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Functional connectivity to a right hemisphere language center in prematurely born adolescents

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ABSTRACT

Prematurely born children are at increased risk for language deficits at school age and beyond, but the neurobiological basis of these findings remains poorly understood. Thirty-one PT adolescents (600–1250 g birth weight) and 36 T controls were evaluated using an fMRI passive language task and neurodevelopmental assessments including: the Wechsler Intelligence Scale for Children-III (WISC-III), the Peabody Picture Vocabulary Test-Revised (PPVT-R), the Comprehensive Test of Phonological Processing (CTOPP) and the Test of Word Reading Efficiency (TOWRE) at 16 years of age. Neural activity was assessed for language processing and the data were evaluated for connectivity and correlations to cognitive outcomes. PT subjects scored significantly lower on all components of the WISC-III ($p<0.05$) compared to term subjects, but there was no significant difference in PPVT-R scores between the groups. Functional connectivity (fcMRI) between Wernicke's area (left BA 22) and the right supramarginal gyrus (BA 40) was increased in preterm subjects relative to term controls ($p=0.03$), and the strength of this connection was inversely related to performance on both the PPVT-R ($R^2=0.553$, $p=0.002$), and the verbal comprehension index ($R^2=0.439$, $p=0.019$). Preterm adolescents engage a dorsal right hemisphere region for language at age 16 years. Those with the greatest cognitive deficits demonstrate increasing reliance on this alternate pathway.

Introduction

Preterm birth represents a major pediatric public health problem in the United States and Europe today(Behrman and Stith Butler, 2007). The neurocognitive sequelae of preterm birth have been well described (Allin et al., 2008; Hack et al., 2009; Hille et al., 2007; Saigal and Doyle, 2008; Verrips et al., 2008), and the development of sophisticated magnetic resonance imaging (MRI) strategies has provided significant information about the impact of preterm birth on the developing brain. Preterm subjects have widespread structural and microstructural changes when compared to term control subjects in studies ranging from the newborn period to adolescence and young adulthood (Anjari et al., 2009; Dubois et al., 2008; Gimenez et al., 2008; Nagy and Jonsson, 2009; Skranes et al., 2009). In contrast to these presumptive markers of adverse outcome, functional MRI (fMRI) strategies from several investigators demonstrate the recruitment of alternative neural systems for language in the prematurely born (Ment et al., 2006b; Narberhaus et al., 2009; Nosarti et al., 2009; Rushe et al., 2004), and several recent reports suggest that cognitive outcomes for this vulnerable population may depend not only on the gestational age at birth but also on the maternal level of education (Hack et al., 2009; Weisglas-Kuperus et al., 2009). Functional connectivity (fcMRI), which assesses the functional organization of the developing brain, has been less well studied than other imaging strategies in the preterm population. By identifying those regions that activate together either during a particular task or at resting state, fcMRI may provide important information about the differential engagement of alternative neural systems in the developing preterm brain.

Abbreviations: BA, Brodmann's area; CTOPP, Comprehensive Test of Phonological Processing; fcMRI, Functional Connectivity Magnetic Resonance Imaging; fMRI, Functional Magnetic Resonance Imaging; FSIQ, Full Scale Intelligence Quotient; GLM, General Linear Model; PIQ, Performance Intelligence Quotient; PPVT-R, Peabody Picture Vocabulary Test-Revised; PT, Preterm; ROI, Region of Interest; SPM, Statistical Parametric Mapping; T, Term; TOWRE, Test of Word Reading Efficiency; VCI, Verbal Comprehension Index; VIQ, Verbal Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children-III.

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Numerous cohort studies have revealed inferior educational outcomes in preterm subjects. At school entry, minor developmental impairment is diagnosed in 30–40% and major disabilities are found in almost 20% of preterm children (Allen, 2008; Larroque et al., 2008; Neubauer et al., 2008; Saigal and Doyle, 2008; Voss et al., 2007). Over half require special assistance in the classroom, 20% are in special education and 15% have repeated at least one grade in school (Aylward, 2005; Bhutta et al., 2002). Furthermore, although a majority of prematurely born neonates have recently been shown to become independent adults, the intellectual deficits of preterm subjects may persist through adolescence and young adulthood (Saigal et al., 2006).

Imaging plays an important role in understanding the neurobiology underlying the cognitive deficits of preterm children. When compared to term control subjects, preterm subjects have global and regional decreases in cortical gray and deep gray matter, less myelinated white matter, smaller corpus callosal areas and significant ventriculomegaly (Allin et al., 2004; Boardman et al., 2007; Huppi et al., 1998; Inder et al., 1999, 2005; Mewes et al., 2006; Peterson et al., 2003). Diffusion tensor imaging (DTI) provides information about the microstructure of the developing brain through measures such as fractional anisotropy (FA). FA increases with increasing myelination, axonal diameter and fiber bundle packing. Widespread decreases in FA have been reported in PT children compared to term controls in studies ranging from infancy through young adulthood (Anjari et al., 2007, 2009; Skranes et al., 2007) and DTI parameters have been shown to significantly correlate with cognitive and motor outcomes for the prematurely born (Constable et al., 2008; Counsell et al., 2008; Skranes et al., 2009).

More recently, studies using fMRI have identified differences in the brain areas activated during language and executive tasks in preterm children when compared to term control subjects, and preliminary studies investigating fcMRI in preterm subjects during the newborn period and at school age suggest that, when compared to term control subjects, preterm subjects exhibit different patterns of connectivity between brain areas both at rest and during a functional task (Doria et al., 2008, 2009; Fransson et al., 2007; Gozzo et al., 2009; Smyser et al., 2009). Resting state literature suggests that functional connectivity is at least partially anatomically determined, but the role of these alternative pathways remains poorly understood.

In order to test the hypothesis that the alternative neural connections found in prematurely born subjects at adolescence may be associated with cognitive measures including language skills, the connectivity between language regions during an fMRI language task was investigated in preterm and term subjects by correlating the strength of the differential connections with language measures. Wernicke's area, in the left superior temporal gyrus (left Brodmann's area 22), was chosen as a reference region for functional connectivity analysis based on findings from a previous study showing significant differences in functional connectivity levels between eight year old preterms and terms. Functional connectivity to Wernicke's area was evaluated in other primary language regions in the left hemisphere and their right-sided homologues.

Because intraventricular hemorrhage, periventricular leukomalacia and low-pressure ventriculomegaly have been associated with adverse cognitive outcomes in the prematurely born (Ment et al., 1996), our *a priori* hypothesis was tested in preterm subjects who were free of these lesions in both neonatal cranial ultrasound studies and magnetic resonance images at age 16 years.

Methods

This study was performed at Yale University School of Medicine, New Haven, CT, and Warren Alpert Brown Medical School, Providence RI. The protocols were reviewed and approved by institutional review boards at each location. All scans were obtained and analyzed at Yale University.

Subjects

The preterm cohort consisted of children who were enrolled in the follow-up MRI component of the Multicenter Randomized Indomethacin IVH Prevention Trial at Yale University School of Medicine and Brown University (Ment et al., 1994). Only those preterm children who lived within 200 miles of the Yale MRI Research Facility were eligible for this protocol. From a potential pool of 191 preterm subjects, 43 preterm children provided written assent, parental written consent, and participated in a scanning session. Of these 43, data from 12 were removed from analysis because of the presence of intraventricular hemorrhage, ventriculomegaly or periventricular leukomalacia (11) or excess motion artifact on MRI (1). Term control children were recruited from the local communities of the study children. They were group-matched to the PT children for age, sex, and minority status. Forty-two term children provided written assent, parental written consent and participated in a scanning session. Of these 42, data from 6 were removed from analysis because of excess motion artifact (4) or because of poor performance on the in magnet assessment designed to evaluate the subjects' understanding of the in magnet task (2). Thus, of the 85 total children who participated in the scanning session, 67 were eligible for analysis, with a total of 5 subjects removed from analysis due to excess motion artifact. There was no difference in motion artifact between the groups ($p = 0.38$). Mothers were interviewed at the time of enrollment as to their level of educational attainment.

Neurodevelopmental assessment

Blinded assessment was performed at 16 years of age in a separate session from the fMRI scan using the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991), the Peabody Picture Vocabulary Test-Revised (PPVT-R) (Peabody, 1981), the Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999) and the Test of Word Reading Efficiency (TOWRE) (Torgesen et al., 1999). The WISC-III is an intelligence test with scores assessing full scale intelligence quotient (FSIQ), performance IQ (PIQ), verbal IQ (VIQ) and the verbal comprehension index (VCI). The VCI score is derived from four subscales: vocabulary, similarities, information and comprehension. The PPVT-R is designed to assess receptive vocabulary, while the CTOPP provides measures of phonologic awareness, phonological memory, and rapid naming.

Task paradigm during fMRI scanning

We employed an event-related cue-target identity task that required a match/mismatch judgment between pictures and words that were presented acoustically and/or in printed form on each trial. Responses were made via a button press. Between 8 and 10 runs were completed per subject. This task is described in detail in Frost et al. (2009).

fMRI data analysis

Preprocessing

All data were converted from Digital Imaging and Communication in Medicine (DICOM) format to Analyze format using XMedCon (http://xmedcon.sourceforge.net/). During the conversion process, the first four images at the beginning of each of the ten functional series were discarded to enable the signal to achieve steady-state, leaving 109 measurements for analysis. Images were first slice time corrected using sinc interpolation and then motion corrected using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Runs