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Language at rest: A longitudinal study of intrinsic functional connectivity in preterm children☆,☆☆,☆☆☆

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ABSTRACT

Background: Preterm (PT) children show early cognitive and language deficits and display altered cortical connectivity for language compared to term (T) children. Developmentally, functional connectivity networks become more segregated and integrated, through the weakening of short-range and strengthening of long-range connections.
Methods: Longitudinal intrinsic connectivity distribution (ICD) values were assessed in PT ($n = 13$) compared to T children ($n = 12$) at ages 8 vs. 16 using a Linear Mixed Effects model. Connectivity values in regions generated by the group × age interaction analysis were then correlated to scores on full IQ (FSIQ), verbal IQ (VIQ), verbal comprehension IQ (VCIQ), performance IQ (PIQ), Peabody picture vocabulary test—revised (PPVT-R), and Rapid Naming Composite (RDRL_Cmp).
Results: Nine regions were generated by the group × age interaction analysis. PT connectivity significantly increased over time in all but two regions, and they ultimately displayed greater relative connectivity at age 16 than Ts in all areas except the left occipito-temporal cortex (OTC). PTs underwent significant connectivity reductions in the left OTC, which corresponded with worse performance on FSIQ, VIQ, and PIQ. These findings differed from Ts, who did not undergo any significant changes in connectivity over time.
Conclusions: These findings suggest that the developmental alterations in connectivity in PT children at adolescence are both pervasive and widespread. The persistent and worsening cognitive and language deficits noted in the PT subjects may be attributed to the loss of connections in the left OTC.

1. Introduction

1.1. Cognitive impairment in PTs

Preterm (PT) birth is a major global health burden, with up to 11% of all live born infants worldwide being born at less than 37 weeks gestation (Blencowe et al., 2012; Beck et al., 2010), and as many as one-third of prematurely born infants suffering from significant cognitive impairments during early childhood (Blencowe et al., 2013; Neubauer et al., 2013; Robertson et al., 2009; Saigal and Doyle, 2008). While Saigal et al. (2006) demonstrated that, by adulthood, PTs are comparable to their term (T) peers in educational attainment and functional independence, several studies have shown that PTs persistently display global impairment in cognition, language, and motor function (Botting et al., 1998; Bowen et al., 2002; Hack, 2009).

Even in early childhood, language deficits are evident. At age 2.5, PT had lower scores on tasks of cognition, receptive and expressive communication, with over 10% of PT children showing moderate–severe

Abbreviations: BA, Brodmann area; FSIQ, full scale IQ; OTC, occipito-temporal cortex; PIQ, performance IQ; PPVT, Peabody picture vocabulary test; PT, preterm; RDRL_Cmp, Rapid Naming Composite; ROI, region of interest; RSC, resting state connectivity; RSN, resting state network; T, term; VCIQ, verbal comprehension IQ; VIQ, verbal IQ; VWFA, visual word form area.

☆ Ethics: This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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delay in these areas (Mansson and Stjernqvist, 2014). Similarly, at age 6, PTs had significantly poorer reading, vocabulary and comprehension than Ts (Pritchard et al., 2009).

Promisingly, there is some evidence to suggest that these early language deficits in PTs may improve with age. Luu et al. (2009) found that from ages 3 to 12, PTs had poorer receptive vocabulary compared to controls, but they improved over time and nearly approached the normative values by age 12. These "catch-up gains" in receptive vocabulary were also seen at age 16, although they continued to show impairment in phonology (Luu et al., 2011).

1.2. Altered neural structures in PTs

PT birth substantially alters neurodevelopment, with the brains of PT, school-age children being 5–6% smaller than those of matched T controls (Nosarti et al., 2002; Peterson et al., 2000). During childhood and adolescence, PT brains fail to undergo similar white matter expansion and gray matter pruning in temporal and frontal lobes (Ment et al., 2009), resulting in significant decreases in left frontal and bilateral temporal white matter volumes (Schafer et al., 2009). At young adulthood, PTs display alterations in both regional volume and microstructural connectivity in language areas, including the left frontal language regions, temporal and parietal cortices, and both cerebellar hemispheres (Boardman et al., 2010; Haldipur et al., 2011; Lind et al., 2011; Nosarti et al., 2011; Tam et al., 2009).

Several studies have noted that these structural alterations mediate cognitive deficits. Nosarti et al. (2008) observed that PTs had diffuse decreases in regional volumes compared to Ts, which correlated with greater cognitive impairment. Parker et al. (2008) also showed that PTs had reduced cerebellar volumes compared to Ts, and although initial cognitive measures showed a positive correlation with cerebellar volume, this did not persist after controlling for white matter volume.

Notably, Schafer et al. (2009) found that, despite PTs having significant differences in functional connectivity to language areas as well as a reduction in left frontal and bilateral temporal white matter, PT subjects performed comparably on semantic language tasks to normal term controls. Lubsen et al. (2011) echoed these findings, demonstrating that despite PTs having lower fractional anisotropy values, a marker of microstructural connectivity, in several language regions, they performed comparably to Ts.

1.3. Development of resting state functional connectivity networks

Recently, resting state functional connectivity MRI has come into focus as a method for identifying functional neural networks. It is based on the finding that distinct neural regions that display temporally related spontaneous BOLD fluctuations at rest reflect a functionally connected network (Cohen et al., 2008).

Few studies have investigated resting state connectivity (RSC) in children or across development. Of these studies, it has been reported that the functional organization of the brain in children is significantly different than that of adults. Children display more local, short-range connections between adjacent brain regions, which eventually shift to more long-range, distributed connections in adults (Dosenbach et al., 2010). This developmental trend encompasses "segregation" of neural networks via the weakening of short-range connections and concurrent "integration" of distant regions into functional networks via the strengthening of long-range connections (Fair et al., 2009).

The evolving functional architecture over development appears to correspond to maturing behavioral and cognitive abilities. Neural regions that subserve higher level functioning exhibit stronger functional activation or deactivation over time, enhancing cognitive maturity (Rubia, 2013). A synchrony of stronger activation within networks and enhanced deactivation of antagonistic networks has been shown to correlate with more mature performance on tasks of higher order executive function, such as attention, working memory, and regulatory control (Barber et al., 2013; Marsh et al., 2006).

While this trend of "segregation and integration" seems to characterize maturation in a number of neural networks, little is known about the development and refinement of language network connectivity, or how this development is affected by PT birth. At adolescence, PTs display globally stronger intra- and inter-hemispheric connectivity to the superior temporal lobes than Ts, but functional connectivity between these language regions and overall network efficiency are reduced in PTs (Wilke et al., 2014). PTs continue to demonstrate greater connectivity at age 20 in hypothesized language processing areas, including left temporal–parietal areas, left and right inferior temporal lobes, and the medial frontal lobes (Scheinost et al., 2012). Although previous studies have demonstrated significant connectivity differences between PTs and Ts (Wilke et al., 2014; Scheinost et al., 2012), it is unclear whether these connections are present at birth and are not pruned through the course of development or if they develop over time.

Furthermore, the use of resting state functional MRI data has several limitations. For one, it relies on pre-selected regions of interest (ROI) to be investigated and thus may overlook non-selected areas that similarly display differential connectivity. Also, it relies on arbitrarily defined correlation thresholds to describe functional connectivity differences. To overcome these limitations, Scheinost et al. (2012) utilized intrinsic connectivity distribution (ICD). ICD allows for the characterization of all connections via whole-brain survey, without requiring a priori defined ROIs or connectivity thresholds. It measures the connectivity of each voxel to all other neural voxels and allows for elaboration of a specific voxel's degree of connectivity throughout the brain without being limited to connectivity within a pre-defined network (Scheinost et al., 2015).

In this longitudinal study, we investigate how intrinsic functional connectivity is altered from childhood through adolescence in PTs compared to Ts, as well as how these changes in connectivity relate to cognitive, semantic, and phonologic testing scores. We hypothesize that, when compared to Ts, PTs will display altered connectivity trajectories between childhood and adolescence. Functional connectivity will be correlated with performance on language tasks.

2. Materials and methods

This study was performed at the Yale University School of Medicine, New Haven, CT and Brown Medical School, Providence, RI. The protocols were reviewed and approved by institutional review boards at each location. Children provided written assent; parent(s) provided written consent for the study. All scans were obtained at Yale University and were analyzed at Yale University.

2.1. Subjects

The PT cohort consisted of children who were enrolled in the follow-up MRI component of the Multicenter Randomized Indomethacin Intraventricular Hemorrhage Prevention Trial (Ment et al., 1994). Only those PT children without evidence of intraventricular hemorrhage, periventricular leukomalacia and/or low-pressure ventriculomegaly and who lived within 200 miles of the Yale study center were included. T 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. Minority status was defined as being of non-Caucasian race and was reported by parents at the time of the assessment. Only PTs and Ts with data collected at both 8 years and 16 years of age were included.

2.2. Neurodevelopmental assessments

Serial standardized neuropsychological assessments were performed by testers blinded to the randomization status of the subjects