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Developmental synchrony of thalamocortical circuits in the neonatal brain

Joann S. Poh [a,c], Yue Li [a], Nagulan Ratnarajah [a], Marielle V. Fortier [d], Yap-Seng Chong [c,e], Kenneth Kwek [f], Seang-Mei Saw [g], Peter D. Gluckman [c,h], Michael J. Meaney [c,i,j], Anqi Qiu [a,b,c,*]

[a] Department of Biomedical Engineering, National University of Singapore, Singapore
[b] Clinical Imaging Research Centre, National University of Singapore, Singapore
[c] Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore
[d] Department of Diagnostic and Interventional Imaging, KK Women's and Children's Hospital, Singapore
[e] Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore
[f] Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore
[g] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore
[h] Liggins Institute, University of Auckland, Auckland, New Zealand
[i] Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, Canada
[j] Sackler Program for Epigenetics and Psychobiology, McGill University, Canada

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ABSTRACT

The thalamus is a deep gray matter structure and consists of axonal fibers projecting to the entire cortex, which provide the anatomical support for its sensorimotor and higher-level cognitive functions. There is limited *in vivo* evidence on the normal thalamocortical development, especially in early life. In this study, we aimed to investigate the developmental patterns of the cerebral cortex, the thalamic substructures, and their connectivity with the cortex in the first few weeks of the postnatal brain. We hypothesized that there is developmental synchrony of the thalamus, its cortical projections, and corresponding target cortical structures. We employed diffusion tensor imaging (DTI) and divided the thalamus into five substructures respectively connecting to the frontal, precentral, postcentral, temporal, and parietal and occipital cortex. T_2-weighted magnetic resonance imaging (MRI) was used to measure cortical thickness. We found age-related increases in cortical thickness of bilateral frontal cortex and left temporal cortex in the early postnatal brain. We also found that the development of the thalamic substructures was synchronized with that of their respective thalamocortical connectivity in the first few weeks of the postnatal life. In particular, the right thalamo-frontal substructure had the fastest growth in the early postnatal brain. Our study suggests that the distinct growth patterns of the thalamic substructures are in synchrony with those of the cortex in early life, which may be critical for the development of the cortical and subcortical functional specialization.

Introduction

The thalamocortical circuitry stems from the thalamus, a deep gray matter structure that relays and modulates information to and from the cortex. The thalamocortical circuitry undergoes rapid morphological growth to adapt to the needs of numerous sensorimotor, cognitive, and attentional functions in early life (Gilmore et al., 2012; Holland et al., 2014; Qiu et al., 2013). Thalamocortical dysconnectivity, both structural and functional, has been implicated in children with autism spectrum disorder (Nair et al., 2013), attention deficit hyperactivity disorder (ADHD; Bush, 2011; Van Ewijka et al., 2012), and schizophrenia (Jones, 1997; Woodward et al., 2012). Abnormal thalamic development has also been found in preterm infants (Ball et al., 2012; Srinivasan et al., 2007), and survivors often suffer from cognitive and behavioral deficits and have an increased risk of developing autism and ADHD (D'Onofrio et al., 2013; Delobel-Ayoub et al., 2009). It has therefore been suggested that the thalamocortical circuitry might be neural substrates for understanding the biological origin of neurodevelopmental disorders (Marlow et al., 2005; Tillman et al., 2008). Hence, establishing a baseline for normal development of the thalamocortical circuits in early life is clinically relevant to understanding which characteristics of thalamocortical development may be selectively vulnerable to injury and leads to neurodevelopmental disorders.

The development of thalamocortical connections starts prenatally and continues into the neonatal period, which has been demonstrated by histochemical studies in the human newborn cortex (Mrzljak et al., 1988). Abnormal prenatal thalamic development is associated with

* Corresponding author at: Department of Biomedical Engineering, National University of Singapore, 9 Engineering Drive 1, Block EA #03-12, Singapore 117576, Singapore. Fax: +65 6872 3069.
E-mail address: bieqa@nus.edu.sg (A. Qiu).

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changes in structural alterations of the thalamocortical white matter and affiliated cortex, suggesting a close relationship among the thalamus, cortical structures, and white matter tracts connecting them. In preterm infants, reduced thalamic volume was found to be correlated with reductions in both the microstructure of the thalamic radiations (afferents to the cortex) and the cortical volume (Ball et al., 2012). This suggests a possibility that tissue volume in the thalamus and cortex reflects the thalamocortical connectivity, and is dependent on the growth and integrity of the white matter tracts connecting them. The mediodorsal thalamic volume has been implicated in schizophrenia neuropathology, and it has been speculated that decreases in its activity during early development, before the age of 2 years, could result in a loss of synaptic drive to the prefrontal cortex, leading to a decrease in prefrontal synaptic density (Ferguson & Gao, 2015; Huttenlocher, 1979). This hypoinnervation may underlie possible mechanisms of cortical gray matter reductions that have been observed in schizophrenic patients in adulthood. In addition, previous diffusion tensor imaging (DTI) studies showed that an increase in fractional anisotropy (FA) and decreases in axial diffusivity (AD) and radial diffusivity (RD) in the thalamus is in parallel with an increase FA in thalamic radiations, major white matter tracts for the thalamocortical connection (Aeby et al., 2009; Qiu et al., 2013). Altogether, there seems to be synchronous development among the thalamus, cortex, and their connectivity.

Currently, understanding the normal development of the thalamus in early life is limited as thalamic size is largely assessed using traditional methods such as T1-weighted and/or T2-weighted magnetic resonance imaging (MRI) and its microstructure is largely assessed using DTI. However, the thalamus is a fairly complicated structure and consists of axonal fibers projecting to the entire cortex, which provide the anatomical support for its numerous functions, including sensory and motor functions, as well as high-level cognition (Sherman, 2007). Based on the pattern of this widespread thalamocortical connections, the thalamus can be further divided into substructures that are composed of nuclei clusters (Herrero et al., 2002; Sim et al., 2006). However, there is limited *in vivo* evidence on the normal development of individual thalamic substructures, partly because of the lack of any distinction on their appearance on T1- and T2-weighted MRI data. Moving beyond early structural imaging studies on size, investigations of the thalamus can also be benefited by using other imaging-based methods such as DTI. Behrens et al. (2003) showed that using DTI tractography classification of the thalamic gray matter, based on the thalamocortical connectivity patterns, have revealed distinct substructures whose locations correspond to thalamic nuclei described previously in histological studies.

In this study, we aimed to investigate the developmental patterns of the cerebral cortex in terms of cortical thickness, as well as the thalamic substructures and their respective connectivity with the cortex in the first few weeks of the postnatal brain. We employed DTI and divided the thalamus into 5 substructures respectively connecting to the frontal, precentral, postcentral, temporal, and parietal and occipital cortex. The cortical development was characterized by cortical thickness assessed using T2-weighted MRI. The thalamocortical connectivity was measured using DTI. Based on the aforementioned findings, we therefore hypothesized that even shortly after birth, the growth pattern of the thalamic substructures is parallel to that of their respective thalamocortical connectivity and corresponding cortical structures.

Materials and methods

Subjects

One-hundred and eighty-nine infants of mothers who participated in the prospective GUSTO birth cohort study were recruited for neuroimaging. The GUSTO cohort consisted of pregnant Asian women attending the first trimester prenatal ultrasound scan clinic at the National University Hospital (NUH) and KK Women's and Children's Hospital (KKH) in Singapore. The parents were Singapore citizens or Permanent Residents of Chinese, Malay, or Indian ethnic background. Mothers on chemotherapy, psychotropic drugs, or with type I diabetes mellitus were excluded. Only women who agreed to donate birth tissues including cord, placenta, and cord blood at delivery were included. The cohort inclusion and exclusion criteria were described in Soh et al. (2014). The GUSTO cohort study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the SingHealth Centralized Institutional Review Board (CIRB). Written consent was obtained from mothers. Birth outcome and pregnancy measures were obtained from hospital records. This study included neonates whose postmenstrual age was of at least 35 weeks, birth weight equal or larger than 2500 g, and a minimum 5-minute APGAR score of 9.

MRI acquisition

At 5 to 17 days of life, neonates underwent fast spin-echo T2-weighted MRI and single-shot echo-planar DTI images using a 1.5-Tesla GE scanner at the Department of Diagnostic and Interventional Imaging of the KKH. The images were acquired when subjects were sleeping in the scanner. No sedation was used and precautions were taken to reduce exposure to the MRI scanner noise. A neonatologist was present during each scan session. A pulse oximeter was used to monitor heart rate and oxygen saturation throughout the entire session.

The imaging protocols included (i) fast spin-echo T2-weighted MRI (TR = 3500 ms; TE = 110 ms; FOV = 256 mm × 256 mm; matrix size = 256 × 256) and (ii) single-shot echo-planar DTI (TR = 7000 ms; TE = 56 ms; flip angle = 90°, FOV = 200 mm × 200 mm; matrix size = 64 × 64). For T2-weighted MRI, 50 axial slices with 2.0 mm thickness were acquired parallel to the anterior–posterior commissure line. Two T2-weighted images were acquired per subject. For DTI, 40 to 50 axial slices with 3.0 mm thickness were acquired parallel to the anterior–posterior commissure line. Nineteen diffusion-weighted images (DWIs) with b = 600 s/mm^2 and 1 baseline with b = 0 s/mm^2 were also obtained.

All 189 neonates had the T2-weighted MRI data, while only 142 neonates had the DTI data. Through visual inspection, only 122 neonates had a good DTI data, partially because DTI was last acquired and sensitive to head motion.

Cortical thickness analysis

Within individual subjects, when possible, two T2-weighted MRI acquisitions were first rigidly aligned and averaged to increase signal-to-noise ratio. In cases where only one scan was acquired, data from one scan was used in lieu of the average axial image. The skull of the averaged axial image was removed using Brain Extraction Tool (BET; Smith, 2002). A Markov random field model (MRF) was used to automatically delineate gray matter, white matter, and cerebrospinal fluid (CSF) from the neonatal T2-weighted MRI data. The mathematical model of MRF was detailed in Fischl et al. (2002). The MRF model has been considered as one of robust automatic brain segmentation approaches because it incorporates the anatomical prior information obtained from a manually labeled training set. In our study, our training set consisted of twenty T2-weighted MRI data sets randomly selected from our sample. We employed the leave-one-out validation approach to evaluate the MRF segmentation accuracy for gray matter and white matter. The nineteen images with the manual label were used as training sets in MRF and one image with the manual label was used as a testing set. The accuracies of the MRF segmentation for gray and white matter were respectively 0.793 and 0.862.

Based on the above tissue segmentation, a cortical surface was constructed at the boundary between gray and white matter using graph-based topology correction algorithm (Han et al., 2002). The cortical thickness was measured as the distance between the cortical surface and gray matter voxels at the boundary between gray matter and CSF.