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Injury and recovery in the developing brain: evidence from functional MRI studies of prematurely born children

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SUMMARY

Functional MRI (fMRI) might provide important insights into emerging data that suggest that recovery from injury can occur in the brains of children born prematurely. Strategies employing auditory stimulation demonstrate blood-oxygen-level-dependent (BOLD) activation in preterm infants as young as 33 weeks' gestational age, and reliable BOLD signal in response to visual stimulation occurs at term-equivalent age. Strategies based on fMRI are particularly suited to the study of language and memory, and emerging data are likely to provide insights into perplexing reports that have demonstrated improving cognitive scores but persistent volumetric and microstructural changes in frontotemporal language systems in the prematurely born. Even when sex, gestational age and early medical and environmental interventions are taken into account, fMRI data from several investigators suggest the engagement of alternative neural networks for language and memory in the developing preterm brain.

Keywords

effects; functional MRI; language; memory; preterm birth

INTRODUCTION

Preterm birth is the main cause of neonatal mortality in the US,¹ and the neurodevelopmental disabilities of the prematurely born have been well described for over 40 years. Converging data, however, suggest recovery from injury sustained in the developing brain. Numerous MRI studies have explored the structural, volumetric and microstructural sequelae of preterm birth. In spite of these predictors of adverse outcome, several recent studies document improvements in testing scores and school performance over time in the prematurely born.^{2–5} Functional MRI (fMRI), which assesses neural processing, has been less well studied than other imaging

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REVIEW CRITERIA We performed a search of the PubMed database for articles on functional MRI studies in premature neonates published between January 1989 and February 2007. We used combinations of the following search terms: “infant”, “neonate”, “child”, “adolescent”, “adult”, “preterm”, “premature”, “prematurely born”, “functional magnetic resonance imaging”, “fMRI”, “language”, “phonology”, “semantics”, “orthography”, “memory”, “attention”, “inhibition”, “executive function”, “motor stimulation” and “vision”. We reviewed all 15 published articles relating to functional MRI studies in prematurely born individuals and selected them all, as we judged each to have had considerable impact on the field. Articles not written in English were excluded from this review.

Competing interests The authors declared no competing interests.

strategies in the preterm population, and it has the potential to offer important insights into the neurobiological mechanisms that support brain development in the prematurely born.

In this Review, we describe fMRI studies of preterm children and matched control individuals to compare the development of neural systems across time in these groups and to consider the variables that might influence the interpretation of fMRI signal changes in the prematurely born. fMRI studies of preterm children ranging in age from 33 weeks' postmenstrual age (PMA) through to young adulthood are included in this Review, and fMRI paradigms include not only visual, auditory and motor stimulation, but also studies of language and memory processing in the developing brain.

SEQUELAE OF PRETERM BIRTH

Prematurely born infants are at high risk of brain injury. Between 15% and 25% experience intraventricular hemorrhage, and 7-12% have parenchymal involvement of hemorrhage. Perhaps more importantly, as many as 80% have diffuse excessive high signal intensity within the white matter in the newborn period.⁶⁻⁹ All of these events have the potential to disrupt the genetically programmed pattern of brain development and subsequent cognition in the preterm brain.

In parallel with reports of cognitive and functional recovery in preclinical studies of injury to the developing brain,¹⁰⁻¹⁴ several authors have suggested recovery from cognitive impairments associated with preterm birth.^{2,15} Others have reported a reduction in memory deficits¹⁶ and significant improvement in academic performance at adolescence in children born preterm who have undergone serial testing beginning at school age.^{4,17} Finally, Hack *et al.* found that almost three-quarters of a cohort with extremely low birth weight (ELBW) had graduated from high school and 40% were enrolled in a college program,³ and Saigal *et al.* noted no significant differences in education or employment variables in 166 ELBW individuals and 145 matched controls at ages 22-25 years, suggesting that the majority of ELBW children had recovered from those injuries associated with preterm birth.¹⁸

VOLUMETRIC IMAGING AND MICROSTRUCTURAL ANALYSES

Several studies have demonstrated that preterm children have relatively small brain volumes at adolescence and beyond, and lower cortical gray matter, cortical white matter, deep gray matter and cerebellar volumes have been reported in preterm individuals compared with term controls.¹⁹⁻²² In addition, several authors have commented on the regional vulnerability of the preterm brain, and studies of preterm individuals ranging from school age to young adulthood have reported both gray and white matter changes in the frontotemporal and hippocampal regions bilaterally.²³⁻²⁶

The left temporal region is more markedly affected than the right, and preterm males are more likely to experience both decreases in volume and abnormalities of gyrification in the temporal lobes when compared with preterm females.^{20,22,27} By contrast, Kesler *et al.* reported disproportionately enlarged frontal gray matter in preterm children compared with term controls at 8 years of age.²⁶

Diffusion-tensor imaging (DTI) permits the investigation of microstructural white matter alterations in the developing brain through measures such as fractional anisotropy (FA), which describes the degree to which water diffusion is directionally restricted.²⁸ FA values rise with increasing myelination, axon diameter and degree of fiber bundle packing. At adolescence, individuals born preterm show decreased FA not only in the corpus callosum (CC), but also in the intrahemispheric association fibers that subserve language skills,²⁹ and FA values in the

external capsule and middle superior and inferior fasciculi have been shown to correlate with cognitive impairments at 15 years of age in children who were born preterm.³⁰

MRI FINDINGS AND COGNITIVE SKILLS IN THE PREMATURELY BORN

Several investigators have demonstrated a correlation between whole-brain gray matter volumes and intelligence measures in typically developing children, but the available data examining brain-behavior relationships for prematurely born children are less robust. Peterson *et al.* noted that volume reductions in the temporal and sensorimotor language regions correlated with IQ scores in 8-year-old preterm individuals,²⁵ whereas Lodygensky *et al.* found only modest correlations for preterm children between whole cortical gray matter volumes and IQ scores at the same age.²¹ In typically developing individuals, activation of the thalamus correlates with verbal fluency,³¹ and impairment of verbal fluency has been reported in patients with thalamic stroke.^{32,33} Gimenez *et al.* demonstrated that thalamic volumes correlated with verbal fluency in prematurely born children at 14 years of age,³⁴ and Nosarti *et al.* found that midsagittal CC size correlated with verbal fluency in males aged 14-15 years born preterm.³⁵ Finally, decreases in hippocampal volumes have been shown to correlate with memory deficits in adolescents who were born prematurely.²⁷

FUNCTIONAL IMAGING

The fMRI approach has the potential to inform scientists and clinicians alike about neural systems in the developing brain. This technique exploits the different magnetic properties of deoxygenated and oxygenated blood, making it sensitive to relative changes in the concentrations of oxyhemoglobin and deoxyhemoglobin that occur in response to neuronal activity. As Fox and Raichle demonstrated with PET over 20 years ago,³⁶ neuronal activation leads to an increase in tissue oxygenation over and above the increase in oxygen demand. This physiological response is exploited in fMRI, and is referred to as blood-oxygenation-level-dependent (BOLD) contrast.

Signal intensity changes related to relative blood oxygenation levels provide only an indirect measure of neuronal activity. A study by Logothetis *et al.* using simultaneous intracortical recordings of neural signals and fMRI demonstrated that the BOLD response is closely related to local field potentials, reflecting input and intracortical processing for a given cortical region rather than spike output.³⁷ Other indirect indices of neuronal activity include magnetic resonance measures of cerebral blood flow and cerebral blood volume.^{38,39} Measurements of cerebral blood flow and oxygenation can be combined in a calibrated BOLD experiment, providing a measure that reflects the cerebral rate of metabolic oxygen consumption.⁴⁰

fMRI experiments detect relative changes in signal intensity between two different conditions. Only brain regions that are differently involved in the two conditions will demonstrate signal change on subtraction. Consequently, regions that are equally active in both conditions and regions that are not involved in either condition will not appear in difference maps. Furthermore, although fMRI shows regions that are differentially involved in a task, it does not indicate whether or not these regions are critical to task performance.

Functional MRI studies assess sensory modalities in the prematurely born

In view of the fact that fMRI offers the possibility of understanding the impact of injury on developing neural systems, several investigators have employed this technique to study sensory development in preterm infants (Table 1). Born *et al.* demonstrated visual activation in preterm infants with structurally normal and abnormal visual systems at term-equivalent age,^{41,42} and Erberich *et al.* demonstrated positive BOLD responses to both motor and visual stimulation in infants (gestational age 24-39 weeks) studied at term-equivalent to 58 weeks' PMA.⁴³

The central processing of auditory information is critical to the synthesis of language systems in the developing brain, and we detected reliable fMRI auditory activation in infants ranging from 33 to 47 weeks' PMA.⁴⁴ We found little relationship between PMA and signs of auditory activation within the age range studied. By contrast, the response of the visual cortex consistently seems to reverse during infancy. In the study by Born *et al.*, infants older than 50 weeks' PMA predominantly showed negative activation in the visual cortex, infants aged between 40 and 50 weeks' PMA demonstrated mostly positive activation, and those aged 40 weeks' PMA or less had no measurable response.^{41,42}

Erberich *et al.* recently used fMRI to study cortical BOLD signal induced by passive extension and flexion of the hand in 24 preterm and term infants; a group of 6 term infants aged 3-9 months served as controls.⁴⁵ In contrast to the contralateral localization of BOLD response found in the older control infants, BOLD signal in response to unilateral stimulation was found in the somatosensory areas in the precentral and postcentral gyri of both hemispheres of the neonatal group at term-equivalent age.

These results suggest that the neural and vascular components of the auditory cortex respond to sensory stimulation at an earlier age than does the visual system. In addition, there might be a critical period during the development of the sensorimotor system in the developing brain, such that refinement of the sensorimotor pathways most probably occurs in the post-neonatal period.

Language studies

Initially employed to study sensorimotor tasks such as those described above, fMRI strategies were quickly developed for the study of language systems in children and adults. As shown in Table 2, language can be divided into three component parts: phonology, semantics and orthography. Phonology involves breaking the written or auditory word into component parts, or phonemes, and is thought to be central to all language functions. Semantics, or the 'understanding' of words, is a higher-level cerebral skill. Orthography describes those functions required for reading the written word.

Although language systems are traditionally thought to encompass the classical Broca's and Wernicke's regions in the left frontal and temporal lobes, respectively, fMRI studies have demonstrated activation of a number of different language systems in both the left and right hemispheres in typically developing right-handed adults and children, depending on the task and presentation modality employed (Table 2). Furthermore, the development of the phonological and semantic systems seems to depend on both age and environment, suggesting plasticity for language in the developing brain.

MRI studies evaluating the cerebral structural sequelae of preterm birth have consistently reported alterations in the regions subserving language, but the functional organization of auditory processing and language in prematurely born children is only just beginning to be explored (Table 3). Preterm individuals have been shown to have CC thinning,^{25,35} and Santhouse tested the hypothesis that CC abnormalities might have functional significance.⁴⁶ Three groups of individuals aged 18-20 years matched for handedness and intelligence were examined: preterm individuals with CC thinning, preterm individuals with normal CC volumes, and term controls. In response to an fMRI auditory paradigm designed to require callosal transfer of information, preterm individuals with CC thinning showed greater activation in the right superior temporal gyrus than did either group of controls. In view of the fact that the CC thinning group performed timbre and bilateral field comparison tasks significantly less well than did the two control groups, Santhouse proposed that this group of preterm subjects had developed alternative neural strategies to compensate for the (presumably) perinatal structural damage. To further support this hypothesis, in an analogous

visual stimulation task administered to the same three groups, the preterm individuals with CC thinning had additional BOLD signal in the right dorsolateral prefrontal cortex, possibly because the task was accomplished by storing information in working memory.

Phonological processing abilities are critical for the acquisition of both reading and spelling skills, and impairments in phonological processing have been repeatedly shown to contribute to the need for special educational services at school age.⁴⁷ Peterson *et al.* compared brain activity associated with phonological and semantic processing by use of a passive listening task in preterm individuals and term controls at 8 years of age (Table 3).⁴⁸ During phonological processing, term controls showed deactivation of extensive regions of the prefrontal cortex including Brodmann's areas 10, 46 and 47, as well as exhibiting negative BOLD signal in the ventral anterior cingulum. During semantic activation, the term controls had bilateral positive BOLD signal in both the inferior frontal gyri (Broca's region) and the superior temporal gyri (Wernicke's region). By contrast, the pattern of brain activity identified in the semantic processing task for the preterm children closely resembled that identified in the phonological task in the term controls, suggesting aberrant processing of language for the preterm group. The greater this resemblance, the lower the verbal comprehension IQ scores of the preterm children and the poorer their language comprehension during the scanning task.

Language scores of preterm children have been shown to improve over time, so our group used the same passive listening task to test the hypothesis that individuals who were born prematurely would develop alternative systems for processing language.^{5,49} In contrast to our report of children at 8 years of age, we studied only preterm children who had no known ultrasonographic evidence of neonatal brain injury and had normal ventricular size at 12 years of age. Although there were significant differences in semantic processing scores between the preterm and control children, there were no significant differences in the phonology scores between the study groups. Preterm and term children demonstrated similar BOLD patterns during semantic processing, but the term individuals had significantly greater signal change, both positive and negative, than did the preterm individuals.

During phonological processing, preterm study participants exhibited strongly positive BOLD signals in the left parahippocampal gyrus, the posterior cingulate gyrus, the right anterior middle temporal gyrus, and the region encompassing the left middle temporal gyrus and superior temporal gyrus. By contrast, a negative BOLD signal was found in these four regions in the term controls, even when the data were adjusted for verbal IQ and age at scan. These data indicate that children born prematurely engage different networks for phonological processing yet have no differences in phonological testing scores compared with matched term children at 12 years of age.

Rushe *et al.* examined phonological processing in 14-year-old preterm children,⁵⁰ testing the hypothesis that children with evidence of CC thinning would display incomplete lateralization of language function to the left hemisphere. Performing a non-word rhyme task, the preterm group showed significantly reduced BOLD response in the left peristriae cortex, left cerebellum and right precuneus compared with term controls, despite there being no difference in task performance scores between the two groups. In addition, the preterm individuals exhibited significantly increased activation in the right precentral gyrus and superior frontal cortex, suggesting the development of compensatory systems, or 'hyperfrontality', in the preterm brain.

During orthographic processing, the preterm group showed significantly less BOLD response in the left precuneus and peristriae cortex than did the term controls. The peristriae cortex has been termed the 'visual word form (VWF) system', and is believed by many to be critical to the successful development of reading skills.⁴⁷ Reduced BOLD signal in this region might

occur as a result of an inefficient VWF system and the adoption of an alternative neural strategy for language by preterm children to keep their performance commensurate with that of controls.

Effects of hippocampal damage on functional MRI regional activations

The hippocampus plays a crucial role in memory. Deficits in long-term memory have been demonstrated in preterm individuals, and several fMRI studies have examined the impact of preterm birth on memory in the developing brain. Maguire *et al.* studied the effects of bilateral hippocampal damage attributed to perinatal events on memory systems in a single very-low-birth-weight young adult with memory deficits relative to six term adult controls (Table 3).⁵¹ Group data for memory tasks demonstrated BOLD signal changes in a predominantly medial and left-lateralized network consisting of medial frontal cortex, temporal pole, hippocampus, anterior middle temporal gyrus, parahippocampal gyrus, retrosplenial cortex and temporoparietal junction. The very-low-birth-weight preterm individual demonstrated increased activation in the hippocampal regions and medial frontal cortices bilaterally compared with controls. Furthermore, in contrast to controls, this individual activated many homologous regions in the right hemisphere, including the right anterior middle temporal gyrus, right temporoparietal junction and right inferior frontal gyrus.

More recently, Gimenez *et al.* mapped hippocampal activation during a novel face-name pair memory task in preterm and matched term controls aged 12-18 years.⁵² Notably, out-of-magnet testing showed that the preterm individuals performed significantly less well in measures of free recall and recognition and had significantly lower scores on measures of visual memory than did the controls. During encoding of the word-face association, preterm children exhibited greater activity in the right hippocampus than did term controls. In addition, there was a positive correlation in the preterm group between right hippocampal activation and face-name recognition. Volumetric analyses of the study children showed significant left hippocampal volume loss in the preterm group, and the functional data correlated with the structural data; that is, right hippocampal activation positively correlated with right hippocampal volume.

Curtis *et al.* also employed fMRI strategies to assess memory-induced activation in the caudate-hippocampal-prefrontal cortical system in preterm children and matched controls aged 12-16 years.¹⁶ There were no significant differences with respect to in-magnet behavioral data for the two groups, suggesting that memory function for the preterm children was statistically equivalent to that of controls. Although the groups did not differ in activation of the hippocampus during any of the memory tasks, caudate BOLD signals were significantly different for the two groups. During the encoding phase of the memory tasks, the preterm group showed greater activation in the right caudate than did the controls, suggesting that prematurely born individuals recruit bilateral regions during memory retrieval.

Functional MRI tasks assessing attention and executive function in preterm children

Preterm children are at high risk for attentional and behavioral disorders at school age, and both attention and response inhibition are critical to executive function and subsequently to academic success. Carmody *et al.* studied preterm individuals aged 15-16 years with no evidence of neonatal intraventricular hemorrhage to test the hypothesis that the fMRI BOLD responses of preterm children would correlate with performance on out-of-magnet attention tasks (Table 3).⁵³ fMRI analyses showed frontal, temporal and parietal activation during an attention task, with greater activation of the left superior temporal and left supramarginal gyri being associated with better performance.

Nosarti *et al.* tested response inhibition in 16-year-old preterm males and matched controls and found that, despite good task performance, preterm individuals demonstrated different BOLD

responses in selective brain areas.⁵⁴ In this test of executive function, the preterm group demonstrated decreased BOLD signal in the cerebellum, right caudate and thalamus and left inferior frontal gyrus and anterior cingulum relative to term controls. Preterm children also showed increased BOLD signal in the right middle frontal gyrus, middle temporal gyrus and superior temporal gyrus compared with term controls. Such neural activation might underline the use of alternative strategies when preterm individuals are challenged with response inhibition processing.

CHALLENGES IN FUNCTIONAL MRI METHODOLOGY

fMRI represents an important tool for the noninvasive assessment of brain development in the preterm population. Unlike other MRI modalities, however, fMRI presents special challenges, both for those who perform the studies and for those who interpret the data.

Imaging the newborn brain

Rivkin *et al.* have reviewed the factors that might necessitate important changes in neonatal fMRI strategies.⁵⁵ The newborn brain has higher water content, lower macromolecular concentration and lower synaptic density than that of older children, and these differences might necessitate changes in relaxation times for fMRI studies. Rivkin *et al.* employed spoiled gradient echo measurements of T2* values within the brains of newborns, 9-month-old infants and adults, and found significantly higher values within the neonatal group than in either of the other groups. These results have important implications for neonatal fMRI studies, and they indicate that the echo time used for studies of infants should be considerably longer than the times used for older children and adults.

Sedation

A recent publication describing the NIH MRI study of normal brain development reviews the challenges of scanning nonsedated infants and young children.⁵⁶ Although some research studies permit sedation of this patient population, who experience particular difficulties in adaptation and habituation to the MRI scanner, the effects of anesthesia on the interpretation of the BOLD response of the developing newborn brain remain largely unknown.⁴⁴ Yamada *et al.* reported only positive BOLD signal change in response to visual stimulation in infants under 6 weeks of age who were sedated with pento-barbital, whereas Born *et al.* noted both negative and positive BOLD responses in a similar population.^{41,57} Furthermore, the depth of this type of anesthesia has been shown to influence the BOLD signal from the visual cortex of typically developing young children.⁵⁸

Although several studies have demonstrated a change in functional BOLD signal between awake and anesthetic states in neonates, it is essential in studies of this kind to dissociate direct flow effects, which can change the coupling between neuronal activity, cerebral blood flow and cerebral blood volume, from neuronal effects. In older populations, the influence of anesthetics on BOLD depends not only on the specific anesthetic but also on the dose employed; furthermore, most published studies demonstrate decreases in BOLD signal with increases in the level of the anesthesia achieved.⁵⁹⁻⁶² Finally, Heinke and Koelsch have suggested that these effects might be region-specific.⁶⁰

Intermagnet variability

An important factor that must be considered is the influence that the magnetic resonance imager itself might have on the data. Differences in the manufacturer, field strength and software and hardware capabilities might all influence the signal-to-noise ratio, scaling, stability and detectability of the effect of interest. Multisite studies investigating scanner fluctuations have been performed for structural MRI,^{63,64} fMRI⁶⁵ and DTI.⁶⁶ Although intersubject noise

dominates in most fMRI studies,⁶⁷ the signal-to-fluctuation-noise ratio can vary markedly across scanners, even with the same model from the same manufacturer.⁶⁵ These issues cannot be ignored when considering studies performed at multiple sites.^{68,69}

Negative blood-oxygen-level-dependent signal

Several studies in very young children have revealed negative BOLD signals throughout the developing brain.^{41,42,44,70} Born *et al.* reported negative BOLD signal in association with reduction of regional blood flow as determined by perfusion MRI,⁷¹ and Meek *et al.* hypothesized that this might be attributable to an inability of the neonatal vascular system to respond to the need for increased oxygen demand.⁷² Negative BOLD signal changes are observed in both visual and auditory processing regions, and as the infant matures the polarity of the activation signal changes. Furthermore, the age at which the signal changes differs according to the developmental stage of each cortical region.

It should be noted that the source of negative BOLD signal changes remains poorly understood for all ages of study participants. Published potential sources for negative BOLD signal include the following: decreases in neuronal activity below traditionally recognized levels of spontaneous activity;⁷³⁻⁷⁶ changes in coupling between flow and metabolism secondary to alterations in blood vessel reactivity;⁷¹ and the vascular steal phenomenon, in which blood is shunted from an inactive brain region to an active one.^{77,78} Finally, Raichle demonstrated that there are regions that show a consistent decrease in activation amplitude when individuals engage in specific tasks relative to a rest or fixation control condition. These regions have been termed the default mode areas—regions that are highly active when the subject is not engaged in a complex task.⁷⁵

Analysis of functional MRI data

The signal changes observed on fMRI are typically very small, and sophisticated statistical analysis procedures must be performed to localize activations in individuals and to make population predictions on the basis of data from a group of trial participants. The pre-analysis steps often include motion correction, data normalization and removal of signal drift terms. All of these steps, if not correctly performed, can lead to the detection of spurious activations. To enable accurate developmental BOLD detection and assessment of changes over time within preterm populations, it will be vital to develop an appropriate common coordinate system, or statistical atlas, for neonates and children of differing ages.⁷⁹⁻⁸²

The main effects analysis for fMRI data is performed using a general linear model to generate beta coefficients, which can be tested against the null hypothesis in a group-level analysis. Corrections are made for multiple comparisons, typically with some form of cluster analysis, and ANOVA (analysis of variance) or ANCOVA (analysis of covariance) analyses are run across groups and tasks and conditions to determine the significance of the effects observed. It should be noted that activation detection in fMRI for single subject or group maps is generally based on arbitrary thresholds at *P*-value levels of 0.05 or 0.01 corrected for multiple comparisons. More-relaxed or more-stringent statistical thresholds result in more or less detected activation and typically larger or smaller activated regions, respectively.

COVARIATES TO BE CONSIDERED

A number of factors must be controlled for when considering group studies that involve preterm infants, children and adolescents, including gestational age, sex, injury data, ventricular size, interventions and maternal education. Each of these factors is discussed briefly in the paragraphs that follow.

Comparison of groups of individuals must factor in gestational age. Gestational age is significantly correlated with both white matter volume measurements^{22,83} and fractional anisotropy as measured with DTI in preterm infants and children.^{84,85}

Sex effects are demonstrated across a number of measures, including the response to indometacin,⁸⁶ language organization as revealed by fMRI,⁴⁹ and white matter microstructural changes as indicated by fractional anisotropy.⁸⁷ Figure 1 demonstrates different activation patterns in a category task for male and female trial participants.

Morphological changes can influence the findings in fMRI studies. Decreased gray matter volume associated with hippocampal atrophy can lead to increased partial volume effects and secondary decreases in fMRI signal changes. In addition, cortical thickness differences have been demonstrated to influence fMRI signal change, and such changes have been shown to be sex-specific⁸⁸ and to change with normal brain growth.⁸⁹ Preterm children often have multiple morphological changes including changes in ventricular size, and these can impact on registration methods, making regional comparisons between groups with different ventricular sizes difficult.²⁶ The influence of group registration differences from a common reference space might then propagate errors that span all measures, be it fMRI, morphological data or fractional anisotropy. Figure 2 shows a subtraction between preterm individuals with normal ventricular size and those with ventriculomegaly, to illustrate that intergroup anatomical differences might lead to erroneous BOLD subtractions.

Neonatal medical and environmental interventions should also be considered. As shown in Table 3, we employed a passive listening task designed to activate phonological and semantic systems to test the hypothesis that neonatal indometacin treatment would differentially affect brain activation across sexes in school-aged, prematurely born children. These studies demonstrated significant treatment-by-sex effects in three regions: the left inferior parietal lobule, the left inferior frontal gyrus and the right dorsolateral prefrontal cortex.⁸⁶ Similarly, Als *et al.* demonstrated that the Newborn Individualized Developmental Care and Assessment Program initiated within 72 hours of admission to the intensive care unit and continuing to the age of 2 weeks led to significantly higher relative white matter anisotropy in the treated group than in controls.⁹⁰

Maternal education has been shown to covary with brain volume and cognitive outcome in preterm infants,²⁵ and also with functional imaging of language processing⁴⁸ and measures of regional volumes reflecting cerebral development in the prematurely born.²⁶

Another important issue is that of performance and its influence in fMRI studies. There is evidence for both increases and decreases in BOLD signal change as a function of behavioral performance across a range of studies. For example, activation has been shown to vary according to whether the task is easy versus difficult.⁹¹ In memory tasks, activation varies according to whether memory retrieval was successful versus unsuccessful,⁹² and activation has been shown to vary as a function of visuomotor learning.⁹³ An open question is the issue of how to balance different groups—should they be equated in terms of effort required to perform a task (and if so, how is effort determined?), or the ability to perform the task (in which case the task might need to be simple for one group and more complicated for another to yield similar performance)? In the early stages of learning a task, there seems to be heightened activation associated with effort and novelty effects, and as subjects develop expertise in a task, the level of activation often decreases. There is also evidence, however, that specific expertise areas might arise that nonexperts do not activate.⁹⁴

Behavioral data are helpful to ensure that the participants are actually performing the task. Not all tasks are easily categorized in terms of behavior, however, and it is clearly not possible to relate all cognitive processes to reaction time and accuracy data. Evidence of different patterns

of brain activation with the same behavioral data is found in our data and those of others.^{49, 95} The opposite effect—marked behavioral changes without differences in the imaging data—can also be observed.⁹⁶

CONCLUSIONS

The neurobehavioral sequelae of preterm birth is one of the major pediatric public health issues of our time,^{3,97-99} and emerging data suggest a dissociation between improving cognitive performance and long-term cerebral structural and microstructural changes in the prematurely born. Language and memory scores do not appreciably differ between preterm and term controls at adolescence, but volumetric and microstructural studies suggest marked changes in frontotemporal language systems and structures subserving memory in preterm groups. Although just beginning to be explored in this subject population, functional imaging could potentially provide important insights into the neurobiological mechanisms that support recovery from brain injury in the prematurely born.

It is well known that different brain regions mature at different rates,¹⁰⁰⁻¹⁰² and recent fMRI studies of healthy term control children suggest that the developing brain undergoes marked changes in functional organization with increasing age and skill.¹⁰³⁻¹⁰⁵ fMRI studies of preterm infants demonstrate that auditory activation can be detected as early as the thirty-third week of gestation, and that detection of BOLD signal to visual stimulation begins about term-equivalent age. More importantly, depending on the patient population and the age at which the individuals were studied, fMRI studies of language in preterm children at adolescence suggest a 'hyperfrontality' of response, such that BOLD signals classically expected in temporal regions are detected in the right frontal lobes, as shown in Figure 3. Furthermore, both volumetric and DTI studies indicate relative vulnerability of the structures subserving language in the left hemisphere, and several authors have noted BOLD signal in response to phonological testing paradigms in the right frontal and temporal lobes. Similarly, although limited in number, fMRI studies of memory, attention and executive function suggest a predominance of right-hemisphere BOLD responses and differing task-related neural systems in preterm adolescents when compared with matched term controls.

Numerous authors have shown that experience and function can cause structural alterations in the developing brain,^{90,106} and recent data suggest that intervention strategies might also alter fMRI results.¹⁰⁷ As neuroscientists begin to develop a connection matrix of the human brain¹⁰⁸ and neurogeneticists identify the imaging patterns evoked by interactions between the environment and the genome,¹⁰⁹ it will be of both clinical and neurobiological importance to employ fMRI strategies to investigate the adaptive mechanisms of the developing preterm brain.

KEY POINTS

- Functional MRI (fMRI) might provide insight into the neurobiological mechanisms supporting recovery from injury in prematurely born individuals
- fMRI can detect activation to auditory stimuli in preterm neonates as early as 33 weeks' postmenstrual age; blood-oxygen-level-dependent signal to visual stimulation can be reliably detected in preterm infants at term-equivalent age
- fMRI investigations of language suggest the engagement of alternative compensatory neural systems in preterm children at school age and beyond
- Gestational age, sex and structural and microstructural cerebral changes must be considered when evaluating fMRI tasks in the prematurely born population

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Figure 1.

Blood-oxygen-level-dependent group difference maps (preterm minus term) at 12 years of age in a category language task for males (top row) and females (bottom row). This task is characterized by both positive and negative signal changes. Negative signal changes are shown in blue and violet; positive activations are shown in red and yellow. Male preterm individuals preferentially demonstrate positive blood-oxygen-level-dependent signal in the right language homologs to Broca's region (inferior frontal gyrus) and Wernicke's region (superior temporal gyrus), whereas preterm females do not.

Figure 2.

Ventricular size mismatch across groups can provide erroneous evidence for functional differences. In this subtraction, 12-year-old preterm individuals with normal ventricular size and those with ventricular volume measurements at least two standard deviations above the mean were contrasted. Note the positive periventricular blood-oxygen-level-dependent signal shown in red and yellow that arises from a subtraction of white matter (in the normal individuals) and cerebrospinal fluid (in those with ventriculomegaly).

Figure 3. Group difference maps (preterm minus term control study participants) at 12 years of age during a semantic task. As shown by the positive blood-oxygen-level-dependent signals shown in red and yellow, the data indicate a right frontal shift in the language network in the prematurely born children.

Table 1

Neonatal functional MRI studies.

Reference	Number of participants	Strategy	Results
Born <i>et al.</i> (1998) ⁴¹ Born <i>et al.</i> (2000) ⁴²	15 control preterm infants; 12 infants with cortical visual impairment; 10 term control infants; studied at term-equivalent age	Stroboscopic light stimulation	Occipital BOLD signal in all infants with PMA >41 weeks; BOLD signal decreased in children with cortical visual impairment
Erberich <i>et al.</i> (2003) ⁴³	7 preterm neonates; studied at PMA 34-58 weeks	Two sensorimotor tasks; one visual stimulation task	BOLD signal detected in 6 out of 7 neonates; motor stimulation resulted in BOLD signal in contralateral hemisphere in 5 of 6 and bilateral BOLD signal in 1 of 6; 6 of 7 had BOLD signal in occipital regions in response to visual stimulation
Anderson <i>et al.</i> (2002) ⁴⁴	7 preterm infants; 13 term control infants; studied at term-equivalent age	Frequency-modulated pure tone	BOLD signal detected in bilateral temporal cortices in 14 out of 20 neonates
Erberich <i>et al.</i> (2006) ⁴⁵	24 preterm and term infants studied at PMA 38-49 weeks; 6 control infants 3-9 months of age	Passive hand extension and flexion	In contrast to response seen in older, control infants, somatosensory areas in the precentral and postcentral gyri of the neonate showed no significant hemispheric lateralization at term-equivalent age

Abbreviations: BOLD, blood-oxygen-level-dependent; PMA, postmenstrual age.

Table 2

Functional MRI to assess cerebral regions associated with language skills.

Language skill	Definition	Associated cerebral regions
Phonology	Processing the elemental particles of words (phonemes)	Left hemisphere: PCG, IFG, STG, MTG, IPL Right hemisphere: lateral orbital gyrus, pHG
Semantics	Giving meaning to the spoken or written word	Left hemisphere: IFG, STG, AG/SMG, ITG, STG, MTG Right hemisphere: IFG, fusiform gyrus, cuneus Left dentate nucleus, right vermis (lobule IX), cerebellar crus I/II
Orthography	Reading the written word	Left hemisphere: IFG, AG, SMG, STG, MTG, MOG, LG, cuneus, basal ganglia Right hemisphere: anterior cingulate gyrus, cuneus, LG, MOG, aSTG, aMTG

Abbreviations: AG, angular gyrus; aMTG, anterior middle temporal gyrus; aSTG, anterior superior temporal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LG, lingual gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PCG, precentral gyrus; pHG, parahippocampal gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus.

Table 3
Functional MRI studies of prematurely born individuals.

Reference	Number of participants	Age (years)	Task	Results
Language				
Santhouse <i>et al.</i> (2002) ⁴⁶	7 preterm children with CC thinning; 9 preterm children with normal CC; 7 term controls	18-20	Auditory paradigm judging whether pairs of sounds were similar or different	Preterm damaged CC group showed greater activation of right STG than did both groups of control subjects
Peterson <i>et al.</i> (2002) ⁴⁸	26 preterm children; 13 term controls	8	Passive language task; semantic and phonological subtractions	Phonological: term controls deactivate PFC; preterms deactivate left cingulate, hippocampus, cerebellum Semantic: term controls activate left IFG and left STG; preterm children deactivate PFC Preterm semantic subtraction is similar to term phonological subtraction
Ment <i>et al.</i> (2006) ⁴⁹	14 preterm children with normal neonatal ultrasound results and normal MRI results at age 12 years; 10 term control children	12	Passive language task; phonological and semantic subtractions	Semantic: preterm and term children activate same regions (left IPL, left MTG, left AG, pCingG, right IFG) but preterm show lower BOLD signal than term Phonological: preterm children activate left STG/MTG, left paHG, pCingG, right aMTG; term children deactivate left OG, left MTG/STG, pCingG, right OG, right aMTG
Rushe <i>et al.</i> (2004) ⁵⁰	6 preterm males with CC damage; 6 term controls	14	Phonological processing	Preterm group showed increased BOLD signal in right PCG, right STG, right SFG, and decreased BOLD signal in left peristriate cortex, left cerebellum, right precuneus
			Orthographic processing	Compared with preterm group, controls showed increased signal in left visual word form region
Memory				
Maguire <i>et al.</i> (2001) ⁵¹	1 preterm male (26 weeks' gestational age); 6 term controls (4 females, 2 males)	22 28-33	Memory retrieval task: autobiographical events, public events, autobiographical facts and general knowledge	Despite 50% volume loss of hippocampi, the preterm individual demonstrated increased bilateral hippocampal BOLD compared with controls
Gimenez <i>et al.</i> (2005) ⁵²	14 preterm children; 14 term controls	12-18	Declarative memory task	Both groups had increased BOLD signal during learning task compared with control task in right fusiform gyrus and left IOG; preterm group had significantly increased BOLD signal in right hippocampus compared with term controls; right hippocampal BOLD

Reference	Number of participants	Age (years)	Task	Results
Curtis <i>et al.</i> (2006) ¹⁶	9 preterm children; 9 term controls	12-15	Declarative and spatial memory tasks: delayed match to sample, delayed non-match to sample, and spatial memory span tasks, as well as two analogous perceptuomotor tasks that placed no demands on memory	signal correlated with right hippocampal volume in preterm children No significant differences in in-magnet behavioral data; during encoding phase of spatial memory task preterm children had significantly increased BOLD signal in right caudate compared with term controls; during test phase, preterm children had significantly decreased BOLD signal in right caudate compared with term controls
Attention and executive function				
Carmody <i>et al.</i> (2006) ⁵³	10 preterm children with no evidence of intraventricular hemorrhage	15-16	Attention task	Frontal, temporal and parietal activation bilaterally with increased activation of left STG and left SMG associated with better task performance
Nosarti <i>et al.</i> (2006) ⁵⁴	8 preterm males; 14 term control males	16	Executive function: 'go-no-go' task to assess response selection and inhibition in response to a visual stimulus	Preterm males showed decreased BOLD signal in cerebellum, right caudate/thalamus, left IFG and left aCingG, and increased BOLD signal in right IFG, right OFG, right MTG, left ITG, left MTG and right STG compared with controls
Neonatal intervention				
Ment <i>et al.</i> (2006) ⁸⁶	47 preterm children; 24 term controls	8	Passive language task; semantic and phonological subtractions to test the hypothesis that indometacin would differentially affect brain activation across sex	During phonological processing, a significant treatment- by-sex effect in three regions: left IPL, left IFG and right dorsolateral PFC; no effect on semantic processing

Abbreviations: aCingG, anterior cingulate gyrus; AG, angular gyrus; aMTG, anterior middle temporal gyrus; BOLD, blood-oxygen-level-dependent; CC, corpus callosum; IFG, inferior frontal gyrus; IOG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; OFG, orbital frontal gyrus; OG, occipital gyrus; paHG, parahippocampal gyrus; pCingG, posterior cingulated gyrus; PCG, precentral gyrus; PFC, prefrontal cortex; SFG, superior frontal gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus.