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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

into two groups based on degree/severity of non-cystic WMI (cases with cystic periventricular leukomalacia and periventricular venous infarction/hemorrhage were excluded like cohort 1). Preterm cases that exhibited punctate white matter lesions, moderate ventriculomegaly, moderate subarachnoid space/sulcal enlargement and moderate/severe DEHSI were included in the moderate-severe non-cystic white matter injury group (preterm-mod/severe non-cystic WMI). Preterm cases without punctate white matter lesions, normal to mild ventriculomegaly, normal to mild enlarged subarachnoid spaces/sulcal enlargement and normal/mild DEHSI were included in the less severe preterm non-cystic WMI group (preterm-mild non-cystic WMI). Our classification of DEHSI has been previously described (Maalouf et al., 1999).

2.3. Visual functional MRI imaging protocol (cohort 1)

For all of the visual functional MR studies, the influence of MR gradient noise was substantially reduced by (i) using a double-walled MR-compatible incubator, (ii) an MR-compatible head-set, specifically designed for newborns and infants (Resonance Technology Inc., Northridge, California). Imaging was performed with a 1.5 T MR system (CV/i, 9.1 software GE/MS Milwaukee). Functional acquisition: BOLD (Blood Oxygen Level Dependent) single shot gradient-echo echo planar imaging (GR-EPI) sequence (TR3000, TE60, FOV180, FA90, 64 × 64 matrix, 3 × 3 × 3 voxel resolution) and high resolution T2-weighted FSE images used to overlay and thalamic volume segmentation (see below). The functional imaging paradigm was a block design consisted of 3 alternating epochs of control (darkness) and activation (flicker light at 1 Hz). Statistical Parametric Mapping software (SPM99) was used for spatial pre-processing and *t*-test statistics. The visual paradigm consisted of alternating 30 s blocks of control and test conditions. During test blocks neonate subject participants were exposed to bright light switched on and off at 1 Hz as compared to control blocks during which they were exposed to constant darkness. We choose a block-design paradigm of 3 alternating epochs of control (C — resting with no stimulation) and activation conditions (A — bright light flickering on and off). Starting with a control-condition, conditions were performed for 30 s alternating for a total of 3 min (CACACA paradigm). Ambient light was controlled during experiments with identical conditions for all subjects. Functional imaging was preceded by three excitations, excluded from post-processing, in order to archive steady-state magnetization of the brain tissue. A high-resolution anatomical image was obtained to locate activated areas using a T2-weighted fast spin-echo (FSE) sequence with improved delineation between white/gray matter of the newborn brain. Imaging parameters: 512 × 512 voxel matrix, TR = 3 ms, TE = 20 ms, FOV = 180 mm², slice thickness 3 mm, 30 axial slices oriented identical to functional images. Data processing of the functional images consists of spatial pre-processing, statistical time-series analysis, and brain map visualization. All post-processing was performed using Statistical Parametric Mapping (SPM99, http://www.fil.ion.ucl.ac.uk/spm). Time series volumes (fMRI) and T2 volume (MRI) of each subject were inspected visually and by automatic image histogram comparison to detect imaging artifacts. Volumes in each fMRI scan were realigned to the first temporal volume of the series to adjust for micro head movement. We used 6-parameter affine transformation (ridged body) with sinc-interpolation to estimate transformation parameters by least squares optimization between volume pairs and for final transformation. 120 realigned functional volumes, 60 volumes per task, of each subject were co-registered with its individual anatomical reference image (T2-weighted volume). We used the SPM co-registration for MRI volumes, a linear 12-parameter affine transformation (rotation, translation, sheer and zoom), to estimate transformation parameters and to spatially co-register the fMRI volumes. Areas of activation/deactivation were identified ($p < 0.01$) and mapped onto the anatomical T2 correlate. Using the normalized mean T2*-image, dephasing artifacts between the time series images which occur from inhomogeneity of the magnetic field was avoided. We collected the frequency of activation (positive) and deactivation (negative) responses in the calcarine cortex of the neonate. A relative percent visual activation was estimated by measuring the areas of visual activation and dividing by the term control with the largest areas of activation. Our methodology of acquisition post-processing of functional MR in the newborn has been previously described (Erberich et al., 2003, 2004, 2006; Panigrahy et al., 2010).

2.4. Diffusion tensor imaging protocol (cohort 2)

All imaging was performed on the same 1.5 T General Electric System (Ge-Medical Systems, Milwaukee, WI) described above with a neonatal receive-transmit head coil. The following imaging sequences were acquired and diffusion tensor imaging protocol included: echo-planar imaging (EPI) sequence with the following parameters (TE/TR = 80/10,000 ms, field of view = 22 cm, matrix = 128 × 128; in plane resolution 1.7 mm) applied along 25 non-collinear directions with a b-value of 700 s/mm^2. In this study, we used two main methods for post-processing of neonatal diffusion tensor imaging data including: 1) TBSS (for unbiased whole brain analysis of white matter tracts) and 2) probabilistic tractography for selected cortico-cortical association tracts (Fig. 1). We used a modified version of tract-based spatial statistics (TBSS), which is an advanced post-processing registration approach, which improves the sensitivity, and interpretability of analysis on groups of DTI studies. Further modification of this technique has shown linear association between respiratory morbidity and microstructural alterations in white matter of preterms (Ball et al., 2010). Our methodology of ROI and TBSS in neonatal brain has been previously described in detail (Paquette et al., 2013). Probabilistic tractography was performed using Oxford University's FMRIB software library (FSL). Prior to estimation of diffusion parameters for probabilistic tracking, subject DTI images were first motion and eddy current corrected using a rigid body registration, followed by brain extraction using FSL's Brain Extraction Tool. Our tracts of interest were splenium of corpus callosum, PTR (posterior thalamic radiations), ILF and IFOF (Thomas et al., 2009). Mask was manually drawn around the seed ROI in individual subject diffusion space. The splenium of the corpus callosum were delineated using an overlapping two seed ROI approach where one seed was placed on a sagittal slice in each hemisphere, with one contralateral seed serving as the waypoint mask for the other. The age range in our population presents the issue of varying brain volumes and subsequent ROI size. To account for this, extracted tracts were normalized by conservatively thresholding to only include voxels that receive a total number of streamlines equivalent to at least 1% of the waytotal (i.e., streamlines that successfully traversed the corresponding waypoint mask). In the splenium of the corpus callosum, the inferior longitudinal fasciculus, and inferior frontal orbital fasciculus, two ROIs were used as seeds, and the combined waytotal was used for thresholding. These thresholded tracts were then binarized and overlaid onto the diffusivity maps of interest in order to acquire mean values along the individual tracts. Paired *t*-tests were performed between bilateral tracts, thresholded at $p < 0.01$, in order to test for asymmetry. Tracts with no significant contralateral difference were averaged for all subsequent analyses. Each subject's fractional anisotropy maps were first linearly registered to MNI152 standard space using FSL's FLIRT linear registrations tool using a 12 degree of freedom affine transformation. The resulting transformation matrices were then applied to the subject's corresponding binarized delineated tracts. The transformed FA images were then non-linearly registered to FMRIB58 FA standard space using FSL's FNIRT non-linear registration tool. The subsequent transformation matrices were applied to the corresponding, previously transformed tracts. In order to purely compare general tract distribution among the cohorts, right and left spatially normalized tracts were averaged on each population by flipping the left side tracts over the *y* axis and averaging with their contralateral counterparts. The spatial distribution maps were generated by overlaying each

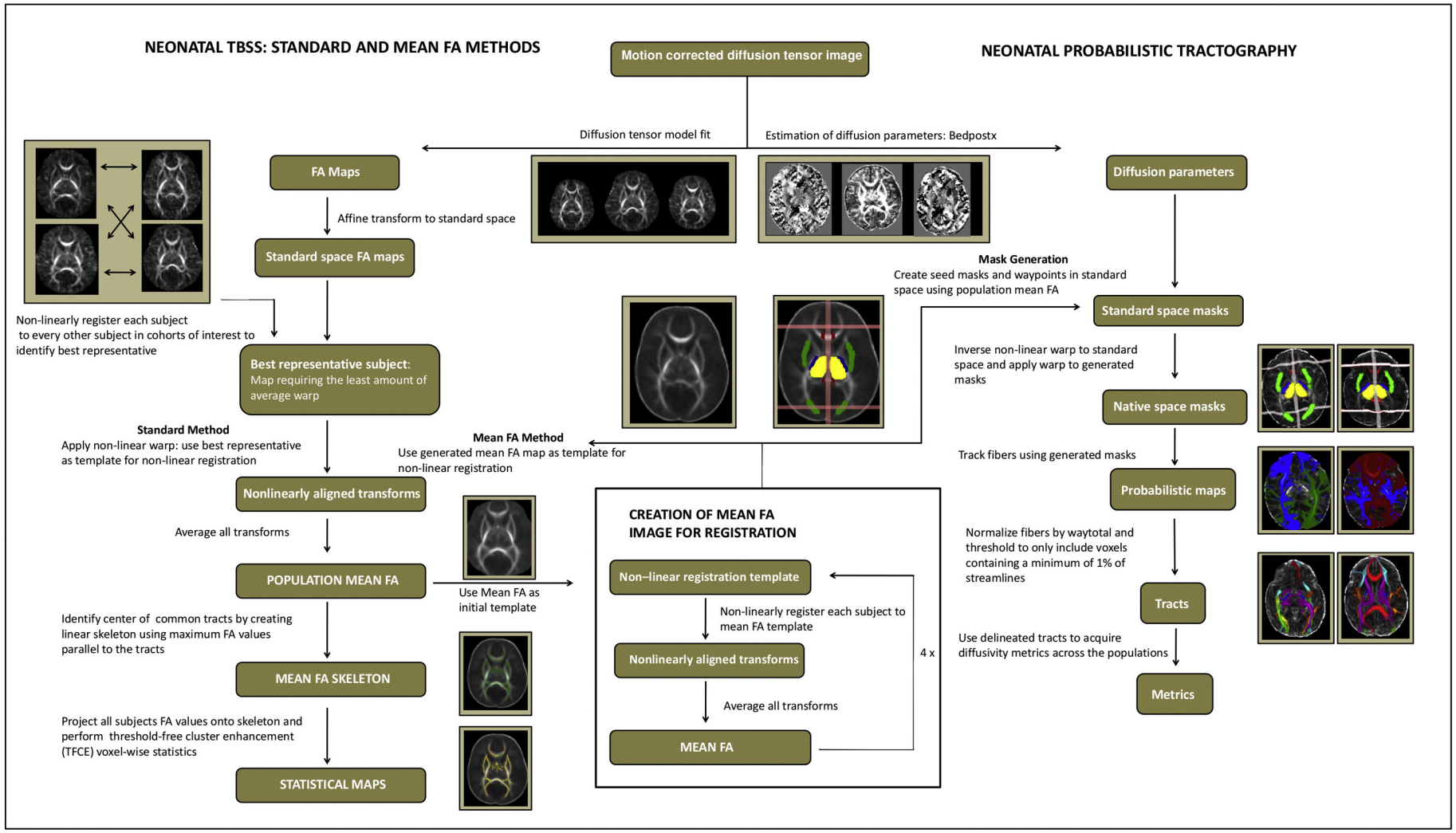

Fig. 1. Methodology for neonatal TBSS/probabilistic analysis performed in FSL. After motion correction of raw DTI data, the right side depicts the pipeline for the TBSS processing and the left side depicts the pipeline for the probabilistic tractography processing (see Materials and methods section for more detail).

cohort's averaged bilateral tracts onto standard space and thresholding to only include voxels containing at least 10% of subject tracts.

2.5. Manual thalamic segmentation and brain metric measurements (cohorts 1 and 2)

The bilateral regions of the thalamus were manually traced on the 3D coronal SPGR images using ITK-SNAP (Yushkevich et al., 2006). The margins of the neonatal thalamus were determined by reference to the *Stereotactic Atlas of the Human Thalamus and Basal Ganglia* by Anne Morel (Erbetta et al., 2009; Niemann et al., 2000; Wiegell et al., 2003). High resolution axial T2 and coronal 3D SPGR images were co-registered when available to help with placement of the contours. Inter-rater and intra-rater reliability of thalamic volume measurement was tested in a subset of cases ($n = 5$) and determined to be approximately .85 and .93. To also assess the relationship of thalamic volume to overall brain volume, we performed brain metric measurements of extracerebral space, brain parenchyma and ventricular size, which has been previously described for similar preterm infant and validated with outcome studies (Nguyen The Tich et al., 2009; Tich et al., 2011). Fifteen standard head and brain measurements (bifrontal diameter, left and right frontal height, brain and bone biparietal diameter, frontal–occipital diameter, length of corpus callosum, surface of the vermis and transverse cerebellar diameter) were acquired by a single individual who was blind to subject status, which were then confirmed by a senior neuroradiologist. "Fluid" measures of the pericerebral space (interhemispheric distance, cranial caudal left and right interopercular distances) and the intracerebral spaces (diameter of the right and left lateral ventricles, third ventricle diameter) were manually measured on four selected slices.

2.6. Statistical analyses

Analysis of Variance (ANOVA), Fisher's Exact tests, and chi-square tests were used for comparing clinical variables between different preterm cohorts. R statistical language program was used to perform linear regression analysis between thalamic volume and both functional MRI measurements and probabilistic tractography measurements. Full partial correlations between thalamic volume and functional/structural measurements, controlling for postconceptional age (PCA) ($R_{vol,FA \mid PCA}$) were calculated in R. This was done by first regressing each coefficient of interest with PCA, followed by running a second regression using the calculated residuals. A similar process was used to also control for gestational age. We also used this type of regression analysis to explore the relationship of thalamic volume to brain metrics measurements in both cohort 1 and 2. All correlations were corrected for family-wise error rate using the Bonferroni method.

3. Results

3.1. Clinical characterization of preterm cohorts

For cohort 1 (visual functional MRI group) a total of 38 cases met the inclusion/exclusion criteria and had analyzable imaging data. Within cohort 1, there were 12 preterm with non-cystic WMI, and 10 preterm with IVH, and 16 term control cases. For cohort 2 (diffusion tensor MRI group), a total of 89 neonates fit the inclusion/exclusion criteria for this study and had analyzable imaging data. Within cohort 2, there were 27 preterm with mild non-cystic WMI, and 34 preterm with moderate/severe non-cystic WMI, and 28 term control cases. Mean gestational age and post-conceptional age at the time of scan was not significantly different between any of the preterm groups within cohort 1 and cohort 2. There were no statistically significant differences between any of the clinical variables collected between preterm non-cystic WMI injury groups within cohort 1 and cohort 2 including birth weight, antenatal steroids, Apgar score (1 and 5 min), head circumference, postnatal sepsis or necrotizing enterocolitis, and number of days ventilated.

3.2. Thalamic volume: correlation with functional visual MRI (cohort 1)

The term control group within the functional MRI cohort shows reliable and well-defined activation in the region of the calcarine cortex (primary visual cortex) for the 1 Hz task, comparable to what has been demonstrated previously in adult subjects (Fig. 2). In contrast, the preterm group with IVH demonstrated the least amount of significant voxels within the region of the calcarine cortex or primary visual cortex (Fig. 2). The preterm group with WMI demonstrated variable amount of significant voxels within the region of the calcarine cortex or primary visual cortex. When comparing thalamic volume among the three groups, the preterm IVH group had the lowest thalamic volume and the term comparison group had the highest thalamic volume. The preterm non-cystic WMI group had the most variable thalamic volume, between the term control and preterm IVH group. When correlation analysis with thalamic volume was performed, the preterm group with non-cystic WMI demonstrated a strong correlation between percent visual activation and thalamic volume ($r = 0.81$, $p = 0.001$) (Fig. 2). In contrast, there was no significant correlation between thalamic volume and percent visual activation ratio in the preterm IVH group (Fig. 2). Of note, there was no correlation found between thalamic volume and brain metric measurements (extra-axial fluid, brain parenchymal, or ventricular) in either preterm group. In addition, there was no correlation between visual percentage activation and brain metric measurements (extra-axial fluid, brain parenchymal, or ventricular) in the preterm PVL group.

3.3. Thalamic volume: correlation with cortical association connectivity (cohort 2)

We then used TBSS to globally assess microstructural changes on an unbiased voxel-wise basis between the three comparison groups within cohort 2. For the mild non-cystic WMI preterm group TBSS analysis, there was no difference detected between the preterm group and term comparison group for the corrected analysis. Therefore, the uncorrected analysis was examined (Fig. 3). The uncorrected TBSS analysis ($p < 0.05$; Fig. 3) showed significant voxel, which represented decreased anisotropy in the splenium, the right forceps major, and the fimbria/fornix region in the preterm group with mild non-cystic WMI compared to the term control group. In contrast, the mod-severe non-cystic WMI preterm group patients were found to have significantly reduced fractional anisotropy (FA) in large sectors of the central and posterior white matter, bilaterally, (Fig. 3) compared to the term control group. This included key regions not only within the developing visual system (i.e., posterior temporal-occipital white matter in region of the optic radiations, the inferior frontal–occipital fasciculus (IFOF), inferior longitudinal fasciculus, and the splenium of the corpus callosum), but also the developing limbic system (i.e., cingulum, fimbria, fornix) and motor system (i.e., corona radiata, body of the corpus callosum, posterior limb of the internal capsule) (Fig. 3).

We then used the probabilistic tractography data to correlate thalamic volume measurements with selected cerebral white matter cortical visual association connectivity including interhemispheric cortico-cortical connectivity measurements (splenium), thalamo-cortical connectivity (PTR) and ipsilateral cortico-cortical connectivity (IFOF and ILF) (Fig. 4). In the mild non-cystic WMI preterm group, there was reduced FA noted in the splenium compared to the term control group. In contrast, there were multiple reduced areas of FA in not only the ventral visual stream tract, including the ILF and the IFOF, but also the splenium in the mod/severe noncystic-WMI preterm group compared to the term controls (Fig. 4-top row, left). After age correction, there was significant correlation between thalamic volume and microstructural measurements for the splenium in the mod/severe

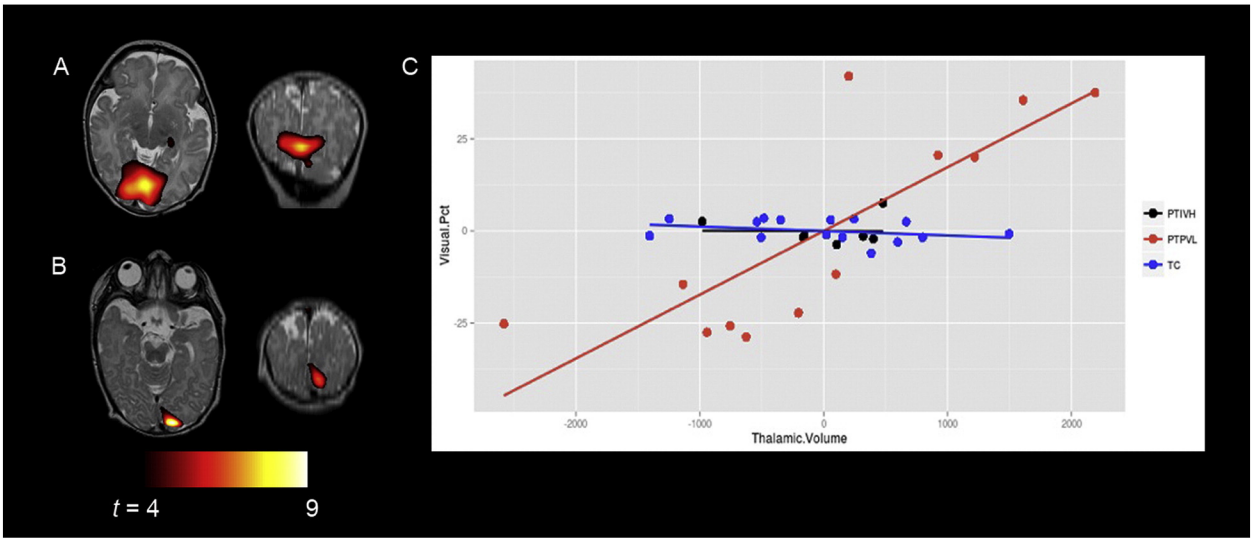

Fig. 2. The term controls within the functional MRI cohort shows reliable and well-defined bilateral activation in the region of the calcarine cortex (primary visual cortex) for the 1 Hz task, comparable to what has been demonstrated previously in adult subjects (A, top row, both axial and reformatted coronal shown). In contrast, the preterm group with non-cystic WMI demonstrated relatively decreased and variable activation within the region of the calcarine cortex or primary visual cortex (B, bottom row, both axial and reformatted coronal shown). When correlation analysis of relative percent of visual activation with thalamic volume was performed, the preterm group with non-cystic WMI (preterm-PVL) demonstrated a strong correlation between percent visual activation and thalamic volume (C). In contrast, there was no significant correlation between thalamic volume and percent visual activation in the preterm IVH group (C).

noncystic-WMI preterm group (Fig. 4-bottom row, right panel). In contrast, there was no significant correlation between thalamic volume and the ventral stream visual tract correlates (ILF and IFOF, representing ipsilateral intra-cortical cortical connectivity) (Fig. 4-bottom row, left and middle panel). Of note, there was a significant correlation between thalamic volume and bi-parietal diameter ($r = .7, p < 0.0001$), bi-frontal diameter ($r = .5$, $p = 0.003$), frontal lobe height ($r = .5$, $p = 0.02$) and cerebellar transverse diameter ($r = .7$, $p = <0.00001$) in the mild non-cystic WMI preterm group (all correlations corrected for family-wise error rate using the Bonferroni method). In contrast, there was no significant correlation in thalamic volume and structural brain measurements in the moderate-severe non-cystic WMI preterm group. Of note, thalamic volume did increase with thalamic parenchyma fractional anisotropy to the greatest degree in the term controls and relatively less in the preterm group with mild non-cystic WMI and the preterm group with moderate-severe non-cystic WMI (Fig. 5A). In contrast, there was an inverse relation between thalamic volume and radial diffusivity in the preterm group with moderate-severe non-cystic WMI (Fig. 5B).

4. Discussion

Multi-modal MR is a powerful way to delineate structural and functional relationship in vivo and could be potentially used to elucidate altered network connectivity in relation to preterm white matter vulnerability and injury. There are very few studies to date in preterm neonates that have attempted interrelated function (either resting state or stimulated) and structure in the context of specific neural system. Functional MRI is a well-established technique to measure brain activation from passive or active tasks performed during imaging,

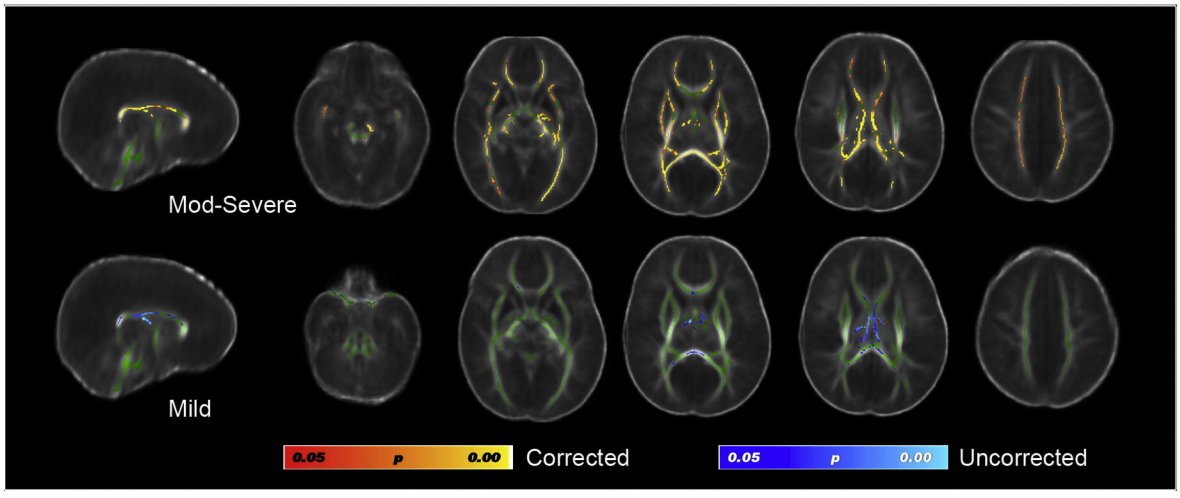

Fig. 3. TBSS was used to globally assess microstructural changes on an unbiased voxel-wise basis among the three cohorts. Compared to the term neonates, the mod-severe non-cystic WMI preterm group patients were found to have significantly reduced fractional anisotropy within the developing visual system (i.e., posterior temporal–occipital white matter in region of the optic radiations, the inferior frontal–occipital fasciculus (IFOF), inferior longitudinal fasciculus, and the splenium of the corpus callosum), the developing limbic system (i.e., cingulum, fimbria, fornix) and the developing motor system (i.e., corona radiata, body of the corpus callosum, posterior limb of the internal capsule, crus pedunculi, middle cerebellar peduncles, and inferior cerebellar peduncles) (top row). The uncorrected TBSS analysis ($p < 0.05$; bottom row) showed significant voxels with decreased anisotropy and increased radial diffusivity in the splenium and the right forceps major in the preterm group with mild non-cystic WMI compared to the term control group.

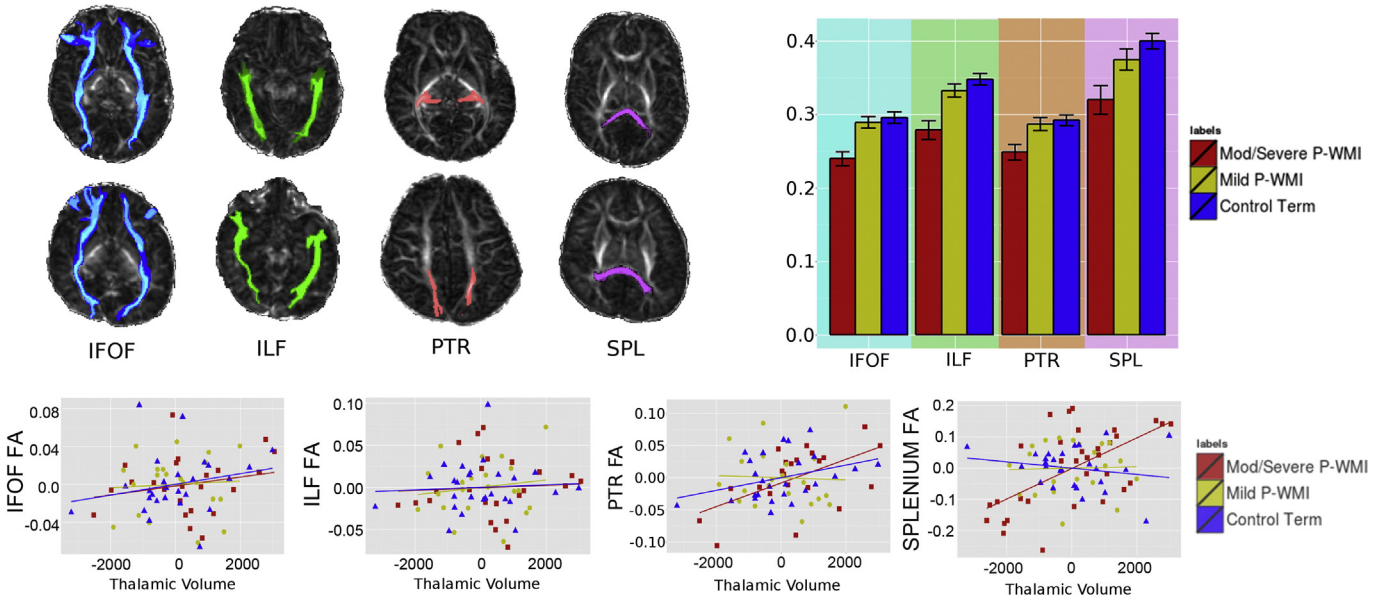

Fig. 4. Probabilistic tractography shows reduced FA in not only the ventral visual stream cortical association tract, including the ILF and the IFOF, but also the PTR and the splenium in the mod/severe non-cystic WMI preterm group compared to the term controls (top row). After age correction (gestational age and postconceptional), there were significant correlation between thalamic volume and microstructural measurements for the splenium and the posterior thalamic radiation. In contrast, there was no significant correlation between thalamic volume and the ventral stream visual tract correlates (ILF and IFOF), representing intra-hemispheric cortico-cortical connectivity, compared to PTR and splenium (bottom row).

including the primary visual cortex (V1). Diffusion tensor imaging can provide information about the microstructural integrity of white matter tracts, which may underlie not only the retrogeniculate pathways, but also cortico-cortical association pathways. In this study, we used thalamic volume as a surrogate measure of diffuse thalamo-cortical connectivity and sought to identify associations between thalamic volume and both primary visual cortical function and selected visual cortical association connectivity in preterm neonates with WMI. We tested the hypothesis that in preterm neonates, thalamic morphometry (i.e., thalamic volume) would be strongly associated with primary visual function and associated with the microstructural integrity of cortico-cortical association pathways. Overall, we did find that there was a strong correlation between thalamic volume and primary visual function in preterms particularly in those with non-cystic white matter injury. Incidentally, the low correlation observed in the IVH cohort was expected due to post-hemorrhagic hydrocephalous. However, with regards to correlation with cortico-cortical association pathways, we found that thalamic volume strongly correlated with posterior interhemispheric connectivity (splenium), but not with selected cortico-cortical intrahemispheric connectivity of ventral visual correlates of white matter tracts (IFOF and ILF). This finding is compatible with the spatial–temporal overlap of the development of interhemispheric cortico-cortical connectivity with thalamo-cortical connectivity development during the period of high risk for non-cystic WMI in the early preterm period. The key regions of selective vulnerability of visual association connectivity include both subplate and adjacent periventricular crossing fiber regions, which are known to be vulnerable to white matter injury. These results also provide compelling evidence that the interhemispheric cortical networks seen in the last trimester in resting functional MRI studies likely have developmental synchronicity with thalamo-cortical connectivity in preterm infants.

We did find a strong correlation between thalamic volume and primary visual activation which is additive information to other studies that have correlated visual function with optic radiations in preterm infants and children (Bassi et al., 2008; Berman et al., 2009; Glass et al., 2010; Groppo et al., 2014; Thompson et al., 2014). There is recent evidence suggesting that multiple thalamic nuclei, beyond the lateral geniculate and the pulvinar, are intimately involved in regulation of visual function at different points of the lifespan (Maurer et al., 2007; Rosander, 2007; Sillito et al., 2006; Wurtz et al., 2011). There is

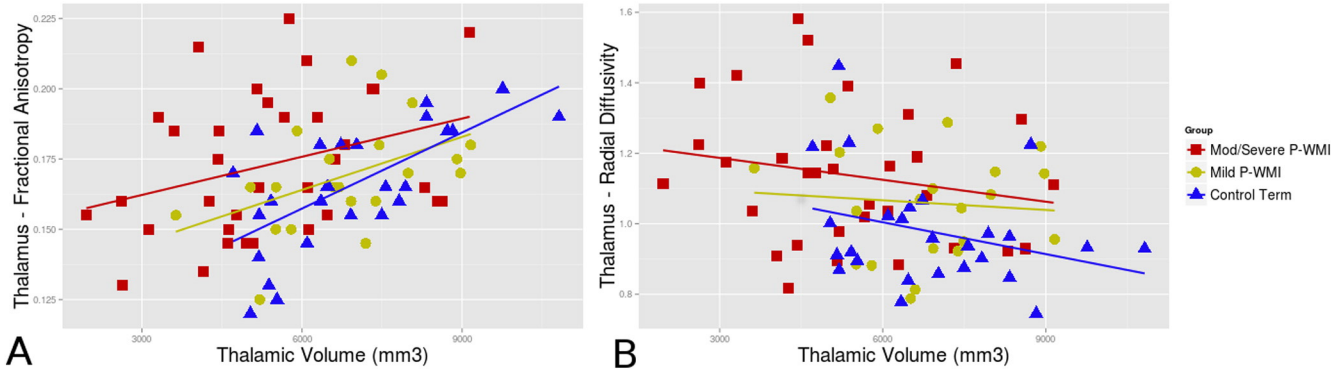

Fig. 5. Thalamic volume and thalamic parenchymal microstructural correlates: A: fractional anisotropy and B: radial diffusivity. Thalamic volume did increase with thalamic parenchyma fractional anisotropy to the greatest degree in the term controls and relatively less in the preterm group with mild non-cystic WMI and the preterm group with moderate–severe non-cystic WMI. In contrast, there was an inverse relation between thalamic volume and radial diffusivity in the preterm group with moderate–severe non-cystic WMI.

comparable development of the spatial temporal profile of the afferent connection originating in the pulvinar of the thalamus to the extra striate cortex between primates and humans (Kostovic and Rakic, 1984). More recently, the pulvinar has been shown to be intimately involved in regulation of cortical network oscillations in relation to visual attention (Saalmann et al., 2012). In addition, early development of the visual system is dependent on thalamo-cortical connectivity in animal models and in vitro systems (Allendoerfer and Shatz, 1994; Bourne, 2010; Ghosh and Shatz, 1993; Lein et al., 1999). The timing of early preterm white matter injury corresponds to a peak period of development of thalamo-cortical connectivity mostly via subplate mechanisms (McQuillen et al., 2002, 2003; McQuillen and Ferriero, 2005). In support of this, binocular enucleation performed at mid-gestation in macaque led to loss of retinofugal and subsequent thalamocortical connection and affected the development of visual cortex, resulting in a "hybrid cortex" (Dehay et al., 1996; Rakic et al., 1991; Windrem and Finlay, 1991). Thalamus is also involved in the activation in middle temporal (MT) or dorsal stream region in the setting of developmental V1 lesions or retrogeniculate lesions and thalamocortical connections are also intimately involved in development of the MT region (Bourne, 2010; Warner et al., 2012). Temporary waiting of thalamocortical fibers in the subplate has been demonstrated in the human visual system in a previous DiI study of human fetal cortex (Hevner, 2000). We also found that thalamic volume also correlated with interhemispheric connectivity (splenium) in the preterm cases with non-cystic WMI suggesting that there is an overlap in the development of thalamo-cortical and interhemispheric cortico-cortical callosal connections. Indeed, callosal afferents do spread throughout the subplate zone during the peak risk for white matter injury, contributing to the thickness of the subplate (Kostovic and Judas, 2006). However, the growth of callosal and long associative cortical–cortical fiber systems is protracted and continues during the late prenatal period that overlaps with late prematurity (Kostovic and Judas, 2007, 2010).

This study highlights that both thalamo-cortical and interhemispheric connectivity likely synergistically play a role in the development of visual functions in the preterm infant. Central to preterm neurodisabilities are different forms of cognitive visual dysfunction (CVD) including visual perception deficits, visual spatial working memory and integration deficits, and visual attention deficits across the life span (Chau et al., 2013; Clark and Woodward, 2010; Ricci et al., 2006, 2007, 2008a,b, 2010a,b; Romeo et al., 2012). The neural substrate of these different forms of CVD, and their co-existence with different domains of neurocognitive deficits is poorly understood. Retrogeniculate injury has been well documented in preterm neonates, but optic radiation injury alone is unlikely to account for the higher order visual deficits displayed in some forms of CVD (Bassi et al., 2008; Berman et al., 2009; Glass et al., 2010; Thompson et al., 2014). The focus of most studies about the visual system in the preterm neonates has been on optic radiation and occipital cortex (Shah et al., 2006; Thompson et al., 2014). More specifically, diffusion tensor imaging of the optic radiation in the neonates has been correlated with eye-fixation examination and with visual evoked potentials (Berman et al., 2009; Glass et al., 2010). Neurocognitive studies in preterm children have suggested a dorsal stream visual system vulnerability is associated with a greater neural network alteration (Atkinson and Braddick, 2007). The neural substrate of preterm dorsal visual stream vulnerability and its associated widespread neural network alteration is unknown. The thalamus is a relay structure, which could potentially link different cortical function/abnormality to dorsal stream visual vulnerability, but there have been no in vivo studies that have linked thalamo-cortical connectivity and dorsal stream visual vulnerability in the preterm infants. Our findings suggest greater earlier vulnerability of the dorsal stream pathways (splenium) compared to ventral stream pathways (ILF, IFOF) relative to thalamic abnormalities in preterms with a spectrum of white matter injury. Studies have shown that relatively healthier and lower risk preterms seem to have predominately dorsal stream visual vulnerability compared to children with more severe evidence of PVL in which both dorsal and ventral stream structures appear to be involved (Geldof et al., 2012; Ortibus et al., 2011; Santos et al., 2009, 2010). Preterm neonates do exhibit signs of cognitive visual dysfunction at term with abnormal fixation shift tests noted in this group (Ramenghi et al., 2010; Ricci et al., 2008b). Visual motor and visual perceptional problems have been identified in preterm infants and children and are thought to contribute to many of the learning deficits exhibited by preterm children including non-phonological reading and mathematics (Atkinson and Braddick, 2007).

The thalamus has been shown to demonstrate abnormal morphology in relation to preterm white matter injury both during the vulnerable perinatal period and during the period of compensatory neuronal adaptation in childhood (Nagasunder et al., 2011a). Thalamic abnormalities in preterm children have been shown to correlate with poor neurocognitive, motor and sensory outcomes (Zubiaurre-Elorza et al., 2012). In preterm neonates with evidence of mild white matter injury, the thalamus had been shown to be associated with abnormal regional cortical development (Ball et al., 2012). Preterm neonates and children that exhibit different components of the spectrum of white matter injury have also been shown to demonstrate specific volumetric/morphological, microstructural and neuropathologic abnormalities in the reticular nucleus, medial dorsal nucleus and pulvinar nucleus of the thalamus (Boardman et al., 2006, 2010; Ligam et al., 2009; Nagasunder et al., 2011b). One common element of these three nuclei is that they are intimately related to visual function modulation and regulation. Interhemispheric connectivity has been shown to be altered in preterm at different stages of the lifespan (Pandit et al., 2013). However, the relationship between visual function, cortical thalamic and interhemispheric alterations in preterms with white matter injury is unknown.

Both our visual functional MRI findings and diffusion tensor imaging findings taken alone have been previously described in other preterm studies (Lee et al., 2012; Pandit et al., 2013; Seghier et al., 2006; Sie et al., 2001). There are recent data to suggest that there are limitations to studying preterm neonates at earlier gestational ages, and that this limitation may be related to difference in preterm HRF (hemodynamic response) differences (Arichi et al., 2012; Lee et al., 2012). In our study, the functional visual MRI of the preterm neonates at term equivalent age, and therefore, we do not suspect that differences in the HRF contributed to our findings. In the DTI analyses of our preterm cohort in comparison to our term infants, we found a predominate pattern of decreased anisotropy and increased $\lambda_{\perp}$ (radial diffusivity) in selected structures, particularly the splenium of the corpus callosum. This finding has been replicated in an animal model of perinatal white matter injury in which endotoxin injected into the corpus callosum of the rat, resulted in microstructural injury of decreased anisotropy and radial diffusivity similar to the findings in our study (Lodygensky et al., 2010). Pathological significance of these DTI metrics based on prior animal and human studies (Counsell et al., 2006; Sun et al., 2006) indicates a relation to primary demyelination in preferential regions attributable to either delayed development or deficient oligodendrocyte wrapping. Thalamic correlates of cerebral white matter DTI and structural cortical measurements have been described that have similarities and difference with our study which may be related to the differences in degree of preterm white matter injury and also post-processing techniques (Ball et al., 2012). We did find structural covariance between the thalamus and frontal lobe regions, and the thalamus volume and thalamic microstructure similar to Ball et al. (2012). However, thalamic volume correlated in our study with the splenium FA in contrast to genu FA in their study, which could reflect difference in degree of non-cystic white matter injury between the studies. Some other limitations of our study also include that we did not assess cortical thickness in relation to thalamic volume, functional MRI and DTI connectivity measurements.

In summary, our study suggests that a strong correlation between thalamic volume and primary visual function and posterior inter-

hemispheric callosal structural connectivity that coincides with the vulnerability of the subplate and adjacent crossing fiber region and highest risk of preterm non-cystic WMI. We suggest that there is a spectrum of abnormalities of visual network connectivity, which may be related to co-morbid risk factors including to degree of non-cystic white matter injury. These visual related abnormalities likely underlie the learning deficits that preterm neonates face when they are school age including non-phonological reading and mathematical deficiencies. This work is relevant in determining neuroimaging biomarkers to predict specific visual neural phenotypes in preterm infants, which may facilitate targeting specific types of behavior interventions.

Conflicts of interest

The authors declare that no competing financial interests exist.

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