problems, all previously significant relations persisted, with the same 2 exceptions as for IQ (Table 6).

COMMENT

This prospective epidemiologic study of the relation of neonatal HUS abnormalities in preterm infants to adolescent psychiatric disorders has 3 principal findings. First, HUS-detected uncomplicated GM/IVH increased risk for current MDD and OCD, whereas PL/VE increased risk for current ADHD–inattentive type, any TD, and OCD. The results were similar for lifetime disorders, except for the relation of PL/VE to ADHD–inattentive type, which was not significant. Second, these relations withstood control for other potentially explanatory early biological and social risk factors. Third, these relations, for the most part, withstood control for cognitive and motor problems.

Although MRI is more sensitive to some abnormalities (eg, diffuse WM injury) than HUS and has played

an important role in understanding the encephalopathy of prematurity,¹⁴ HUS is still the standard of care for evaluating preterm infants for brain injury in the newborn intensive care unit.^{19,20} Because bedside HUS detects 2 important early component injuries of the encephalopathy of prematurity, namely GM/IVH and PL/VE, and is safe, relatively inexpensive, and widely available, it is an invaluable tool for prospective epidemiologic research.

COMPARISON WITH OTHER STUDIES

Comparison with other studies is complicated by differences in design, sample definition, and size; classification of brain injury; and outcome measures. Closest to the NBHS cohort in terms of birth years is a population-based Norwegian low-birth-weight (<1500 g) cohort, born from 1986 to 1988. Indredavik et al⁶⁴ recently reported on the relation of neonatal HUS-detected IVH (retrospectively obtained from hospital records) to psychiatric disorder and dimensional measures of psychiatric disorders and symptoms in this Norwegian cohort at age 14 years. Psychiatric disorder was assessed with a semi-structured psychiatric diagnostic interview, the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), which covers a range of diagnoses comparable with the DISC-IVP used in the present study. Intraventricular hemorrhage, defined as either grades I or II (comparable with GM/IVH) or grades III or IV (comparable with PL/VE), was not related to psychiatric disorder but was related to inattentive symptoms on a questionnaire measure; the sample size, however, was small (n=65). The same group reported earlier that indicators of WM reduction on qualitative MRI obtained at age 14 years was related selectively to ADHD symptoms ($\geq 75\%$ of DSM-IV symptom criteria on the K-SADS) at age 14. The same group also reports that, on diffusion tensor imaging at age 14, lower fractional anisotropy values (a marker for disturbance of WM tracts) in several areas regarded as likely sites of perinatal WM injury were related to both symptoms and full diagnoses of ADHD at age 14.⁶⁵ These recent findings are consistent with those of Stewart et al,⁶⁶ who found that neonatal HUS abnormalities consistent with PL/VE were highly associated 14 years later with MRI indicators of WM injury, which, in turn, were associated with adolescent behavior problems.⁶⁶

A recent report by the EPICure study group⁶⁷ of a very low-birth-weight cohort followed up prospectively found no relation of HUS status (or any other neonatal variable) to psychiatric disorder, as assessed with the Development and Well-being Assessment, but this may reflect the younger age and smaller size of their sample. A prospective study conducted by Luu et al⁶⁸ examined only severe brain injury (corresponding to PL/VE in the present study) and studied 375 premature infants using a dimensional outcome measure, the Achenbach Child Behavior Checklist at adolescence.⁶⁹ Compared with term controls, preterm infants with severe brain injury scored as a group in the clinical range on attention problems and on social and thought problems. It is noteworthy that Hille et al⁷⁰ found that attention, social, and thought problems were elevated in school-age children born weighing less than 1000 g, a group at high risk for the type of

severe brain injury studied by Luu et al.⁶⁸ In light of our findings, the relation of GM/IVH, a brain injury category not examined by Luu et al, to the Anxious/Depressed Subscale of the Child Behavior Checklist and to a derived Obsessive-Compulsive Scale⁷¹ would be of interest.

RELEVANCE FOR DEVELOPMENTAL NEUROPSYCHIATRY

This study provides strong evidence for the concept, first promulgated by Pasamanick et al,¹ that injury to the fetal-neonatal brain alters risk for later psychiatric disorder.

For the 2 components of the encephalopathy of prematurity studied here, the increase in risk was diagnostically quite specific: GM/IVH increased risk for OCD and MDD, whereas PL/VE increased risk for ADHD—inattentive type, OCD, and TD. Attention-deficit/hyperactivity disorder, TD, OCD, and MDD each belong to a group of disorders sometimes referred to as the neurodevelopmental frontostriatal disorders.²⁴ The importance of subcortical structures (particularly the basal ganglia) in childhood-onset forms of the neurodevelopmental frontostriatal disorders has recently been emphasized by others.⁷²⁻⁷⁵ Structural and functional brain imaging studies of children and adolescents with frontostriatal disorders suggest that distinct neural circuits subserve ADHD, TD, MDD, and OCD. The finding here that PL/VE is related to ADHD and TD suggests that PL/VE affects the thalamocortical circuit implicated in ADHD^{72,76-79} and the striatocortical circuits implicated in TD.⁸⁰⁻⁸³ These possibilities are consistent with evidence of an association between PL/VE and postmortem findings of injury to the thalamus and basal ganglia^{11,31} and quantitative MRI findings of reduced thalamic and basal ganglia volumes at term age.⁴⁸⁻⁵⁰ The finding that GM/IVH is related to MDD suggests that GM/IVH may affect the amygdalo-striatal-dorso-medial prefrontal circuits whose dysfunction has been implicated in MDD.^{73,84-86} This possibility is consistent, in turn, with the finding that uncomplicated GM/IVH is associated with lower cortical volumes at term on quantitative MRI³³ and with the suggestion that GM/IVH could affect development of the amygdala.^{87,88} The finding that both GM/IVH and PL/VE are related to OCD supports the speculation that both may affect, possibly at different locations, the orbitofrontal-anterior cingulate-striatal circuit implicated in OCD^{75,89-91} or (alternatively) globus pallidus-putamen-thalamus-prefrontal circuits.^{73,92}

Other disorders that have been considered to be part of the neurodevelopmental frontostriatal group include autism, bulimia, and schizophrenia.^{24,93-96} Autism as a diagnosis was not assessed at this follow-up. The low prevalence of bulimia and schizophrenia in this cohort at age 16 precluded analysis of their relation to HUS status. Perhaps most importantly, the emergence of new relations of GM/IVH to psychiatric disorders between the age 6 and age 16 follow-ups of the NBHS cohort suggests that further follow-up may find that GM/IVH and/or PL/VE may increase risk for disorders that typically have an even later onset. One such disorder, long thought to be at the “devastating intersection between development and disease,”⁹⁸ is schizophrenia.^{2,93,97}

The relation of neonatal HUS status to adolescent psychiatric disorder in the NBHS cohort did not appear to be accounted for by other early medical risk factors. Concurrent cognitive and motor problems did not account for the relation of GM/IVH to OCD or the relation of PL/VE to ADHD or TD. The finding that the relation of GM/IVH to MDD and that of PL/VE to OCD did not withstand control for motor or cognitive problems may reflect a common cause or the presence of a neurodevelopmental syndrome; the exploration of these alternative possibilities is beyond the scope of this article.

The present findings may have relevance to some term infants as well. Preliminary evidence from fetal neuroimaging suggests that some fetuses sustain GMH/IVH and PL/VE in utero at the same GAs as preterm neonates, but are carried to term.⁹⁸ Term infants with certain forms of congenital heart disease show patterns of WM and gray matter injury similar to that seen in preterm infants.⁶ Psychiatric outcomes in term infants who sustained prenatal injury and in term infants with congenital heart disease are not known but deserve study.

STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study are the (1) use of a large regional birth cohort, (2) rigor of the protocol for HUS, (3) prospective and systematic ascertainment of a rich set of early medical complications, (4) structured assessment of both common and rare psychiatric disorders in mid-adolescence, and (5) concurrent assessment of cognitive and motor functioning.

Limitations include (1) the lack of a normal birth weight or term control group, precluding determination of whether low-birth-weight/preterm infants, as a group, are at excess risk for psychiatric disorders; (2) the inability of HUS as used in this cohort to detect diffuse WM injury as well as cerebellar hemorrhages in preterm infants^{14,99}; (3) the selective loss of those at greater social risk, which may have influenced the prevalence of disorders sensitive to social risk; (4) ascertainment of the cohort by birth weight rather than GA; (5) the reliance on parent report, which might underestimate internalizing disorders (ie, anxiety disorders and depression)¹⁰⁰; and (6) the use of subthreshold criteria for some diagnoses.

In conclusion, HUS-detected uncomplicated GM/IVH and PL/VE in preterm neonates both selectively increase risk for the emergence of psychiatric disorders in which abnormal subcortical-cortical connectivity has been implicated.

Submitted for Publication: June 30, 2010; final revision received November 24, 2010; accepted January 3, 2011.

Correspondence: Agnes H. Whitaker, MD, Unit 74, Division of Adolescent and Child Psychiatry, Columbia University Medical Center, New York State Psychiatric Institute, 1051 Riverside Dr, New York, NY 10032 (whitakea@childpsych.columbia.edu).

Financial Disclosure: None reported.

Funding/Support: This work was supported by grant NS-20713 (Dr Paneth, NBHS birth data collection); grant 5 R01 MH57514 from the National Institute of Mental

Health (Dr Whitaker, age 16 follow-up); grants 12-FY03-46 (Dr Whitaker, age 16 follow-up) and P30 MH 071478 and P30 MH60570 (Dr Shaffer, assessment procedures and training) from the March of Dimes; and the Ruane Fund (Dr Shaffer, psychiatric interview algorithms).

Online-Only Material: An eAppendix and 3 eTables are available at <http://www.archgenpsychiatry.com>.

Additional Contributions: We extend our deepest gratitude to the participating adolescents and their families, who made this study possible. Janet Baxendale, Marlon Nieto, Marlene Comer, and Heather McCulloch Mistretta assisted with data collection and management; Anna Silberman, BS, provided proofreading assistance; and Andrew Gerber, PhD, MD, provided helpful comments on the manuscript.

REFERENCES

1. Pasamanick B, Rogers ME, Lilienfeld AM. Pregnancy experience and the development of behavior disorders in children. *Am J Psychiatry*. 1956;112(8):613-618.
2. Weinberger DR, Hirsch SR. Schizophrenia as a neurodevelopmental disorder. In: Weinberger DR, Hirsch SR, eds. *Schizophrenia*. Cambridge, MA: Blackwell Science; 1995:293-323.
3. Peterson B, Leckman J, Cohen D. Tourette's syndrome: a genetically predisposed and an environmentally specified developmental psychopathology. In: Cicchetti D, Cohen D, eds. *Developmental Psychopathology*. New York, NY: Wiley; 1995:213-241.
4. Rutter M. Concepts of brain dysfunction syndromes. In: Rutter M, ed. *Developmental Neuropsychiatry*. New York, NY: Guilford Press; 1983:1-11.
5. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci*. 2002;25:409-432.
6. Miller SP, Ferriero DM. From selective vulnerability to connectivity: insights from newborn brain imaging. *Trends Neurosci*. 2009;32(9):496-505.
7. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol*. 2009;8(1):110-124.
8. Kinney HC. The encephalopathy of prematurity: one pediatric neuropathologist's perspective. *Semin Pediatr Neurol*. 2009;16(4):179-190.
9. Truwit CL, Barkovich AJ, Koch TK, Ferriero DM. Cerebral palsy: MR findings in 40 patients. *AJNR Am J Neuroradiol*. 1992;13(1):67-78.
10. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage; III: gray matter lesions of the neocortex. *J Neuropathol Exp Neurol*. 1999;58(5):407-429.
11. Pierson CR, Folkerth RD, Billiards SS, Trachtenberg FL, Drinkwater ME, Volpe JJ, Kinney HC. Gray matter injury associated with periventricular leukomalacia in the premature infant. *Acta Neuropathol*. 2007;114(6):619-631.
12. Andiman SE, Haynes RL, Trachtenberg FL, Billiards SS, Folkerth RD, Volpe JJ, Kinney HC. The cerebral cortex overlying periventricular leukomalacia: analysis of pyramidal neurons. *Brain Pathol*. 2010;20(4):803-814.
13. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics*. 2005;115(2):286-294.
14. Boardman JP, Craven C, Valappil S, Counsell SJ, Dyet LE, Rueckert D, Aljabar P, Rutherford MA, Chew AT, Allsop JM, Cowan F, Edwards AD. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *Neuroimage*. 2010;52(2):409-414.
15. Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, Neil JJ. Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex*. 2010;20(12):2852-2862.
16. Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. *Lancet Neurol*. 2009;8(11):1042-1055.
17. Volpe JJ. Encephalopathy of prematurity includes neuronal abnormalities. *Pediatrics*. 2005;116(1):221-225.
18. El-Dib M, Massaro AN, Bulas D, Aly H. Neuroimaging and neurodevelopmental outcome of premature infants. *Am J Perinatol*. 2010;27(10):803-818.
19. Hintz SR, O'Shea M. Neuroimaging and neurodevelopmental outcomes in preterm infants. *Semin Perinatol*. 2008;32(1):11-19.
20. Leijser LM, de Bruine FT, Steggerda SJ, van der Grond J, Walther FJ, van Wezel-Meijler G. Brain imaging findings in very preterm infants throughout the neonatal period, I: incidences and evolution of lesions, comparison between ultrasound and MRI. *Early Hum Dev*. 2009;85(2):101-109.

21. Kostović I, Jovanov-Milosević N. The development of cerebral connections during the first 20-45 weeks' gestation. *Semin Fetal Neonatal Med.* 2006;11(6):415-422.
22. Kostović I, Judas M. Correlation between the sequential ingrowth of afferents and transient patterns of cortical lamination in preterm infants. *Anat Rec.* 2002;267(1):1-6.
23. Kostović I, Judas M. The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatr.* 2010;99(8):1119-1127.
24. Bradshaw JL, Sheppard DM. The neurodevelopmental frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization. *Brain Lang.* 2000;73(2):297-320.
25. Bystron I, Blakemore C, Rakic P. Developmental of the human cerebral cortex: Boulder committee revisited. *Nat Rev Neurosci.* 2008;9:110-122.
26. Kostovic I, Vasung L. Insights from in vitro fetal magnetic resonance imaging of cerebral development. *Semin Perinatol.* 2009;33(4):220-233.
27. Gressens P, Richelme C, Kadhim HJ, Gadisseux JF, Evrard P. The germinative zone produces the most cortical astrocytes after neuronal migration in the developing mammalian brain. *Biol Neonate.* 1992;61(1):4-24.
28. Evrard P, Gressens P, Volpe JJ. New concepts to understand the neurological consequences of subcortical lesions in the premature brain. *Biol Neonate.* 1992;61(1):1-3.
29. Anstrom JA, Brown WR, Moody DM, Thore CR, Challa VR, Block SM. Subependymal veins in premature neonates: implications for hemorrhage. *Pediatr Neurol.* 2004;30(1):46-53.
30. Kuban K, Sanocka U, Leviton A, Allred EN, Pagano M, Dammann O, Share J, Rosenfeld D, Abiri M, DiSalvo D, Doubilet P, Kairam R, Kazam E, Kirkekar M, Schonfeld S; Developmental Epidemiology Network. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. *J Pediatr.* 1999;134(5):539-546.
31. Paneth N, Rudelli R, Kazam E, Monte WA. *Brain Damage in the Preterm Infant.* London, England: MacKeith Press; 1994.
32. Ajayi-Obe M, Saeed N, Cowan FM, Rutherford MA, Edwards AD. Reduced development of cerebral cortex in extremely preterm infants. *Lancet.* 2000;356(9236):1162-1163.
33. Vasileiadis GT, Gelman N, Han VKM, Williams LA, Mann R, Bureau Y, Thompson RT. Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age. *Pediatrics.* 2004;114(3):e367-e372. doi:10.1542/peds.2004-0500.
34. Ross G, Tesman J, Auld PAM, Nass R. Effects of subependymal and mild intraventricular lesions on visual attention and memory in premature infants. *Dev Psychol.* 1992;28(6):1067-1074.
35. Ross G, Boatright S, Auld PA, Nass R. Specific cognitive abilities in 2-year-old children with subependymal and mild intraventricular hemorrhage. *Brain Cogn.* 1996;32(1):1-13.
36. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. *J Pediatr.* 2006;149(2):169-173.
37. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population [published correction appears in *Pediatrics.* 2001;108(2):238]. *Pediatrics.* 1995;95(2):249-254.
38. Pinto-Martin JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low-birthweight infants to motor or cognitive performance at ages 2, 6, and 9 years. *Dev Med Child Neurol.* 1999;41(12):826-833.
39. Whitaker AH, Feldman JF, Lorenz JM, Shen S, McNicholas F, Nieto M, McCulloch D, Pinto-Martin JA, Paneth N. Motor and cognitive outcomes in nondisabled low-birth-weight adolescents: early determinants. *Arch Pediatr Adolesc Med.* 2006;160(10):1040-1046.
40. Whitaker AH, Feldman JF, Van Rossem R, Schonfeld IS, Pinto-Martin JA, Torre C, Blumenthal SR, Paneth NS. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at age six. *Pediatrics.* 1996;98(4):719-729.
41. Ganat Y, Soni S, Chacon M, Schwartz ML, Vaccarino FM. Chronic hypoxia up-regulates fibroblast growth factor ligands in the perinatal brain and induces fibroblast growth factor-responsive radial glial cells in the sub-ependymal zone. *Neuroscience.* 2002;112(4):977-991.
42. Vaccarino FM, Ment LR. Injury and repair in developing brain. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(3):F190-F192.
43. Inder TE. Neurodevelopmental impact of low-grade intraventricular hemorrhage in very preterm infants. *J Pediatr.* 2006;149(2):152-154.
44. Back SA, Riddle A, McClure MM. Maturation-dependent vulnerability of perinatal white matter in premature birth. *Stroke.* 2007;38(2)(suppl):724-730.
45. Kaindl AM, Favrais G, Gressens P. Molecular mechanisms involved in injury to the preterm brain. *J Child Neurol.* 2009;24(9):1112-1118.
46. Banker BQ, Larroche JC. Periventricular leukomalacia of infancy: a form of neonatal anoxic encephalopathy. *Arch Neurol.* 1962;7:386-410.
47. Leviton A, Gressens P. Neuronal damage accompanies perinatal white-matter damage. *Trends Neurosci.* 2007;30(9):473-478.
48. Boardman JP, Counsell SJ, Rueckert D, Kapellou O, Bhatia KK, Aljabar P, Hajnal J, Allsop JM, Rutherford MA, Edwards AD. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. *Neuroimage.* 2006;32(1):70-78.
49. Lin Y, Okumura A, Hayakawa F, Kato K, Kuno T, Watanabe K. Quantitative evaluation of thalami and basal ganglia in infants with periventricular leukomalacia. *Dev Med Child Neurol.* 2001;43(7):481-485.
50. Srinivasan L, Dutta R, Counsell SJ, Allsop JM, Boardman JP, Rutherford MA, Edwards AD. Quantification of deep gray matter in preterm infants at term-equivalent age using manual volumetry of 3-tesla magnetic resonance images. *Pediatrics.* 2007;119(4):759-765.
51. Taylor HG, Minich N, Bangert B, Filipek PA, Hack M. Long-term neuropsychological outcomes of very low birth weight: associations with early risks for periventricular brain insults. *J Int Neuropsychol Soc.* 2004;10(7):987-1004.
52. Pinto-Martin J, Paneth N, Witomski T, Stein I, Schonfeld S, Rosenfeld D, Rose W, Kazam E, Kairam R, Katsikiotis V, Susser M. The central New Jersey neonatal brain hemorrhage study: design of the study and reliability of ultrasound diagnosis. *Paediatr Perinat Epidemiol.* 1992;6(2):273-284.
53. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* 1978;92(4):529-534.
54. Leviton A, Kuban K, Paneth N. Intraventricular haemorrhage grading scheme: time to abandon? *Acta Paediatr.* 2007;96(9):1254-1256.
55. Whitaker AH, Van Rossem R, Feldman JF, Schonfeld IS, Pinto-Martin JA, Tore C, Shaffer D, Paneth N. Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. *Arch Gen Psychiatry.* 1997;54(9):847-856.
56. Kuban KC, Allred EN, Dammann O, Pagano M, Leviton A, Share J, Abiri M, Di Salvo D, Doubilet P, Kairam R, Kazam E, Kirkekar M, Rosenfeld DL, Sanocka UM, Schonfeld SM; Developmental Epidemiology Network. Topography of cerebral white-matter disease of prematurity studied prospectively in 1607 very-low-birthweight infants. *J Child Neurol.* 2001;16(6):401-408.
57. O'Shea TM, Kuban KC, Allred EN, Paneth N, Pagano M, Dammann O, Bostic L, Brooklier K, Butler S, Goldstein DJ, Hounshell G, Keller C, McQuiston S, Miller A, Pasternak S, Plesha-Troyke S, Price J, Romano E, Solomon KM, Jacobson A, Westra S, Leviton A; Extremely Low Gestational Age Newborns Study Investigators. Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics.* 2008;122(3):e662-e669. doi:10.1542/peds.2008-0594.
58. 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(1):28-38.
59. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: American Psychiatric Association; 2000.
60. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: American Psychiatric Association; 1994.
61. SPSS for Windows [computer program]. Version 17.0. Chicago, IL: SPSS, Inc; 2009.
62. Jöreskog KG, Sörbom D. *Lisrel 8: User's Reference Guide.* Chicago, IL: Scientific Software International; 1996.
63. Riley GD. *Riley Motor Problems Inventory Manual.* Los Angeles, CA: Western Psychological Services; 1976.
64. Indredavik MS, Skranes JS, Vik T, Heyerdahl S, Romundstad P, Myhr GE, Brubakk AM. Low-birth-weight adolescents: psychiatric symptoms and cerebral MRI abnormalities. *Pediatr Neurol.* 2005;33(4):259-266.
65. Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KAI, Martinussen M, Dale AM, Haraldseth O, Brubakk AM. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain.* 2007;130(pt 3):654-666.
66. Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, Lewis SW, Kingsley DPE, Moseley IF, Foster O, Murray RM. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. *Lancet.* 1999;353(9165):1653-1657.
67. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Child Adolesc Psychiatry.* 2010;49(5):453-463.e1.
68. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. *Pediatrics.* 2009;123(3):1037-1044.
69. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and*

- Profiles*. Burlington: University of Vermont, Research Center for Children, Youth, & Families; 2001.
70. Hille ET, den Ouden AL, Saigal S, Wolke D, Lambert M, Whitaker A, Pinto-Martin JA, Hoult L, Meyer R, Feldman JF, Verloove-Vanhorick SP, Paneth N. Behavioural problems in children who weigh 1000 g or less at birth in four countries. *Lancet*. 2001;357(9269):1641-1643.
 71. Hudziak JJ, Althoff RR, Stanger C, van Beijsterveldt CE, Nelson EC, Hanna GL, Boomsma DI, Todd RD. The Obsessive Compulsive Scale of the Child Behavior Checklist predicts obsessive-compulsive disorder: a receiver operating characteristic curve analysis. *J Child Psychol Psychiatry*. 2006;47(2):160-166.
 72. Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychol Bull*. 2006;132(4):560-581.
 73. Huyser C, Veltman DJ, de Haan E, Boer F. Paediatric obsessive-compulsive disorder, a neurodevelopmental disorder? evidence from neuroimaging. *Neurosci Biobehav Rev*. 2009;33(6):818-830.
 74. Gerard E, Peterson BS. Developmental processes and brain imaging studies in Tourette syndrome. *J Psychosom Res*. 2003;55(1):13-22.
 75. Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol*. 2008;20(4):1251-1283.
 76. Qiu A, Crocetti D, Adler M, Mahone EM, Denckla MB, Miller MI, Mostofsky SH. Basal ganglia volume and shape in children with attention deficit hyperactivity disorder. *Am J Psychiatry*. 2009;166(1):74-82.
 77. Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R. Structural development of the basal ganglia in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Psychiatry Res*. 2009;172(3):220-225.
 78. Stanley JA, Kipp H, Greisenegger E, MacMaster FP, Panchalingam K, Keshavan MS, Bukstein OG, Pettegrew JW. Evidence of developmental alterations in cortical and subcortical regions of children with attention-deficit/hyperactivity disorder: a multivoxel in vivo phosphorus 31 spectroscopy study. *Arch Gen Psychiatry*. 2008;65(12):1419-1428.
 79. Toft PB. Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit-hyperactivity disorder? *Pediatr Neurol*. 1999;21(3):602-610.
 80. Marsh R, Alexander GM, Packard MG, Zhu H, Wingard JC, Quackenbush G, Peterson BS. Habit learning in Tourette syndrome: a translational neuroscience approach to a developmental psychopathology. *Arch Gen Psychiatry*. 2004;61(12):1259-1268.
 81. Marsh R, Zhu H, Schultz RT, Quackenbush G, Royal J, Skudlarski P, Peterson BS. A developmental fMRI study of self-regulatory control. *Hum Brain Mapp*. 2006;27(11):848-863.
 82. Marsh R, Zhu H, Wang Z, Skudlarski P, Peterson BS. A developmental fMRI study of self-regulatory control in Tourette's syndrome. *Am J Psychiatry*. 2007;164(6):955-966.
 83. Marsh R, Gerber AJ, Peterson BS. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. *J Am Acad Child Adolesc Psychiatry*. 2008;47(11):1233-1251.
 84. Matsuo K, Rosenberg DR, Easter PC, MacMaster FP, Chen HH, Nicoletti M, Caetano SC, Hatch JP, Soares JC. Striatal volume abnormalities in treatment-naïve patients diagnosed with pediatric major depressive disorder. *J Child Adolesc Psychopharmacol*. 2008;18(2):121-131.
 85. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyses DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry*. 2009;166(1):64-73.
 86. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. *J Comp Neurol*. 2002;453(2):116-130.
 87. Ulfing N. Ganglionic eminence of the human fetal brain—new vistas. *Anat Rec*. 2002;267(3):191-195.
 88. Ulfing N, Setzer M, Bohl J. Ontogeny of the human amygdala. *Ann N Y Acad Sci*. 2003;985:22-33.
 89. Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, Montrose DM, Pierri JN, Birmaher B. Frontostriatal measurement in treatment-naïve children with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1997;54(9):824-830.
 90. Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, Ivey J, Rose M, Banerjee SP, Bhandari R, Moore GJ, Rosenberg DR. Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2004;161(6):1049-1056.
 91. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K. Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. *Br J Psychiatry*. 2008;192(1):25-31.
 92. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron*. 2000;28(2):343-347.
 93. Gilmore JH, Smith LC, Wolfe HM, Hertzberg BS, Smith JK, Chescheir NC, Evans DD, Kang C, Hamer RM, Lin W, Gerig G. Prenatal mild ventriculomegaly predicts abnormal development of the neonatal brain. *Biol Psychiatry*. 2008;64:1069-1076.
 94. Robbins TW. The case of frontostriatal dysfunction in schizophrenia. *Schizophr Bull*. 1990;16(3):391-402.
 95. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V II, O'Leary DS, Ehrhardt JC, Yuh WT. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. *JAMA*. 1994;272(22):1763-1769.
 96. Beasley CL, Dwork AJ, Rosoklija G, Mann JJ, Mancevski B, Jakovski Z, Davceva N, Tait AR, Straus SK, Honer WG. Metabolic abnormalities in fronto-striatal-thalamic white matter tracts in schizophrenia. *Schizophr Res*. 2009;109(1-3):159-166.
 97. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry*. 2005;10(5):434-449.
 98. Morioka T, Hashiguchi K, Nagata S, Miyagi Y, Mihara F, Hikino S, Tsukimori K, Sasaki T. Fetal germinal matrix and intraventricular hemorrhage. *Pediatr Neurosurg*. 2006;42(6):354-361.
 99. Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, Avery L, Stewart J, Soul JS, Ringer SA, Volpe JJ, duPlessis AJ. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? *Pediatrics*. 2007;120(3):584-593.
 100. Rutter M, Graham P, Yule W. *A Neuropsychiatric Study in Childhood: Clinics in Developmental Medicine*. London, England: Heinemann/Spastics International Medical Publications; 1970. Reports 35/36.