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Advanced neuroimaging and its role in predicting neurodevelopmental outcomes in very preterm infants

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Abstract

Up to 35% of very preterm infants survive with neurodevelopmental impairments (NDI) such as cognitive deficits, cerebral palsy, and attention deficit disorder. Advanced MRI quantitative tools such as brain morphometry, diffusion MRI, magnetic resonance spectroscopy, and functional MRI at term-equivalent age are ideally suited to improve current efforts to predict later development of disabilities. This would facilitate application of targeted early intervention therapies during the first few years of life when neuroplasticity is optimal. A systematic search and review identified 47 published studies of advanced MRI to predict NDI. Diffusion MRI and morphometry studies were the most commonly studied modalities. Despite several limitations, studies clearly showed that brain structural and metabolite biomarkers are promising independent predictors of NDI. Large representative multicenter studies are needed to validate these studies.

Keywords

Infant; Premature; Magnetic resonance imaging (MRI); Morphometry; Diffusion MRI; Functional MRI; Magnetic resonance spectroscopy; Brain metabolites; Microstructure; Cerebral palsy; Cognitive impairment; Neurodevelopmental impairment

Introduction

Every year in the United States, more than 100,000 babies are born very preterm (at ≤32 weeks gestational age). Up to 35% of these infants develop cognitive, behavioral, and/or psychological abnormalities and 10% develop cerebral palsy (CP), thereby increasing their risk for poor educational, health, and social outcomes.[1–3] The continuing high incidence of preterm births in the United States and worldwide—1 out of every 9 births[4]—coupled with improving survival rates that exceed 90% in developed countries is contributing to an increased prevalence of survivors with such neurodevelopmental impairments (NDI).[5,6] The societal economic impact of lifetime care for persons born with CP and cognitive deficits in the United States is estimated to be $15 billion and $64 billion annually, respectively.[7]

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Children with CP typically do not receive a clinical diagnosis until 2 years of age. Cognitive deficits and behavioral/psychological abnormalities cannot be reliably diagnosed until 3–5 years of age.[8–10] Yet, in the first 3 years after birth, the brain undergoes dramatic growth, and trillions of synaptic connections are laid down.[11] These sensitive early years are critical for neuroplasticity.[12] Early diagnosis of developmental disabilities using traditional means is however unlikely because neurologic function is still very immature at birth. Development of imaging prognostic biomarkers at birth could fill this critical need for early diagnosis. Such an advance would facilitate targeted delivery of evidence-based infant stimulation programs or new neuroprotective interventions[13–15] after neonatal intensive care unit (NICU) discharge to preserve brain development and/or promote neuroplasticity. Prognostic biomarkers could also be developed into surrogate endpoints of NDI at term-equivalent age (TEA) for more efficient testing of neuroprotective clinical trials during the initial neonatal intensive care stay.

How accurately do existing biomarkers or statistical models in the neonatal period predict NDI in very preterm infants? Several large studies from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network have attempted to answer this question using clinical risk factors at the time of preterm birth, during the NICU hospitalization, and at NICU discharge.[16–18] Two of these studies also developed risk prediction calculators to help clinicians counsel families about their infant's risk of NDI.[16,17] While these studies did improve prediction accuracy over existing prognostic models, they are still unable to accurately identify eligible babies for early intervention therapies and neurodevelopmental follow-up. Further, they did not examine the value of conventional structural MRI (sMRI) during the initial NICU hospitalization or at TEA. Hintz et al.[19] examined the incremental value of sMRI over clinical factors and early and late cranial ultrasound (US) findings in predicting NDI or death at 18–22 months' corrected age (CA) in 480 extremely preterm infants. The addition of sMRI had only a small impact on prediction accuracy because most major lesions other than cerebellar hemorrhages were readily visible on cranial US. These results are similar to other large qualitative sMRI studies[20] and to a recent meta-analysis of all sMRI studies at TEA in very preterm infants.[21] This meta-analysis examined the prognostic value of white matter abnormalities on term MRI to predict individual and combined NDIs. For moderate to severe WMA, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio to predict CP at ≥18 months was, 67%, 92%, 8.1, and 0.4, respectively and for mental development was, 38%, 87%, 3.0, and 0.7, respectively. Prognostic test properties for a qualitative diagnosis of diffuse excessive high signal intensity (DEHSI) in predicting NDI were even lower.[21]

Clearly, a critical gap continues to exist and there is an urgent need for more effective imaging tools and early prognostic biomarkers. In order to improve prediction accuracy, such biomarkers have to be objective, thereby reducing or ideally eliminating measurement error. They also need to be sensitive, so that subtle structural and functional connectivity and metabolic abnormalities can be accurately diagnosed. Advanced MRI techniques such as volumetric MRI (vMRI), diffusion tensor imaging and diffusion MRI (dMRI), magnetic resonance spectroscopy (MRS), and resting-state functional connectivity MRI (fcMRI) appear to be ideally suited to address these needs (see Toa and Neil[22] for a technical review).

Each of these modalities appears to be more sensitive than sMRI and able to offer complementary brain measurements such as regional volumes, metabolites, microstructural connectivity, and functional network connectivity. The image analysis tools for these novel technologies are increasingly being automated, thereby eliminating subjective human assessments. Their quantitative nature lends far greater study power as compared to categorical measures from cranial US and sMRI. The higher reliability and reduced measurement error also increase study power and improve prediction validity. Overall, these advanced modes of MRI give the best opportunity to identify and develop powerful prognostic biomarkers and surrogate endpoints for clinical trials. The goal of this review is to determine the independent ability of advanced brain MRI biomarkers at TEA to predict NDI in very preterm infants.

Methods

A systematic search strategy was employed to identify and critique all published early advanced MRI studies that predicted one or more neurodevelopmental impairments at 18 months CA or later in very preterm infants. The following inclusion criteria and definitions were used to select eligible studies: (1) very preterm infants, born at or below 32 weeks gestational age (GA) or very low-birth-weight infants (BW < 1500 g); (2) advanced brain MRI: any MRI study that performed dMRI, MRS, fMRI, or quantitative measures of brain macrostructure (morphometry) or lesions; (3) TEA: 37–42 weeks postmenstrual age (PMA); and (4) neurodevelopmental impairment: CP, cognitive or intellectual impairments, social–emotional problems, and/or behavioral/psychological abnormalities diagnosed at a minimum age of 18 months CA or later. Additionally, only longitudinal cohort, nested cohort, and case–control studies were included in the analyses. A few studies that predominantly studied very preterm or very low-birth-weight infants but also included slightly more mature infants (e.g., 33 and 34 weeks' GA) were permitted for inclusion. Only full-text articles were included in this study.

Medline/PubMed database was searched on 3/15/16 using the following systematic search strategy that included Medical Subject Heading (MeSH) and few non-MeSH search terms: ("infant, premature" OR "infant, low-birth-weight") AND ("diffusion tensor imaging" OR "diffusion magnetic resonance imaging" OR "connectome" OR "DTI" OR "diffusion tensor tractography" OR "DTT" OR "functional neuroimaging" OR "magnetic resonance imaging" OR "fMRI" OR "fcMRI" OR "functional connectivity" OR "magnetic resonance spectroscopy" OR "brain/metabolism" OR "brain mapping" OR "brain volume") AND ("neurodevelopmental disorders" OR "developmental disabilities" OR "disability evaluation" OR "cerebral palsy" OR "motor disorders" OR "cognition disorders" OR "cognitive" OR "intellectual disability" OR "intelligence" OR "language development disorders" OR "Bayley" OR "behavior" OR "mental competency" OR "mental disorders" OR "autism spectrum disorder" OR "autistic disorder" OR "attention deficit disorder with hyperactivity" OR "ADHD" OR "child behavior disorders"). The PsycINFO database was also searched for additional relevant articles.

Retrieved articles were screened based on the title and abstract for definite exclusions. For the remainder, full text of each article was accessed and the eligibility criteria applied. Last,

the bibliography of all eligible full-text articles was hand-searched for additional eligible articles. Eligible articles were critically appraised using the Critical Appraisal Worksheet for prognostic studies.[23] Answers to the following questions were sought: (1) Were infants representative of the underlying population; (2) Was reliability of image processing methods adequately tested; (3) Were outcomes clearly defined and evaluated masked to imaging and other prognostic data; (4) What was the follow-up rate at ≥18 months CA; (5) Were there systematic differences in infants with and without follow-up in relation to prognostic factors; (6) Were advanced MRI biomarkers independently/incrementally predictive over known prognostic factors of NDI; (7) Were prognostic test properties such as sensitivity, specificity, and likelihood ratios reported; (8) How precise were the estimates; and (9) Was the prognostic model internally validated?

Results

The search strategy retrieved 438 articles published between August 2001 and December 2015. After articles were reviewed for definite exclusions and the bibliography of eligible articles was hand-searched, 47 articles met the inclusion criteria. The Table presents a list of each of the studies and summarizes their inclusion criteria; advanced MRI measures tested, identified prognostic biomarkers and associated NDI. Overall, the following three types of advanced MRI methods have been tested as prognostic biomarkers of NDI in very preterm infants: (1) morphometric; (2) MRS; and (3) dMRI. No fMRI studies attempting to predict NDI were found. Nine studies evaluated more than one advanced MRI method. Morphometric and dMRI were the most common type of studies, with each modality being tested and reported in 25 studies each. Although MRS has been around the longest, only five studies investigated brain metabolites in very preterm infants. None of the studies reported the value of multimodal advanced MRI biomarkers in predicting NDI in very preterm infants. Most studies used a 1.5 T MRI scanner but more recent studies reported use of 3.0 T scanners in neonates. While a vast majority of studies reported outcomes at 18–24 months CA, a few, primarily from Australia, predicted outcomes up to 7 years of age. The most common outcomes studied included cognitive, language, and motor development at 18–24 months CA as assessed on the Bayley Scales of Infant and Toddler Development (Second or Third Editions; Bayley-II or Bayley-III) and neuromotor exam. More than 90% of these studies were single-center cohorts from level three academic centers from developed nations around the world. There was great variability in image processing tools, regions of brain studied, and outcomes. Due to such excessive heterogeneity, no attempt was made to pool study results for a meta-analysis of prognostic test properties (Table).

The majority of morphometric studies measured brain volumes using conventional or 3-dimensional (3D) MRI sequences. Most studies used manual segmentation approaches to measure structural volumes and neonatal brain atlases for automated tissue/regional volumes. Smaller studies examining brain volumes tended to show a stronger correlation with outcomes, while some larger studies showed no association with cognitive, language, or motor outcomes. A few studies measured brain regions or structures on single slices (e.g., 1D or 2D width and/or height) or determined the shape of structures. Several of these morphometric measures were predictive of NDI. In particular, biparietal width and inter-

hemispheric distance were both predictive of mental and psychomotor development at 2 years CA.[43]

Three studies employed voxel/deformation-based morphometry to determine differences in brain volumes between very preterm and healthy term controls to identify prognostic biomarkers.[35,46,48] Two of these studies reported an association with long-term developmental outcomes up to 7 years of age.[46,48] Two studies reported different automated methods for quantifying DEHSI abnormalities, the most common finding on brain MRI at TEA. Both studies found a strong association between volume of DEHSI and cognitive and language scores on the Bayley-III at 2 years of age.[41,65]

Of the five studies that evaluated the association between MRS and NDI, four identified several prognostic biomarkers, including NAA/choline and NAA/myoinositol metabolite ratios in a variety of white and gray matter regions that were predictive of cognitive, language, and/or motor scores on the Bayley-III.[39,50–52] Three studies utilized single-voxel and two evaluated multi-voxel chemical shift imaging to identify biomarkers. Measurements of NAA/Choline in the central white matter and deep nuclear gray matter were the most predictive of NDI.

Overall, 25 published studies examined regional and/or global microstructural brain development on dMRI and associated these quantitative measurements with one or more NDI outcomes. The vast majority of these studies (23 of 25) reported at least one significant association. While a few studies performed diffusion weighted imaging only (three directions), the rest performed diffusion tensor imaging and none reported use of higher order dMRI models such as diffusion spectrum imaging and high angular resolution diffusion imaging to predict NDI. Diffusion tensor tractography was reported in three studies; all three examined the genu, splenium, and/or whole CC fiber bundle.[40,59,64] Two also examined sensorimotor fiber microstructure running through the posterior limb of the internal capsule.[59,64] In all, 9 of the 25 studies used semi-automated or automated methods to query regional and whole-brain microstructure.

Several patterns emerged following critical appraisal of all the studies. All but two of the studies were from single-center, academic level III/IV NICUs and hence were not representative of the underlying population. For studies that used manual segmentation or region of interest placements, inter-rater reliability (and intra-rater reliability for some studies) was often not reported. Increasingly however, studies employed automated methods to reduce measurement variability. The accuracy and availability of these methods in neonates has improved greatly over time. All studies defined NDI outcomes, but only half reported that outcome assessors were masked to imaging and/or other prognostic data. The follow-up rate at 18 months CA or older was not reported in a few studies and rates for the other studies ranged from 59% to 100%. Assessment for systematic differences in prognostic factors between infants with and without follow-up was not possible for a majority of studies because this data was not reported. Approximately two-thirds of the studies demonstrated that advanced MRI biomarkers were independently predictive over known prognostic factors (e. g., sMRI) of NDI. Three studies reported prognostic test

properties such as sensitivity and specificity and none reported likelihood ratios. Two out of the 47 studies reported that they internally validated their prognostic model.[48,67]

Discussion

This systematic search yielded 47 unique studies that examined the value of advanced MRI biomarkers in predicting NDI at 18 months CA or older. A majority of these studies identified one or more novel brain metabolite, morphometric, or microstructural prognostic biomarkers that were predictive of NDI (Figure 1). Studies that tested dMRI parameters were more likely to report identification of one or more significant prognostic biomarker(s) as compared to vMRI studies. However, the risk of publication bias cannot be ruled out because negative studies are less likely to be submitted or accepted for publication.[71,72] Irrespective of the type of advanced MRI modality utilized, a few brain regions were identified in three or more studies to be predictive of outcomes: corpus callosum, cerebellum, centrum semiovale, sensorimotor, subcortical nuclei, and posterior limb of the internal capsule. Most studies reported outcomes around 2 years CA. Because of our currently limited ability to accurately evaluate cognitive, executive, and behavior function at this early age, additional studies with longer follow-up are needed to fully assess the value of prognostic biomarkers.[8]

Considering the recent development of this area of research, most studies were not representative of the underlying population. Study sample sizes ranged from 10 to 297 very preterm infants with a large majority enrolling less than 100 subjects. About one-third of studies simply compared quantitative MRI measurements between infants with and without NDI and/or did not evaluate the incremental predictive value of significant biomarkers over known prognostic factors of NDI such as injury on sMRI. Analyzed studies rarely reported sensitivity, specificity and likelihood ratios or performed internal validation using cross-validation techniques such as bootstrap.[73] The objective of many of these studies was likely to uncover mechanisms rather than to predict outcomes. Nevertheless, reporting prognostic test properties facilitates ready adoption into clinical practice and ideally improves counseling of families. Furthermore, as scientific investigations have increasingly come under scrutiny for lack of reproducibility, internal validation (followed by external validation) is more important than ever.[74]

Despite such limitations, these studies show that quantitative brain structural and metabolite measurements are promising as prognostic biomarkers of NDI. However, in order to move closer to clinical translation, studies will need to (1) enroll an inception cohort from a geographically defined region, (2) use more objective measures of brain development/injury, and (3) employ a combination of promising multimodal biomarkers to yield robust prognostic models capable of accurate prediction of individual impairments. In addition to utilizing proven approaches such as multivariable regression techniques, use of newer multivariable pattern classification algorithms (e.g., machine learning) may further enhance the ability to accurately predict long-term NDI.[75] These algorithms would ideally discriminate between NDI subgroups of cognitive, behavioral, or motor impairments on the basis of multimodal neuroimaging data (Figure 2). This approach is particularly suited for

the development of MRI-based biomarkers that can be used for phenotypic stratification of patients with different types of developmental impairments.

Of the advanced MRI studies that reported a strength of association with cognitive outcomes, the two studies that objectively quantified DEHSI in the centrum semiovale WM, showed the strongest correlation between DEHSI volume and cognitive and language scores.[41,65] Four additional studies that examined the centrum semiovale also found a significant correlation between diffusion metrics or brain NAA/Choline and cognitive and language scores at 18–24 months CA.[35,50,54,60] This finding is in distinct contrast to studies that have qualitatively evaluated DEHSI and found no association with outcomes.[76–79] One likely explanation for such contrasting outcomes is the inherent subjectivity of qualitative MRI readings. Qualitative assessment of the presence of DEHSI exhibits low intra- and inter-rater reliability.[80,81] Even advanced MRI studies are susceptible to such concerns. Several of the advanced MRI studies in this review did not report the reliability of brain measurements and those that did usually did not report more robust measures such as within-subject standard deviation and repeatability.[82,83] These data suggest a need and an opportunity for objective measures of brain injury and aberrant development. The recent development of neonatal atlases and automated image processing methods can directly address such concerns and reduce measurement error.

There has been increasing interest in studying functional brain networks with resting-state and task-based fMRI. Perhaps because of the more recent development of this tool and associated infant-friendly image-processing techniques, this systematic search did not identify any studies using fMRI functional measures to predict outcomes. Nevertheless, early studies that have examined development of functional networks in very preterm infants have identified dramatic changes in sensory, motor, and executive functional networks over the first 6 months of life that may prove to be independent predictors of NDI.[84–86] For example, new unpublished data from an ongoing longitudinal cohort showed significant connectivity differences in 4 somatosensory and motor networks in 18 very preterm infants without CP as compared to 5 very preterm infants with CP, as diagnosed at 24 months CA (Figure 3). For each of the four regions studied, preterm infants with CP exhibited an overall reduced sensorimotor connectivity as compared to infants without CP.

This systematic review has several limitations. Only two databases were searched and non-English studies were not evaluated. Additionally, only the study author performed the systematic review and critical appraisal. However, hand searches of reference lists should have reduced such biases. Also, few non-English studies were identified and the likelihood that other databases (e.g., CINAHL and EMBASE) would exclusively index neonatal advanced MRI studies is low. The value of predicting NDI outcomes for clinical care remains a matter of debate and discussion.[87,88] Part of this debate arose from inappropriate use of early imaging results to limit intensive care. Unfortunately, the data to support this practice is not available and therefore is prone to errors in prediction and self-fulfilling prophecies. While the evidence is limited,[89] most parents are desirous for more accurate long-term prognostic information, especially by TEA, in order to properly plan post-discharge early intervention support services.

Clinical translation aside, there is great enthusiasm for applying prediction biomarkers/models for early risk stratification so that randomized trials can offer targeted early intervention or neuroprotective therapies to the highest risk infants. To date, clinical trials of neuroprotective interventions have shown small to moderate effect sizes. This is not surprising considering there is genotypic and phenotypic variability with NDI, even when you consider impairments individually. With successful early risk stratification, treatments and interventions can be tailored to the patient's specific predicted motor, cognitive, or behavioral outcome phenotypes. This approach could significantly increase the effect size of interventions in large-scale clinical trials. The development of advanced MRI prognostic biomarkers as surrogate outcomes could also facilitate testing of neuroprotective interventions soon after birth and well before NICU discharge. Currently, it costs approximately $2.6 billion to bring a successful drug to market due to the many drugs that fail in the pipeline and the huge costs of clinical trials.[90] Surrogate outcomes could facilitate: (1) shorter pre-clinical development phase for neuro-protective drugs; (2) use of the same outcome measure for experimental and early phase human trials; and (3) reduced need to evaluate NDI for phase I/II trials.

What are some exciting future developments to expect in this fast evolving research area? One likely development will be the use of combined advanced MRI, genomic/epigenetic biomarkers and sophisticated pattern classification techniques to make personalized predictions for high-risk infants a reality (Figure 4). Newer developments in infant magnetoencephalography[91] and bedside monitoring tools (e.g., high-density EEG and near infrared spectroscopy)[92,93] may also yield novel complementary biomarkers. Such advances will facilitate targeted early intervention therapies and novel neuroprotective interventions to enable improved developmental outcomes. These findings may also be readily translatable to full-term newborns with neonatal encephalopathy, neonatal stroke, and complex congenital heart disease that face an equally high risk of developing disabilities.

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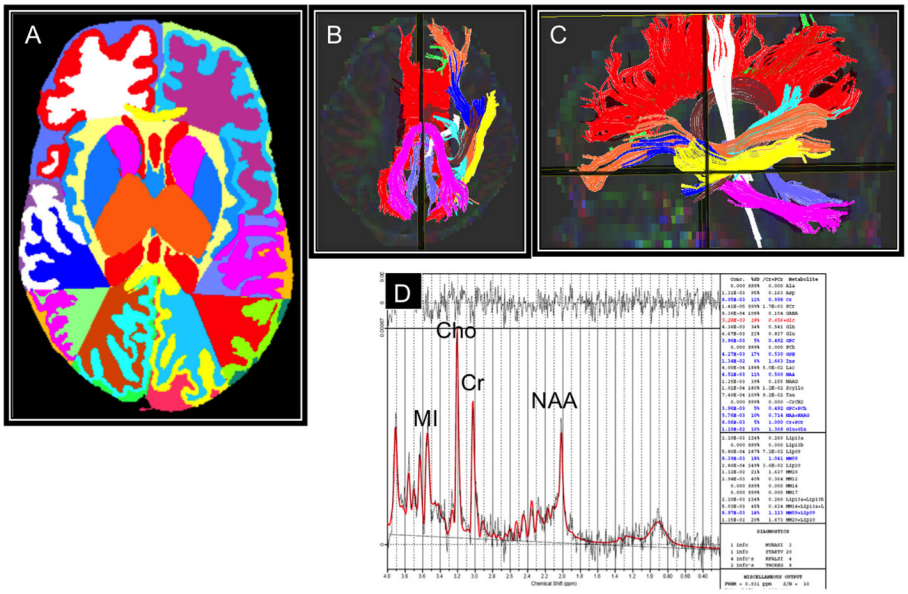

Fig. 1.

Examples of brain advanced MRI measurements including morphometry (A), diffusion tractography (B and C), and magnetic resonance spectroscopy (D). Representative advanced MRI examples at term-equivalent age display an extremely low-birth-weight infant's brain that was segmented into tissues classes, subcortical structures, and lobes (A), 10 white matter tracts, displayed in axial and sagittal orientations (B and C), and a proton MRS spectrum displaying the four main metabolites, including N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myoinositol (MI).

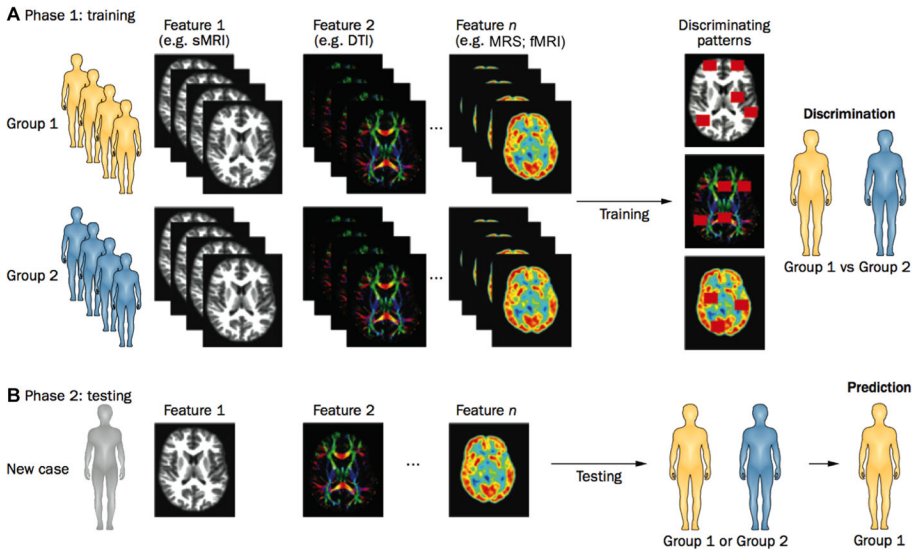

Fig. 2.

Use of multivariable pattern classification to discriminate between multiple subgroups of very preterm infants with cognitive, behavioral, or motor impairments on the basis of multimodal neuroimaging data. (A) Pattern classification models are initially trained (Phase 1) on well-characterized phenotypic data obtained by structural MRI, DTI, MRS, and/or fMRI to identify patterns of potentially discriminative features. (B) These patterns can then be used to determine whether an individual patient in the validation cohort should be assigned to the impaired or control group (Phase 2). Abbreviations: sMRI, structural MRI; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; fMRI, functional MRI. (Adapted with permission from Ecker and Murphy,[75] copyright 2014.)

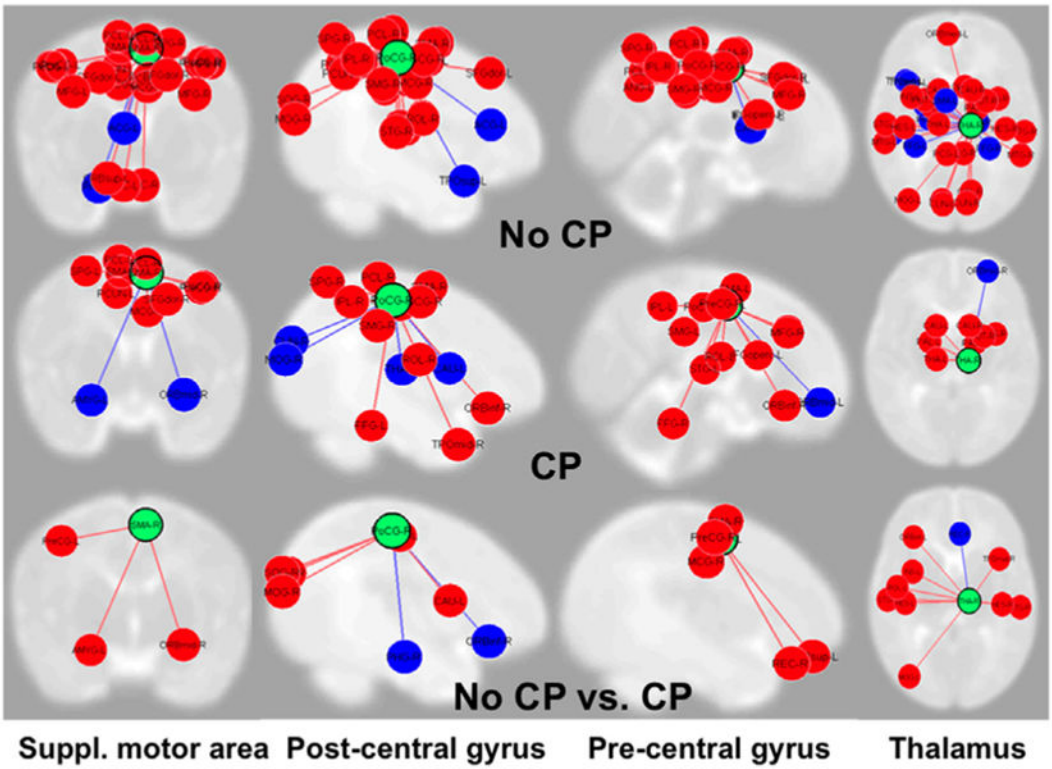

Fig. 3.

Functional connectivity MRI from 4 somatosensory and motor networks from 5 very preterm infants with cerebral palsy (CP) and 18 without CP. The columns and green circles represent the four sensorimotor regions of interest, including supplementary motor area, post-central gyrus, pre-central gyrus, and thalamus. The red and blue circles represent regions of the brain they are connected with; red signifies a positive correlation while blue represents a negative one. Infants with CP exhibited fewer sensorimotor connections (middle panel) than those without CP (top panel). The last panel displays several networks that were present in infants without CP (red connections) but were absent in infants with CP and a few hubs (blue) where infants with CP (blue) had more connections than those without CP.

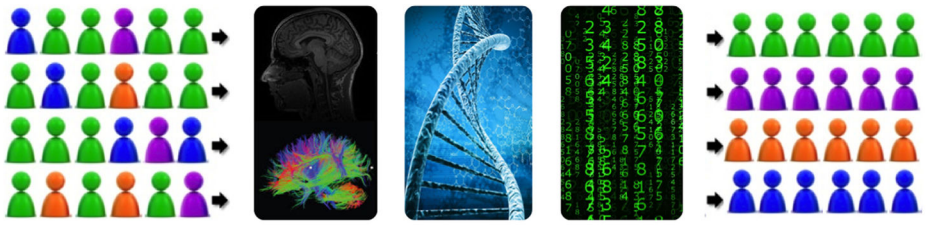

Fig. 4.

The combined use of advanced MRI, genomic/epigenetic biomarkers and sophisticated pattern classification algorithms will make personalized predictions for high-risk infants a reality. A combination of biomarkers from advanced brain MRI and genomic/epigenetic biologic samples and pattern classification algorithms such as machine learning are ideally suited to classify the current heterogeneous mix of very preterm infants into different risk groups. This will facilitate the delivery of more effective personalized treatments for very preterm infants.

Table

Summary of studies found via systematic search of early advanced MRI in very preterm infants and prediction of NDI at 18 months CA or later.

Citation	Subjects	MRI details	Biomarker(s)	Outcome
Morphometric analyses				
Valkama et al.[24]	50 Infants <34 weeks GA and <1800 g BW	1.0 T magnet; eight 1-dimensional brain stem measurements	Medulla oblongata, pons, and mesencephalon	CP and permanent hearing loss at 18 months CA
Peterson et al.[25]	10 “Medically stable” infants (GA and BW not provided)	1.5 T; total brain WM, GM, ventricular, and parcellated lobar volumes	Right sensorimotor and midtemporal WM volumes	Bayley Scales II MDI scores at 18–20 months CA
Woodward et al.[26]	76 Infants ≤32 weeks GA and <1500 g BW	1.5 T; automated regional and total tissue volumes	Sensorimotor, parietooccipital, and premotor regional volumes	Object working memory task
Kapellou et al[27] and Rathbone et al.[28]	63 and 82 Infants <30 weeks GA, respectively; TEA as late as 48 weeks PMA	1 T; cerebrum volume and cortical surface area segmented semi-automatically between 24 and 44 weeks PMA	Cortical surface area and cerebral volume growth	Multiple cognitive and psychological outcomes at 2 and 6 years of age
Shah et al.[29]	83 Infants ≤32 weeks GA	1.5 T; manually segmented cerebellar volume	None	No association with Bayley II MDI or PDI scores
Shah et al.[30]	68 Infants ≤33 weeks GA and <1500 g BW	1.5 T; automated volumes of five cerebral tissue subtypes and eight regions bilaterally	Inferior occipital regional volume	Several measures of oculomotor control
Beauchamp et al.[31]	156 Infants <30 weeks GA and <1250 g BW	1.5 T; manual segmentation of hippocampi and automated regional tissue and lobar volumes	Bilateral hippocampal volumes	Delayed alternation, a measure of working memory
Thompson et al.[32,33] and Rogers et al.[34]	184 Infants <30 weeks GA and <1250 g BW	1.5 T; manually segmented hippocampi volume and shape; bifrontal diameter, bilateral frontal heights, and transverse cerebellar diameter	Hippocampal volume	Mental development at 2 years CA; social–emotional difficulties at 5 years; verbal and visual memory at 7 years
Boardman et al.[35]	80 Infants ≤34 weeks GA	1.5 T; regional volumes derived from deformation-based morphometry	None	No association with Griffiths DQ at mean chronological age of 28 months
Lind et al.[36,37]	97 and 164 infants, respectively with BW <1501 g and GA <37 weeks	0.23 T and 1.5 T; total and regional tissue and structural volumes segmented manually	Cerebellum	Motor outcome; no associations with behavioral measures at age 5 years
Tich et al.[38]	187 Infants <30 weeks GA and <1250 g BW	1.5 T; bifrontal, biparietal and transverse cerebellar diameter	Biparietal diameter	Mental and psychomotor development on the Bayley II MDI and PDI at 24 m CA
van Kooij et al.[39]	112 Infants <31 weeks GA	3.0 T; automated cerebellar volumes	Cerebellar volumes	Cognitive scores on Bayley-III (no association with motor scores)
Thompson et al.[40]	106 Infants <30 weeks GA and/or <1250 g BW	1.5 T; corpus callosum area and shape	Circular corpus callosum	Mental development on the Bayley II MDI at 2 years CA
He et al.[41]	38 infants ≤1000 g BW	3 T; volume of objectively defined	DEHSI volume	Cognitive and language development on the

Citation	Subjects	MRI details	Biomarker(s)	Outcome
		DEHSI abnormalities using clinical T2-weighted images		Bayley III at 18–22 months CA
Bora et al.[42]	110 Infants ≤32 weeks GA	1.5 T; cortical and subcortical GM, WM, and CSF volumes	Total brain tissue volume and dorsal prefrontal, subgenual, and sensorimotor regional volumes	Inattention/ hyperactivity subscale of the strengths and difficulties questionnaire at ages 4, 6, and 9 years
Kidokoro et al.[43]	297 Infants from three cohorts with GA <30 weeks GA and MRI at TEA	1.5 T and 3.0 T; biparietal width and inter-hemispheric distance measured on coronal T2w images	Biparietal width and inter-hemispheric distance	Mental and psychomotor development on the Bayley II MDI and PDI at 2 years CA
Park et al.[44]	90 Infants <1000 g BW and 1000—1499 g BW with clinical indication for MRI (10 were from latter group)	3.0 T; anterior–posterior length of the CC and transcerebellar diameter on conventional sMRI	Anterior–posterior length of the CC and transcerebellar diameter	Mental and psychomotor development on the Bayley II MDI and PDI; CP; and NDI
Paul et al.[45]	27 Infants <30 weeks GA without severe brain injury and scans at TEA	3.0 T; total cerebral volume and cortical surface area	None	No association with Bayley III cognitive, language, or motor scores
Skiold et al.[46]	27 Infants <27 weeks GA at birth with no injury on conventional MRI at TEA	1.5 T; voxel based morphometry; automated regional and total brain volumes	Cerebellum, white matter, and cortical gray matter volumes	Cognitive and language development on Bayley III at 30 months CA
Young et al.[47]	65 Infants <33 weeks GA and MRI at TEA	1.5 T; automated total and regional brain volumes	Volumes of caudate, putamen, and globus pallidus nuclei	Cognitive, language, and visual motor integration on standardized tests at 4 years
Ullman et al.[48]	153 Infants <30 weeks GA and <1250 g BW	1.5 T; deformation-based morphometry	Insula and putamen volumes	Mathematical ability and working memory at 5 and 7 years
Magnetic resonance spectroscopy				
Augustine et al.[49]	36 Infants ≤32 weeks GA and/or ≤1500 g BW	1.5 T; multivoxel MRS from deep nuclear GM and superior WM/GM	None	No association with Bayley II MDI or PDI scores
van Kooij et al.[39]	58 Infants <31 weeks GA	3.0 T; single-voxel MRS in cerebellum	NAA/choline in cerebellum	Cognitive scores on Bayley-III (no association with motor scores) at 2 years CA
Chau et al.[50]	177 Infants 24–32 weeks GA	1.5 T; multivoxel chemical shift imaging in the centrum semiovale and basal ganglia	NAA/choline in centrum semiovale WM and basal ganglia	Cognitive, language, and motor outcomes on Bayley III at 18 months CA
Bapat et al.[51]	38 Infants ≤1000 g BW	3.0 T; single-voxel MRS in hippocampus, subventricular zone and cortex	NAA/choline in subventricular zone and cortex; NAA/myoinositol in subventricular zone	Cognitive and language development on Bayley- III at 18–22 months CA
Hart et al.[52]	67 Infants <35 weeks GA	1.5 T; single-voxel MRS in anterior and posterior WM	NAA/choline, NAA/Cr and lactate in posterior WM	Cognitive, language, and fine motor outcomes on Bayley III at 18 months CA
Diffusion MRI				
Arzoumanian et al.[53]	63 Infants <34 weeks GA and <1800 g BW with no gross injury on anatomic MRI	1.5 T; 6-direction DTI: whole-brain histogram analyses; manual ROI placements in the CC, cerebral WM, anterior	FA of posterior limb of the internal capsule (right)	CP and minor motor abnormalities 18–24 months CA

Citation	Subjects	MRI details	Biomarker(s)	Outcome
		and posterior limb of the internal capsule, subcortical GM nuclei		
Krishnan et al.[54]	38 Infants ≤34 weeks GA and without severe WM abnormality	1.5 T; 3-direction DWI; ADC from manually drawn ROIs in centrum semiovale bilaterally	Centrum semiovale ADC	DQ on Griffith Mental Development Scales at 2 years
Drobyshevsky et al.[55]	24 Infants <32 weeks GA	MRI strength not stated; 6-direction DTI with manually placed ROIs in 19 locations throughout the brain	Change in FA between early and TEA scan in internal capsule and occipital WM	Motor development on Bayley II PDI at 24 months CA
Rose et al.[56]	24 Infants <32 weeks GA, <1500 g BW with and without long-term motor abnormalities	1.5 T; 6-direction DTI; manual ROIs in bilateral PLIC	FA in PLIC	Gross motor outcomes determined using standardized gait and motor testing
Kaukola et al.[57]	30 Infants <30 weeks GA, <1000 g BW	1.5 T; 3-direction DWI; manual ROIs in the PLIC, pons, centrum semiovale, and corona radiata	ADC in corona radiata	Gross motor function on Griffiths gross motor subscale at 2 years CA
Rose et al.[58]	78 Infants <32 weeks GA	1.5 T; 6-direction DTI; manual ROIs in bilateral ALIC and PLIC and genu and splenium of the CC	FA in PLIC and splenium	Motor development on Bayley II PDI at 18–22 months CA; no correlation with MDI
Boardman et al.[35]	80 Infants ≤34 weeks GA	1.5 T; Manually placed ROIs in multiple regions of interest	ADC values in centrum semiovale	Griffiths DQ at mean chronological age of 28 months
Thompson et al.[40]	106 Infants <30 weeks GA and <1250 g BW	1.5 T; 6-direction DTI and probabilistic tractography of CC, manually segmented	FA for CC bundle and splenium of CC	Bayley II PDI scores at 2 years CA
van Kooij et al.[59]	69 Infants <31 weeks GA	3.0 T; 32-direction DTI and deterministic tractography; manually segmented PLIC and CC fiber bundles	None significant in primary analyses	Several associations with Bayley III scores in secondary analyses
Kidokoro et al.[60]	160 Infants <30 weeks GA and/or <1250 g BW	1.5 T; 6-direction DTI; 6 manually placed ROIs in centrum semiovale	FA in anterior and middle centrum semiovale	Mental and motor scores on Bayley II subscales at 2 years CA
Rogers et al.[34]	80 Infants <30 weeks GA and <1250 g BW	1.5 T; several manual ROIs placed in frontal, temporal, & occipital lobes	MD in right orbitofrontal cortex	Peer problem scores on the strengths and difficulties questionnaire at 5 years
van Kooij et al.[61]	63 Infants <31 weeks GA	3.0 T; 32-direction DTI; whole-brain automated tract-based spatial statistics	FA in multiple WM regions	Cognitive, motor, and fine motor scores on Bayley III at 2 years CA
Aeby et al.[62]	41 Infants ≤32 weeks GA and/or ≤1500 g BW without severe brain injury	1.5 T; 32-direction DTI; voxel based analysis	MD, AD, and RD in superior temporal gyrus	Language scores on Bayley III at 2 years CA; no relation with cognition or motor scores
Ball et al.[63]	55 Infants <35 weeks GA without severe brain injury	3.0 T; 15-direction DTI; multiple ROI analyses in the cortex and whole-brain automated DTI analyses	MD in the cortex	DQ on Griffith Mental Development Scales at 2 years
Chau et al.[50]	177 Infants 24–32 weeks GA; infants with large	1.5 T; 12-direction DTI; FA measured in various WM regions and deep	FA measured in various WM regions and deep nuclear GM	Cognitive, language, and motor outcomes on

Citation	Subjects	MRI details	Biomarker(s)	Outcome
	parenchymal venous infracts excluded	nuclear GM manually placed ROIs		Bayley III at 18 months CA
deBruine et al.[64]	84 Infants <32 weeks GA	3.0 T; 32-direction DTI and deterministic tractography; manually segmented PLIC, genu and splenium of the CC fiber bundles	PLIC FA and fiber length; ADC and fiber length of splenium	Cerebral palsy and psychomotor score on Bayley III PDI score at 2 years CA
Parikh et al.[65]	41 Infants ≤1000 g BW	3.0 T; diffusivity and volume measures in objectively defined DEHSI regions	DEHSI volume and diffusivity metrics	Cognitive and language scores on Bayley III at 18–22 months CA
Brouwer et al.[66]	93 Infants <31 weeks GA	3.0 T; 3-direction DWI; manual ROI measures in cerebellum and several cerebral WM regions	Cerebellum ADC	Motor outcome on Bayley III motor subscale at 24 months CA
Hart et al.[52]	67 Infants <35 weeks GA	1.5 T; ADC from 22 regions of interest	None	No association with CP or Bayley III scores
Pogribna et al.[67]	42 Infants with BW ≤1000 g	3.0 T; 15-direction DTI; manual ROI analyses throughout the WM	Centrum semiovale MD; subventricular zone FA	Cognitive and language scores on Bayley III at 18–22 months CA
Skiold et al.[46]	29 Infants <27 weeks GA at birth with no injury on conventional MRI at TEA	1.5 T; whole-brain tract-based spatial statistics	None	No correlation seen with cognitive and language scores on Bayley III at 30 months CA
Thompson et al.[68]	96 Infants <30 weeks GA and/or <1250 g BW	1.5 T; 6-direction DTI; automatically selected ROIs in cerebellum and cerebral WM	Inferior occipital and cerebellar MD	Motor and executive function (Movement ABC and Tower of London) at 7 years
Duerden et al.[69]	153 Infants between 24 and 32 weeks GA	1.5 T; 12-direction DTI; whole-brain tract-based spatial statistics	FA and RD in multiple WM regions including CC and corticospinal tract	Motor and cognitive scores on the Bayley III at 18 months CA
Rose et al.[70]	66 Infants <1500 g BW	3.0 T; 25-direction DTI; semi-automated atlas based segmentation into 126 regions	PLIC MD and genu MD and FA	Cognitive and motor scores on Bayley III at 18–22 months CA and gait velocity
Ullman et al.[48]	93 Infants <30 weeks GA and <1250 g BW	1.5 T; whole-brain group-averaged FA map derived using an automated atlas	Whole-brain FA map	Mathematical ability and working memory at 5 years

AD, axial diffusivity; ADC, apparent diffusion coefficient; BW, birth weight; CA, corrected age; CC, corpus callosum; DQ, developmental quotient; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FA, fractional anisotropy; GA, gestational age; GM, gray matter; MD, mean diffusivity; MDI, metal development index; PDI, psychomotor development index; PLIC, posterior limb of the internal capsule; RD, radial diffusivity; ROI, region of interest; T, tesla; TEA, term-equivalent age; WM, white matter.