



Adaptive mechanisms of developing brain: Cerebral lateralization in the prematurely-born[☆]



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ABSTRACT

Preterm birth results in alterations in neural connectivity, but the impact of prematurity on the functional organization of the developing brain has yet to be explored. To test the hypothesis that preterm birth alters cortical organization during the late second and third trimesters of gestation, we interrogated cerebral lateralization at rest in 26 very preterm subjects (birth weight 500–1500 g) with no evidence of brain injury and 25 healthy term control subjects at term equivalent age. Employing an unbiased voxel-based measure of functional connectivity, these data demonstrated that cerebral lateralization is impaired in the prematurely-born. At term equivalent age, preterm neonates showed significantly less lateralization in regions subserving both receptive and expressive language, left Brodmann (BA) areas insula–BA22–BA21 and L BA45–BA47 ($p < 0.05$ corrected for multiple comparisons for both). Exploratory region of interest analyses demonstrated significantly less inter-hemispheric connectivity from L BA22 to R BA22 in preterm infants compared to term controls ($p < 0.005$) and from R BA22 to its homolog ($p < 0.005$). L BA22, Wernicke's area, was more strongly connected to R BA39, foreshadowing neural networks for language in preterm subjects at school age, adolescence and young adulthood. For these very preterm neonates born at less than 30 weeks' PMA, the degree of prematurity had no influence on lateralization in these differential regions.

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Introduction

While it has been known for many years that prematurity results in disordered neural connectivity (Huppi et al., 1998; Inder et al., 2003; Nosarti et al., 2006; Smyser et al., 2010; White et al., 2014), emerging data suggest that preterm (PT) birth alters the fundamental functional organization of developing brain. Multiple studies across the past decade suggest that alterations in neural networks contribute to the cognitive and behavioral difficulties of the prematurely-born (Doesburg et al., 2011; Ment et al., 2009; Myers et al., 2010; Nosarti, 2013; Salvan et al., 2014), but recent reports demonstrate alterations in the

genetically-determined process of cerebral lateralization in PT subjects at adolescence and young adulthood (Scheinost et al., 2014; Wilke et al., 2014). Lateralization implies localization of a cognitive task to a specific cerebral region, and lateralization of language is a critical characteristic of developing brain (Power et al., 2010; Renteria, 2012).

Functional MRI studies suggest that those regions known to constitute the neural network for language in adults, children and older infants are also activated in newborns in response to language stimulation (Dehaene-Lambertz et al., 2002, 2004, 2010). Consistent with neuropathologic studies (Chi et al., 1977), this network involves both frontal and temporal regions with a clear dominance of the left hemisphere (Pena et al., 2003; Perani et al., 2011), and those regions sub-serving language are functionally connected (Hickok and Poeppel, 2007).

Likewise, studies across the putative third trimester of gestation suggest that healthy PT neonates develop the structural basis for language during this time interval (Dubois et al., 2009; Leroy et al., 2011). Similarly, functional imaging demonstrates the emergence of auditory networks in PT subjects between 30 and 40 weeks of gestation (Doria et al., 2010; Omidvarnia et al., 2013; Smyser et al., 2011). However, relative to term controls, PT neonates exhibit altered discrimination of speech sounds and deficits in auditory memory at term

Abbreviations: BA, Brodmann area; Ch-ICD, cross-hemisphere intrinsic connectivity distribution (i.e., lateralization); GLM, general linear model; ICD, intrinsic connectivity distribution; PMA, postmenstrual age; PT, preterm; TBV, total brain volume.

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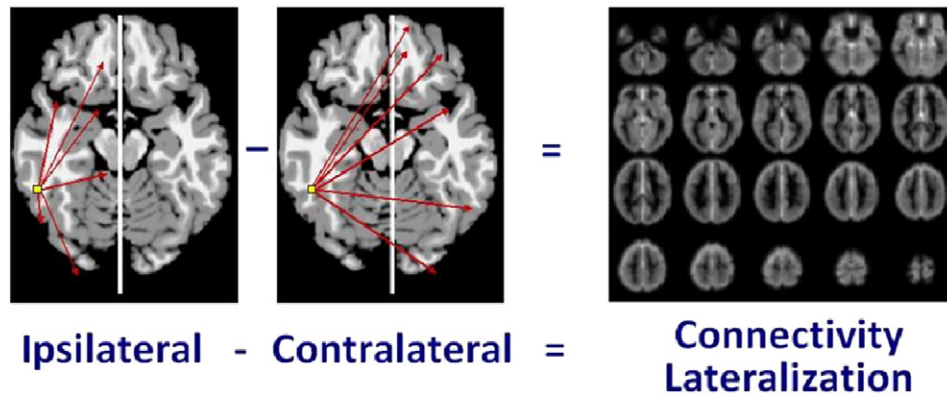


Fig. 1. Cerebral lateralization. Ch-ICD, or cross-hemisphere intrinsic connectivity distribution, is a measure of the cerebral lateralization of any voxel to a particular hemisphere. It independently compares the voxel's connectivity to the intra-hemispheric (ipsilateral) and inter-hemispheric (contralateral) hemisphere and is calculated as ipsilateral connectivity minus contralateral connectivity.

equivalent age and long term deficits in language processing (Luu et al., 2009; Taylor et al., 2004; Therien et al., 2004).

These data suggest that PT birth results in both proximate and long-lasting changes in cerebral functional organization. To test the hypothesis that PT birth alters cortical organization during the late second and third trimesters of gestation, we interrogated cerebral lateralization at rest in very PT subjects and term control subjects at term-equivalent age employing a novel data-driven voxel-based connectivity analysis strategy. Secondary seed-based analyses provided information about neural networks for language in the preterm brain.

Methods

This study was approved by the Yale University Human Investigation Committee.

Subjects

Preterm neonates with a birth weight between 500 and 1500 grams and healthy term controls born between 37 and 41 weeks' postmenstrual age (PMA) were eligible for the protocol and prospectively enrolled between 9-01-10 and 4-30-14. All were inborn and appropriate for gestational age (AGA). Exclusion criteria included evidence of congenital infections, congenital malformations and/or chromosomal disorders, seizures, intraventricular hemorrhage, periventricular leukomalacia or focal abnormalities on any MRI.

Imaging parameters

Subjects were scanned without sedation using a feed-and-wrap protocol in either a 3 T Siemens (Erlangen, Germany) TIM Trio or Verio MR system with a 32-channel parallel receiver head coil. Localizer images were acquired for prescribing the functional image volumes, aligning the seventh or eighth slice parallel to the plane transecting the anterior and posterior commissures. T1-weighted 2D anatomical images were collected (TR = 300 ms, TE = 2.47 ms, FoV = 220 mm, matrix size = 256 × 256, slice thickness = 4 mm, flip angle = 60°,

bandwidth = 300 Hz/pixel with 25 slices) with 25 AC-PC aligned axial-oblique slices in addition to 3D anatomical scans using magnetization prepared rapid gradient echo (MPRAGE) (176 contiguous sagittal slices, slice thickness = 1 mm, matrix size = 256 × 256, FoV = 256 mm, TR = 2530 ms, TE = 2.77, flip angle = 7°, bandwidth = 179 Hz/pixel). After these structural images, acquisition of functional data began in the same slice locations as the axial-oblique T1-weighted data. Functional images were collected using an echo-planar image gradient echo pulse sequence (TR = 1500 ms, TE = 27 ms, FoV = 220 mm, matrix size = 64 × 64, slice thickness = 4 mm, flip angle = 60°, bandwidth = 2520 Hz/pixel, 25 slices). Functional runs consisted of 186 volumes on the TIM Trio system or 235 volumes on the Verio system. The first 6 volumes were removed to allow the magnetization to reach the steady-state.

Connectivity preprocessing

Data analyses were performed as previously described (Kwon et al., 2014). Briefly, data were converted from Digital Imaging and Communication in Medicine format to analyze format using XMedCon (<http://xmedcon.sourceforge.net/>). Images were slice-time-corrected and motion-corrected using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). All further analysis was performed using BiImage Suite (Joshi et al., 2011). Several covariates of no interest were regressed from the data including linear and quadratic drift, six rigid-body motion parameters, mean cerebral-spinal-fluid (CSF) signal, mean white-matter signal, and overall global signal. The data were temporally smoothed with a zero mean unit variance Gaussian filter (approximate cutoff frequency = 0.12 Hz). A gray matter mask was applied to the data so only voxels in the gray matter were used in the calculation. Finally, as motion has been shown to confound connectivity studies (Van Dijk et al., 2012), blocks of data with a displacement greater than 1.5 mm or a rotation greater than 2 degrees of rotation were removed. There were no significant differences for motion when PT infants were compared to term controls ($p = 0.61$). All subjects had at least 2.5 minutes of resting state data.

Table 1

Characteristics of seed regions of interest.

Seed ROI	Volume (mm ³)	Talairach coordinates ^a	Origin of seed regions
L BA22	1018.51	−42, −7, −7	ch-ICD analysis ^b
R BA39	1402.82	29, −71, 31	Seed-based connectivity analysis from L BA22 ^b
R BA22	744.63	54, −36, 14	Seed-based connectivity analysis from L BA22 ^b
L Motor Cortex	4098.75	−44, −17, 42	Control region

^a Talairach coordinates are given for the center of the mass.

^b Seeds are $p < 0.005$ on original maps.

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