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Long-Term Outcome of Preterm Infants and the Role of Neuroimaging

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Introduction

A recent report of the Institute of Medicine defines preterm birth as one of the major public health problems of this decade.¹ With preterm birth come preterm survivors—more every year—and as survival rates increase, the next great imperative for perinatal medicine is understanding and preventing the serious adverse neurodevelopmental outcomes of preterm birth. Neonatology as a field of medicine is recently organized, with the first Neonatal Intensive Care Unit in the United States opening in 1965 at Yale University School of Medicine and with the American Academy of Pediatrics recognizing Neonatology as a subspecialty field in 1975. Exogenous surfactant was first described as a therapy for Respiratory Distress Syndrome in 1980² and surfactant replacement therapy was first recognized in a policy statement by the American Academy of Pediatrics in 1999.³ Antenatal steroid use was formalized in an NIH consensus statement in 1994 and recognized by the American College of Obstetricians and Gynecologists shortly thereafter.⁴ These therapies have revolutionized survival rates for very preterm neonates, but many have questioned the neurodevelopmental cost. An understanding of both changing patterns of survival and emerging long-term neurodevelopmental disability is necessary to address outcome in the prematurely born.

Trends in prevalence, mortality and morbidity

From 1965 through the early 1990s, survival statistics improved annually, with steadily decreasing mortality at every gestational age and birth weight point.¹ Progress since the 1990s to the present is less clear. A review for the NICHD Neonatal Research Network in 2007 found that the infant mortality rate rose between 2001 and 2002—from 6.8 per 1000 live births to 7.0 per 1000 live births—for the first time in 4 decades, while the survival of very low birth weight infants changed “almost imperceptibly” between 1997 and 2002.⁵ At

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the same time, the overall incidence for premature birth is slowly increasing, mostly in the late preterm infant but also in the very and extremely low birth weight infant: from 1.2 percent in 1980 to 1.5 percent in 2006.⁶ These data are particularly useful because they consolidate standardized information across multiple level-3 perinatal centers.

That the incidence of neurodevelopmental disability in preterm populations has been reported to change little over time is a phenomenon documented in several reviews.¹ Taken together, then, the coincidence of increasing incidence of very and extremely low birth weight infants (501 to 1500 gm)—the same infants at highest risk for neurodevelopmental impairment—with the lack of progress in overall morbidity of these infants suggests that increasing numbers of impaired infants are surviving every year. In 2005, Wilson-Costello et al concluded just that; in their single perinatal center, while overall survival increased in the 1990s compared with the 1980s, the risk for significant neurodevelopmental impairment also increased.⁷ This study concludes that the absolute numbers of extremely low birth weight (500 to 999 gm) survivors is increasing in both the unimpaired and impaired groups.

These and other epidemiological studies are difficult to compare because of differences between institutional practices, definitions (particularly comparing birth weight categories with weeks of gestation when describing prematurity), patient populations, and follow-up parameters, but the overall trend in the United States seems to be towards an increasing number of premature births, with increasing survival rates that perhaps outpace improvements in morbidity, such that increasing numbers of both impaired and intact premature infants are surviving every year. In other words, it is possible that overall survival is increasing at the expense of intact survival, although this, too, is impossible to know until the most current generation of survivors reaches follow-up age.

Whether or not increasing incidence of impaired survival is the case, the next imperative in neonatology is to better understand the pathophysiology of preterm birth, the role of neurologic injury on neurodevelopmental impairment, and the potential for recovery in the injured preterm brain. This review will attempt to report the current understanding of neurodevelopmental outcome of premature infants in the post-surfactant/antenatal steroid era, and to describe current practices of monitoring the developing brain.

Present Status of Outcome Data

Outcome for surviving infants is defined by various neurodevelopmental impairments and by general measures of health including chronic respiratory diseases, growth parameters and recurrent infections. This review will focus on the neurodevelopmental dysfunctions. These disabilities—including cerebral palsy, mental retardation, and visual and hearing deficits—exist on a spectrum ranging from mild involvement (including learning disability, language disability, attention deficit-hyperactivity disorder and coordination, behavior, and social-emotional disorders) to profound impairment.¹ This spectrum of deficits represents the sequelae of that injury to the developing brain associated with preterm birth.

The group of premature infants born since 1995, the post-surfactant/antenatal steroid era, is just now reaching adolescence. Little data yet exist describing this cohort's neurodevelopmental outcome at adolescence and beyond. Until studies are published describing this post-1995 cohort, the next best options for understanding the present state of neonatal outcomes are 1) to examine data that describe late outcomes (adolescence and adulthood) of earlier cohorts of infants and 2) to evaluate data that describe early outcomes (toddler and childhood) of more contemporary cohorts. Both options are potentially flawed.

When looking at much earlier cohorts of infants, those born prior to the 1980s, the outcome data must be considered in light of multiple confounding variables: these studies likely

represent the hardiest of preterms who survived in an era when the norm included less aggressive resuscitations and fewer aggressive postnatal interventions (thereby selecting for the most robust of preterms), and probably represent a large percentage of small-for-gestational-age but near-term or term infants, thereby skewing results toward the favorable spectrum. Indeed, studies that describe premature infants born prior to 1950 report none-to-minimal neurodevelopmental impairment in adulthood; however, these survivors of prematurity likely represent the healthiest of preterms.^{8, 9}

Although comparing details of outcome data from multiple institutions and eras is difficult, certain themes emerge. Always, the smallest and most premature infants are at greatest risk for poor neurodevelopmental outcome, and usually, male infants are at increased risk compared with female neonates. In 2000, Saigal and her colleagues reported that 72% of adolescents less than 750 gm birth weight and 53% of those with birth weights of 750–1000 gm had significant deficits at school age; these deficits were present even in children without neurosensory impairments and in those with normal intelligence quotients.¹⁰ More recently, Larroque reported from a nationwide study in France that 42% of children born at 24–28 weeks and 31% born at 29–32 weeks needed special health care support due to neurological sequelae, compared with only 16% of those born at 39–40 weeks.¹¹ Both authors noted that, in addition to those children with the lowest gestational ages, male neonates were most vulnerable to adverse neurodevelopmental outcomes. Being female and having singleton gestation, normal intrauterine growth with increased birth weight, and a complete course of antenatal steroids are all factors associated with higher survival rates.¹²

Early Prognosticating is Unreliable

Outcome data describing more recent cohorts of infants at younger follow-up ages are limited by the testing instruments employed and the timing of the follow up. “Long term” studies often extend follow-up to only 2 or 3 years of age, which may be too early to predict prognosis at school age or beyond. One review by Voss et al. of literature describing prognostic data suggests that follow-up must be at least to age 6 years in order to make a reliable cognitive diagnosis. These authors tracked 129 preterms (median BW 794 gm and 27 weeks GA) for 6–10 years and found that cognitive developmental prognosis at term corrected age was only 49% correct, with almost 40% “false favorable overrating.” Not until age 3 and 4 years was the developmental diagnosis 70% right, and this age group still had almost 15% false favorable overrating.¹³ In this study the “too bad prognosis” (or overly negative diagnosis) remained stable at about 10–15% for all time points. While this study describes an unreliable testing experience with an emphasis on false favorable overrating, other studies describe similar poor predictive validity with an emphasis on false negative scoring. Hack et al. describe 330 preterms (mean BW 811 gm and 26.4 weeks CGA) in whom a subnormal Mental Developmental Index score at corrected age 20 months is poorly predictive of cognitive function at age 8 years. An exception is children with significant neurosensory impairment or severe abnormalities on cranial ultrasound, in whom early scores are predictive of adverse outcome at school age.¹⁴ Both Voss and Hack describe that early testing is generally unreliable for later outcome, with the exception of the most severely and obviously affected children. As will be described later, the potential for predicting the trajectory of a child’s development may be better realized with advances in neuroimaging.

Preterms at Adolescence and Young Adulthood

Recent studies describing adolescent and young adult outcome measures of premature infants report on births that occurred in the late 1970s, a time when overall survival was markedly less than it is now and when perinatal interventions did not include such

interventions as antenatal steroids and surfactant.¹⁵ The survivors described in these studies may therefore represent the most vigorous of premature infants, such that the outcomes described are perhaps skewed towards a positive outlook. An example of this situation is the recent population-based study from Norway describing nearly a million babies born between 1967 and 1983; in this study, while survival of infants at less than 27 6/7 weeks GA was only 17.8%, when these survivors were assessed at ages 20–36 years, they had rates of cerebral palsy of 9.7%, and of mental retardation (MR) of only 4.4%.¹⁶ In contrast, current status of babies born at less than 28 weeks can be extrapolated from the most recent report from the NICHD Neonatal Research Network, in which survival of babies 501–1000 gm ranges from a mean of 55–88%.¹⁷ Current status about incidence of CP and cognitive deficit in babies < 28 weeks is less reassuring, with incidence of CP in babies < 28 weeks ranging from 7–17% and MR ranging from 10–12%.¹ Nevertheless, this and other studies are heartening in the overall picture they paint of adolescent and young adult survivors. Hack et al describe a cohort of young adults born between 1977 and 1979 at a mean birth weight of 1200 grams and a mean gestational age of 29 weeks; this cohort was found to have decreased school performance at 20 years of age, but also decreased risk-taking behaviors, including substance use and abuse, contact with the police, and sexual activity.¹⁸ Similarly reassuring is a report by Saigal et al that ELBW survivors in adolescence, while recognizing and self-reporting more functional disability than term comparisons, place as high a value on health-related *quality* of life as term comparisons. This group of ELBW survivors had good self-reported quality of life despite having, as a group, 27% neurosensory impairment (compared with 2% for term comparisons) and 17% self-reported cognitive impairment (compared with 3% for terms).¹⁹ The findings of Hack and Saigal suggest that many of the outcome measures used to define success of neonatal intervention may not always contribute to the final quality of life of the survivor. Saigal also reports on a cohort of ELBW survivors in whom, even among those deemed impaired at childhood, many make a successful transition from childhood and adolescence to adulthood. Saigal describes this as a “lifetime perspective” in which, over the course of a survivor’s lifetime, subtle deficits are slowly repaired, suggesting a potential recovery of function over time.²⁰

Contemporary Preterms at Childhood

Recent studies describing school-age outcome measures of premature infants report on infants born up to the mid-1990s. These studies report outcomes that reflect the current state of neonatology, in particular the use of antenatal steroids and surfactant. Marlow et al describe a geographic cohort of extremely preterm infants (less than or equal to 25 weeks) born in 1995; at 6 years of age, this group was compared with both normative data (equivalent to a 1970s cohort) and a contemporary cohort. When compared with normative data, the preterms were found to be as impaired as would be expected from past studies; 21% had IQ scores 2 SD below the normative mean. When compared with their peers, twice as many preterms had an IQ more than 2 SD below the contemporary mean. This finding demonstrates the potential for underestimating the impairment of preterm children. This study also reports the percentage of live births surviving without severe to moderate disability: <1% of 22-week gestations, 3% of 23-week gestations, 9% of 24-week gestations, and 20% of 25-week gestations.²¹ A geographic cohort study by Anderson et al describes a group of children of less than 28 weeks or birthweight less than 1000 grams born in 1991–1992. The preterm children were compared at age 8 years with term controls in measures of cognitive ability, behavioral outcome, and educational progress, and were found to be at significantly increased risk for impairment in all three measures. The smallest infants in the preterm group (BW less than 749 grams) had significantly lower cognitive and academic scores than larger preterm infants.²² These and other recent outcome studies at school age provide a sobering reminder that the smallest, most immature infants are particularly vulnerable to injury.

Cerebral Palsy as a Marker of Outcome

Because cerebral palsy is a motor disorder of central origin, and because its incidence is inversely related to gestational age, CP is often used as a marker of neonatal outcome.²³ Follow-up results from the Swedish national prospective study suggested that, for children born in 1990–1992, the incidence of CP was 14% for infants born at 23–24 weeks' GA, 19% for those of 25–26 weeks' GA, and 3% for infants born after 27 weeks of gestation.²⁴ Furthermore, analysis of two large cohort studies suggests no change in CP rates over time for infants born at 32 weeks' gestational age or less, staying at an overall rate of 7–10%.

Cognitive Deficits

Preterm children have IQ scores ranging from within normal range to below range, but even when the scores are within 1 SD of normal they are significantly lower than those of their term peers. The youngest, most immature preterms are the most affected, and Johnson reports a decrease of 1.5–2.5 points per decreasing week of gestational age.²⁵ Importantly, many studies report parental IQ or parental educational attainment as a significant variable in favorable cognitive outcome, suggesting the potential for environmental influence and biological recovery.^{26, 27}

Neurosensory Deficits

As with other neurodevelopmental impairments, the smallest and most immature preterms are at greatest risk for neurosensory deficits as compared with term infants. Since 1970, the incidence of blindness has decreased from up to 10% to less than 3% with current cryo- and laser therapies for retinopathy of prematurity and with attention to supplemental oxygen delivery.²⁸ Even with these techniques, blindness affects up to 8% of the smallest survivors (less than 25 weeks' GA), and corrective lenses are worn by almost 25% of school-age children born at less than 26 weeks' GA compared with only 4% of term controls.²¹ Hearing deficits are similarly prevalent, with up to 7% of babies born at less than 1000 grams having severe hearing loss with unilateral or bilateral deafness. Wilson-Costello report a significant increase in severe hearing deficits from 3% in 1982–1989 to 6% in 1990–1998 in these smallest survivors.⁷ This effect was likely due to postnatal steroid use, as the same group reported a significant decrease in deafness in a subsequent era (2000 to 2002), from 6% to 1%, when postnatal steroid use decreased.²⁹ Another longitudinal review of preterms born at <28 weeks and followed until age 3 years demonstrated an incidence of permanent hearing loss at 3.1%, with no significant change from 1974–2003.³⁰

Longitudinal Outcome Studies

The longitudinal outcome studies presented in Table 1 represent a critical body of work regarding the long-term cognitive and motor impairment outcome of prematurely born infants. Taken together, these data from 1977–1995, bridging multiple generations of neonatal care and dramatically improved survival rates, imply that cognitive scores are not improving over time in preterm children as they enter adolescence and adulthood, and that the neurodevelopmental sequelae present in childhood are persisting into later life. These data highlight the need for improved understanding of the neurologic injury of preterm birth, such that neurodevelopmental outcomes are ameliorated.

Current Perspective on Neuroimaging

As we have reviewed, the neurodevelopmental disabilities of the prematurely born have been extensively described, yet the underlying alterations in brain development responsible for these changes and the time at which these changes become predictive of later outcome

remain poorly understood. New magnetic resonance image (MRI) modalities and analysis tools – including diffusion tensor imaging (DTI) and voxel based morphometry (VBM) – are contributing to the understanding of neurologic sequelae of preterm birth by providing microstructural evidence of injury sustained by the preterm brain. DTI, by assessing water diffusion in cerebral tissues, reveals important information at a microstructural level about both maturational processes and the impact of injury on the developing preterm brain. Likewise, VBM offers automated structural analysis of cerebral images in order to detect regional microstructural morphologic differences. These techniques document changes both in major white matter tracts, including the corpus callosum and internal capsule, and in those subcortical regions serving language and executive function in the prematurely born. Multiple factors including degree of prematurity, alterations in axonal microcircuitry, and vulnerability in oligodendroglial precursors may contribute to these microstructural findings. Taken together, these imaging methods demonstrate alterations in neural connectivity and cortical maturation that perhaps predict long-term outcome in the prematurely born. Given that current testing strategies are poorly predictive of later outcome, and that the markers used to define later outcome are themselves poor indicators of later quality of life, these neuroimaging techniques will likely play a critical role in predicting, understanding, and managing neurodevelopmental injury for future premature infants.

Clinical and Volumetric MRI studies

Numerous magnetic resonance imaging (MRI) studies have documented the macrostructural sequelae of premature birth in the newborn period and beyond.^{31–34} One major finding is that of decreased white matter volumes, even in relatively healthy preterm infants with no evidence of perinatal brain injury at term equivalent age, and the presumptive secondary changes in neural connectivity.^{35–39} A second important finding is that of regional vulnerability. There are regional differences in development in the human brain; these include not only the timing of maximal brain growth, but also patterns of synaptogenesis and cerebral myelination.^{40, 41} These events occur earliest in the primary sensory and motor areas, and latest in the prefrontal cortex.^{42–44} Of significance for the preterm population is the prominent maturation of the central white matter and the temporal auditory cortex during the third trimester of gestation, suggesting that those regions might be most susceptible to the injury of preterm birth.⁴⁵

Studying 8-year-old ex-preterm subjects and term control children, Reiss reported decreased white matter in the central sensory motor regions as well as in the temporal lobes of the preterm group.³⁶ Similarly, Mewes' serial studies of preterm neonates with no evidence for perinatal brain injury demonstrated moderately decreased white matter volumes when compared with matched control infants at term equivalent age.³⁹ White matter of the precentral and central region developed more slowly than that of other regions in the preterm infants, and the data suggested alterations in the course of myelination for preterms.

DTI

Diffusion tensor imaging (DTI), a recent MR modality which assesses the diffusion of water across the axes of white matter bundles, is a powerful technique to explore the structural basis of white matter and cortical development and has been used to evaluate brain injury in preterms.^{46, 47} Water diffusion is impeded by large white matter bundles which themselves delineate functional connectivity, such that the patterns of diffusion in multiple planes suggest the connectivity of anatomically remote areas. Fractional anisotropy (FA) values are a measure of fiber tract organization, and for multiple central white matter regions FA values have been noted to be significantly lower in the preterm group. Those infants with the lowest gestational ages (< 28 weeks GA) had additional reductions in FA in the external

capsule, the posterior limb of the internal capsule (PLIC), and the isthmus and mid-body of the corpus callosum,⁴⁸ and, studying preterm neonates of 26–32 weeks GA, Dudink reported a significant correlation between GA and FA of the PLIC bilaterally.⁴⁹ Taken together, these data suggest that the central white matter is the region of increased vulnerability in the developing preterm brain during the third trimester of gestation, and that this vulnerability is inversely related to gestational age.^{50, 51}

DTI parameters may provide useful neurodevelopmental outcome prognostic data. Gross motor function and CP are attributed to alterations in central white matter development in the preterm population. This has been demonstrated in a DTI study of 137 neonates by Arzoumanian, in which FA values at term equivalent age in the right PLIC were significantly lower for preterm children with cerebral palsy than those with normal motor examinations.⁵² Similarly, Drobyshevsky demonstrated that, for preterm neonates of <32 weeks' GA, the Bayley Psychomotor Developmental Index at 18–24 months correlated with FA values in the internal capsule at 30 weeks GA.⁵³ Also using DTI in 24 preterm infants at term equivalent age, Rose noted highly significant negative correlations between the left and right PLIC and the Gross Motor Functional scale when examined at age 4 years.⁵⁴

Differences in DTI parameters between preterm and term equivalents persist into adolescence. When DTI is used to evaluate VLBW preterms at adolescence, regional differences in FA are associated with neurodevelopmental impairments. Skranes showed that low FA values in the internal capsule were correlated with visual motor and visual perceptual deficits in the preterm group at age 15 years. Low FA values in the external capsule and inferior and middle superior fasciculus were correlated with low IQ. This study offers the first preliminary data indicating that abnormalities in the neonatal period persist into adolescence and that these abnormalities correlate with clinically significant injury⁵⁵ (Figures 1 and 2).

Other DTI regions not yet explored in the newborn period may also be predictive of adverse long-term outcome. Constable showed significant changes in FA in preterms compared with term controls at age 12 years, and these changes were significantly correlated with cognitive testing scores. Constable also noted gender effects; one notable finding was that of reduced FA in the uncinate fasciculus, a critical language pathway, in preterm males, associated with poor cognitive and language scores.⁵⁶

Voxel-Based Morphometry

Voxel-based morphometry (VBM) is a neuroimaging analysis technique that allows detailed anatomic investigation of the white matter microstructure. Only a few VBM studies have been performed on preterm subjects during the newborn period, but many more have examined preterm subjects at adolescence and early adulthood. In one newborn period study, Srinivasan et al noted reduced thalamic and lentiform volumes in deep grey matter in preterm-born infants at term equivalent age, when compared with term-born infants. These reduced volumes were most marked in subjects with supratentorial white matter injury.⁵⁷

Studying ex-preterm infants at age 14 years, Gimenez noted significant differences in thalamic nuclei volume between preterms and term controls; preterm thalamic volumes were significantly decreased, and these volume differences correlated with tests of verbal fluency for the ex-preterm group⁵⁸ (Figure 3). Taken together, these studies suggest that injury to deep grey matter structures is persistent into adolescence and clinically relevant, and might provide a focus for future neuroimaging follow-up studies.

Other VBM studies on ex-preterm infants at adolescence demonstrate clinically significant volume reductions, but there are as yet no neonatal studies with which to compare this work.

Isaacs conducted a neuroimaging study of ex-preterm subjects at adolescence who had been born at < 30 weeks gestation and demonstrated that absolute IQ scores were related to areas in both the parietal and temporal lobes, suggesting that emerging neonatal VBM studies in preterm subjects may also provide data with important predictive possibilities.⁵⁹ Future studies will most certainly interrogate these regions of interest in the prematurely-born at term equivalent (Table 2).

Functional MRI

Functional MRI (fMRI) is an emerging MRI modality which uses the different magnetic properties of oxygenated and deoxygenated blood to track hemodynamic activity. This map of hemodynamic activity – termed blood-oxygenation-level-dependant (BOLD) contrast – allows assessment of both resting state cerebral activity and also neural processing in response to cerebral task.⁶⁰ Although no cognitive correlations are yet described, fMRI will likely play an important role in evaluating the microstructural mechanisms that support brain development.^{61, 62} Most recently, functional neuroimaging data have been used to examine interactions between spatially distinct regions, or “functional connectivity,” in typically developing children and adolescents.^{63, 64}

fMRI has been used with reliability in ex-preterm and term-born neonates in infancy.^{65–67} Seghier et al employed DTI and fMRI to appreciate recovery from injury in the developing brain; a neonate who suffered left-sided visual cortex injury after a perinatal stroke was followed through 20 months of age, at which time there was emergence of BOLD activation in the left optical pathways where previously there had been none.⁶⁸ This report highlights two important themes: first, that the developing brain is resilient, and second, that DTI and fMRI may be used to demonstrate structure-function correlation in preterm subjects.

Evidence for alterations in neural connectivity

Multiple fMRI studies have identified functionally distinct pathways in the preterm developing brain, particularly in the realms of language and memory, and functional connectivity analyses provide additional support for these findings.^{69, 70, 71} The significance of functionally distinct pathways in the preterm brain is that such pathways might represent either compensatory paths or unpruned neonatal systems that allow the preterm to recover from the injury associated with preterm birth. A recent publication demonstrates alterations in functional connectivity for preterms at adolescence. Schafer shows that while preterms and terms at adolescence do similarly well on a simple language task, and activate similar semantic processing areas, the preterms employ different neural pathways for semantic processing.⁷² Similarly, in an auditory task by Santhouse, preterms with corpus callosum (CC) thinning exhibited greater right sided activation than the preterms without CC thinning and the term controls, suggesting that this group of preterms had developed an alternative neural pathway, presumably to compensate for the perinatal injury that resulted in CC thinning. This same group also exhibited increased right-sided activation in a visual stimulation task that required working memory, also suggesting an alternative neural pathway.⁷³

Conclusion

Preterm neonates are at high risk for neurodevelopmental disabilities. Longitudinal data from at least seven different cohorts born between 1977 and 1995 demonstrate several important points: assessment during early childhood may not be predictive of outcome at school and beyond, and, although lower than term controls, testing scores for preterm subjects are stable from school entry through adolescence.

The challenge for neonatologists and neurologists alike is identifying early markers of outcome in the prematurely born. We suggest that the role of neuroimaging in the future will be to identify the babies most at risk. We know already that DTI abnormalities present at term equivalent age and at adolescence are associated with clinically significant deficits, suggesting that the injuries present at term equivalent age might predict impairment in adolescence. Similarly, VBM changes present in term equivalent neonates are also present in adolescents, and correlate with clinically significant cognitive deficits. The next generation of neonatal outcome studies will need to evaluate a large, perhaps multi-center cohort of at-risk infants, employing multiple modalities of serial imaging and retaining the cohort for long-term follow-up.

Maureen Hack describes, in her review of outcome measures of neonatal intensive care survivors, that to best qualify and quantify disability, neonatologists need “specific measures of impairments and their residual disability” rather than subjective assessments.⁷⁴ Neuroimaging will provide those specific measures.

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ABBREVIATIONS and DEFINITIONS

BW	Birth weight
CC	Corpus callosum
CA	Corrected age
CP	Cerebral palsy
DTI	Diffusion tensor imaging
ELBW	Extremely low birth weight (< 1000 grams)
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GA	Gestational age
Late Preterm	34 – 36 6/7 weeks
MRI	Magnetic resonance imaging
PLIC	Posterior limb of the internal capsule
RA	Relative anisotropy
VBM	Voxel-based morphometry
VLBW	Very low birth weight (< 1500 grams)

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Figure 1.

Skranes has shown that the left posterior limb of the internal capsule (PLIC) is associated with visual motor and visual perceptual outcome of preterm infants at adolescence.⁵⁵ In the newborn period, the left PLIC has been shown to correlate with Bayley MDI scores in infants exposed to the Newborn Individualized Developmental Care and Assessment Program (NIDCAP).⁸⁹ Panel A shows an axial image of the left PLIC in preterm subjects scanned at age 12 years. Bayley scores for control and experimental groups at 9 months are shown in Panel B.⁸⁹

Panel A courtesy of C. Lacadie, Magnetic Resonance Research Center, Yale University.

Figure 2.

Skranes has also shown that the left external capsule is associated with lower IQ scores in preterm infants at adolescence.⁵⁵ Panel A shows an axial image of the left external capsule in preterm infants scanned at age 12 years. Total IQ scores for preterm versus term control 12 year olds evaluated by Skranes is shown in panel B.⁵⁵

Panel A courtesy of C. Lacadie, Magnetic Resonance Research Center, Yale University.

Figure 3.

Gimenez employed voxel-based morphometry to demonstrate that prematurely-born subjects have less thalamic gray at age 14 years than term control subjects. These data correlate with verbal fluency scores in the preterm group.⁵⁸ A VBM image of the thalamus of prematurely-born subjects scanned at age 12 years is shown in panel A, and verbal fluency scores for preterms versus term controls as evaluated by Gimenez is shown in panel B.

Panel A courtesy of S. Kesler, Ph.D, Stanford University School of Medicine.

Table 1

Cohorts with longitudinal follow-up

Years cohort born	BW/GA	N born	N survived	Age f/up	N evaluated	Full Scale IQ*	CP
M Hack ^{14, 75}							
1992–1995	< 1000 gm	330	238	20 months	200	MDI 75.6 +/- 16	29 (15%)
				8 years	200	MPC 87.8 +/- 19	31 (16%)
M Hack ^{76, 77}							
1977–1979	< 1500 gm	490	312	8 years	249	VIQ 95.7 +/- 18 PIQ 94.2 +/- 17.7	Not reported
				20 years	242	87 +/- 15	15 (6.2%)
F O'Brien, A Stewart ⁷⁸							
1979–1982	< 33 weeks	320	224	8 years	207	104 +/- 18	8 (5%) n = 150
				14–15 years	151	95 +/- 18	6 (4%) n = 149
HG Taylor, M Hack ^{79, 80}							
1982–1986	< 750 gm	243	73	7 years	68	MPC 87 +/- 15	9 (13%)
				11–14 years	59	Not reported	6 (10%)
JA Pinto-Martin, AH Whitaker ^{81–84}							
1984–1987	< 2000 gm	1105	901	2 years	611	MDI 105.6 +/- 19.7	113 (14.6%)
				6 years	538	SB:FE 103.4 +/- 11.9	Not reported
			868	9 years	488	98.7 +/- 14.3	Not reported
				16 years	474 non-disabled only	97.27 +/- 14.57	Not reported
B Vohr ^{85–87}							
1989–1992	600–1250 gm	505	384	4.5 years	337	86.0 +/- 15.8 to 88.9 +/- 17.8	23 (7%)
				8 years	328	85 +/- 24 to 95.7 +/- 18	26 (7.9%)
				12 years	375	87.9 +/- 18.3	Not reported
S Saigal ^{10, 88}							
1977–1982	501–1000 gm		169	8	113 (only 1977–1981 evaluated)	91 +/- 16	Not reported
				12–16	150 (full cohort evaluated)	89 +/- 19	Not reported

* GCIMcCarthy General Cognitive Index

*MDI Mental Developmental Index of the Bayley Scales of Infant Development

*MPC Mental Processing Composite

*SB:FE Composite Index of the Stanford Binet: Fourth Edition

If not otherwise noted, IQ is full scale IQ from the Wechsler Intelligence Scales for Children.

Table 2

MRI markers of outcome

Author	Number	GA/BW	MRI age	Age Follow-up	MRI change	Clinical correlate
DTI						
Als ⁶⁹	30 PT	28–33 wks	2 weeks CGA	18–24 months	Higher RA Left IC in early intervention group	Improved behavioral function at 9 months correlated with DTI changes
Arzoumanian ⁵²	63 PT	< 33 wks, < 1800 gm	Term	18 – 24 mo CGA	Reduced FA in Right Posterior IC	Abnormal neuro exam, +/- CP, correlated with DTI changes
Skrane ⁵⁵	34 PT, 47 T	BW < 1500 gm	15 years	15 years	Reduced FA in IC, EC, CC, and sup, mid sup and inf fasciculus	Low FA in EC and inf and mid sup fasciculus correlated with low IQ
VBM						
Srinivasan ⁵⁷	40 PT, 8 T	< 34 wks	Term		Thal/lentiform nucleus volumes significantly smaller than term controls	
Gimenez ⁵⁸	30 PT, 30 T	< 33 wks	14 years	14 years	Several thalamic nuclei significantly smaller than term controls	Poor semantic fluency correlated with decreased thalamic volumes

CC Corpus Callosum
 DTI Diffusion Tensor Imaging
 EC External Capsule
 FA Fractional Anisotropy
 IC Internal Capsule
 PT Preterm
 RA Relative Anisotropy
 T Term
 VBM Voxel Based Morphometry