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Developmental synergy between thalamic structure and interhemispheric connectivity in the visual system of preterm infants

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ABSTRACT

Thalamic structural co-variation with cortical regions has been demonstrated in preterm infants, but its relationship to cortical function and severity of non-cystic white matter injury (non-cystic WMI) is unclear. The relationship between thalamic morphology and both cortical network synchronization and cortical structural connectivity has not been established. We tested the hypothesis that in preterm neonates, thalamic volume would correlate with primary cortical visual function and microstructural integrity of cortico-cortical visual association pathways. A total of 80 term-equivalent preterm and 44 term-born infants underwent high-resolution structural imaging coupled with visual functional magnetic resonance imaging or diffusion tensor imaging. There was a strong correlation between thalamic volume and primary visual cortical activation in preterms with non-cystic WMI ($r = 0.81$, p-value $= 0.001$). Thalamic volume also correlated strongly with interhemispheric cortico-cortical connectivity (splenium) in preterm neonates with a relatively higher severity of non-cystic WMI (p-value < 0.001). In contrast, there was lower correlation between thalamic volume and intrahemispheric cortico-cortical connectivity, including the inferior longitudinal fasciculus and inferior frontal orbital fasciculus. This study shows distinct temporal overlap in the disruption of thalamo-cortical and interhemispheric cortico-cortical connectivity in preterm infants suggesting developmental synergy between thalamic morphology and the emergence of cortical networks in the last trimester.

1. Introduction

Recent studies show that thalamo-cortical connectivity is regionally altered in preterm infants and that thalamic volume demonstrates structural co-variance with both cortical volume and microstructure of selected cerebral white matter tracts (Ball et al., 2013a). These studies have also demonstrated that both fronto-temporal and parietal–occipital cortical regions are altered in preterm infants relative to the thalamus, delineated via either structural connectivity (as measured with diffusion tensor imaging) and/or volumetric measurements (Ball et al., 2013b). In parallel, functional neurodevelopment has also recently been assessed in preterm infants using stimulus-driven responses/resting-state networks (functional magnetic resonance imaging) and electrical activity (electroencephalography) (Doria et al., 2010; Smyser et al., 2010). Results from these functional modalities demonstrate the emergence of bilateral homologous cortical network development. For example, recent resting state functional connectivity studies in the preterm infants have demonstrated the existence of multiple bilateral symmetric cortical resting state networks of primary sensory centers in the last trimester of development using either ICA or seed based analytical approaches or in relation to EEG data (Doria et al., 2010; Smyser et al., 2011; Smyser et al., 2013). In addition, different evoked based functional MRI in similar preterm populations have been shown to elicit stimulus related bilateral homologous cortical activation in term-born infants as well as preterm infants at term equivalent age (Seghier et al., 2006). During the same period of development, structural development of homotopic callosal connections via tractography has also been demonstrated (Pandit et al., 2013). Results from each of these modalities suggest a convergent model of cerebral development based on structural and functional interhemispheric associations between homotopic counterparts during the last trimester and has been recently replicated by an in-utero brain functional connectivity study (Thomason et al., 2013). Thalamo-cortical connectivity is also likely related to the development

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of synchronous cortical development in the last trimester, but studies that correlate thalamic structure to both cortical function and cortical microstructural development in preterm neonates are lacking (Ball et al., 2013a). In addition, it is unclear how non-cystic white matter injury modulates the development of thalamo-cortical connectivity and structure–function relations, as many recent studies have excluded large cystic white matter lesion, but have not evaluate the relationship of connectivity to non-cystic white matter injury (focal and diffuse), which is the more common contemporaneous type of white matter lesion seen in preterm infants (Back and Miller, 2014; Volpe, 2009).

At the start of the third trimester of fetal development (~24 weeks post-conceptional age), brain development is characterized by the migration of thalamo-cortical afferents from the subplate, where they have been accumulating since about 13 weeks postconceptional age, into the cerebral cortex (Kostovic et al., 2011, 2014). These axons initially form connections with cells in the deepest layers of the cortex, before establishing their principal connections to neurons in layer 4. At the same time thalamo-cortical afferents are migrating from the subplate into the overlying cortex, cortico-cortical afferents are accumulating in the subplate, led first by the interhemispheric (callosal) afferents in the splenium and later by longitudinal intrahemispheric (associative) afferents (Kostovic et al., 2011; Kostovic and Jovanov-Milosević, 2006; Kostovic and Judas, 2007). Like the thalamo-cortical afferents, these cortico-cortical afferents first form transient synapses with subplate neurons before later migrating into the cortex and ultimately forming principal connections with neurons in layers 2 and 3. The ontogeny of these developmental processes suggests that injury at an early stage of development should not only affect cortico-cortical connections but also thalamo-cortical connections. Moreover, as this pattern involves both cortico-cortical connections and thalamo-cortical connections, in addition to white matter volume loss, this should have the most profound impact on gray matter, both cortically and in the thalamus, affecting the volume of those structures as well. In scans of early preterm neonates, there is a lack of bilateral or unilateral activation to visual stimuli and RSN are not fully developed, suggesting that the last trimester is indeed a critical period in the development of these cortical networks (Doria et al., 2010; Seghier et al., 2006). Therefore, preterm birth and associated injury provide a model to test specific structure–functional relationships using multi-modal MRI.

In this study, we applied this framework toward the study of visual function and visual system organization in preterm-born infants. Cognitive visual dysfunction (CVD) is one of the most common findings among survivors of prematurity, referring to a range of neurocognitive impairments from neurosensory deficits to higher order deficits in visuoperception, visuoattention and visuospatial working memory (Atkinson and Braddick, 2007; Clark and Woodward, 2010; Woodward et al., 2009; Woodward et al., 2011; Woodward et al., 2012). Although deficits in higher-order functions (e.g., visuospatial working memory) are difficult to detect in infants, neurosensory deficits may be demonstrated on clinical examination and on adjuvant tests, such as visual-evoked potentials or visual activation during functional magnetic resonance imaging (fMRI). Additionally, by term equivalency, the tissue microstructure of all of the major tracts associated with visual functions (e.g., optic radiations, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) can be observed with diffusion tensor imaging (DTI) and tractography. We applied fMRI and DTI together with high-resolution anatomic imaging in two cohorts of preterm and term born neonates to identify large-scale patterns in thalamo-cortical and cortico-cortical abnormalities within the visual system. Specifically, we first measured visual activation during passive visual stimulation and correlated the extent of activation with thalamic structure in preterm neonates. Subsequently, in a separate dataset, we then used diffusion tensor imaging to compare associations between thalamic structure and the microstructural integrity of cortico-cortical pathways implicated in visual associative function. Specifically, we examined both interhemispheric cortico-cortical pathways (i.e., forecepts major/splenium including parietal–occipital homologous connectivity which correlate with dorsal stream structures) and intra-hemispheric cortico-cortical association pathways (i.e., inferior longitudinal fasciculus including temporal–occipital connectivity and inferior fronto-occipital fasciculus including frontal–occipital connectivity which correlate with ventral stream structures) in preterm neonates with non-cystic white matter injury. *We tested the hypothesis that in preterm neonates, thalamic morphometry (i.e., thalamic volume) would be strongly correlated with primary cortical visual function and with the microstructural integrity of homotopic cortico-cortical association pathways*. Proving this hypothesis could provide compelling evidence that functional cortical activation patterns and homotopic callosal connections are synchronously related to development of thalamic structure in vulnerable preterm infants, particularly in the setting of non-cystic WMI. Demonstration of these relationships also suggest that these methods provide complementary approaches to the assessment of neurodevelopment and can be used to provide a more complete understanding of the interrelationship between structure and function in the last trimester of development.

2. Materials and methods

2.1. Subject and preterm cohort description

The study consists of two cohorts of term-equivalent preterm neonates consecutively recruited from the same high-risk NICU as previously described in this IRB approved study HIPPA compliant study (Bluml et al., 2014; Wisnowski et al., 2013). Cohort 1 was characterized by neonates that underwent both visual functional MRI and high resolution anatomic MR imaging. Cohort 2 was characterized by neonates that underwent both diffusion tensor imaging and high resolution anatomic MRI imaging. Functional MRI, DTI imaging and high resolution anatomic MRI was integrated into clinically indicated MR scans. Clinical variables were reviewed from the NICU database for the preterm cases for determination of clinical risk factors for cohorts 1 and 2. Our criteria for recruitment of term neonatal controls, as been previously described in detail (Bluml et al., 2014; Wisnowski et al., 2013). All parents gave prospective written consent for the functional MRI portion of the study. IRB approval was obtained for all portions of the study as previously described (Bluml et al., 2014; Wisnowski et al., 2013).

2.2. Classification of preterm non-cystic white matter injury (non-cystic WMI)

Similar to other recent preterm thalamic structural covariate analyses, we excluded large brain parenchymal lesions including large cystic PVL lesions and periventricular hemorrhagic infarction from the main analysis of the preterm cases (Ball et al., 2013a,b). However, different from these studies, we did characterize the severity of non-cystic WMI based on prior published grading scales to classify white matter injury in the premature infants including (1) punctate white matter lesions; (2) diffuse ventriculomegaly; (3) increased subarachnoid space/sulcal enlargement; and (4) diffuse excessive T2 hyperintensity (DEHSI) (Miller et al., 2005; Woodward et al., 2006). For cohort 1 (functional MRI), all preterm cases that were classified as having white matter injury (preterm-WMI) had a combination of the four imaging findings described above. For comparative purposes, we also performed functional MRI in a small cohort of preterm cases (classified as preterm-IVH) that had serial cranial ultrasound evidence of Grade III–IV intraventricular hemorrhages with conventional MR and evidence of post-hemorrhagic hydrocephalous. We used this preterm IVH group for internal comparison because compression of the retrogeniculate pathways was expected from the post-hemorrhagic hydrocephalous, and therefore we expected reduced visual functional activation.

For cohort 2 (diffusion tensor imaging), only preterm cases without evidence of intraventricular hemorrhage were used and were classified