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Research report

The influence of preterm birth on the developing thalamocortical connectome

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ABSTRACT

Introduction: Defining connectivity in the human brain signifies a major neuroscientific goal. Advanced imaging techniques have enabled the non-invasive tracing of brain networks to define the human connectome on a millimetre-scale. During early development, the brain undergoes significant changes that are likely represented in the developing connectome, and preterm birth represents a significant environmental risk factor that impacts negatively on early cerebral development. Using tractography to comprehensively map the connections of the thalamocortical unit, we aim to demonstrate that premature extra-uterine life due to preterm delivery results in significantly decreased thalamocortical connectivity in the developing human neonate.

Methods: T1- and T2-weighted magnetic resonance images and 32-direction diffusion tensor images were acquired from 18 healthy term-born neonates (median gestational age: 41^{+3}) and 47 preterm infants (median gestational age: 28^{+3}) scanned at term-equivalent age. Using a novel processing pipeline for tracing connections in the neonatal brain we map and compare the thalamocortical macro-connectome between groups.

Results: We demonstrate that connections between the thalamus and the frontal cortices, supplementary motor areas, occipital lobe and temporal gyri are significantly diminished in preterm infants (FDR-corrected, $p < .001$).

Conclusions: This supports the hypothesis that the thalamocortical system is vulnerable following preterm birth and the tractographic framework presented represents a method for analysing system connectivity that can be readily applied to other populations and neural systems.

1. Introduction

A grand challenge in neuroscience is the precise description of brain connectivity and its variability. Diffusion tractography has been used to non-invasively map putative long-distance connections through the brain to infer dense structural networks of information flow, or connectomes, that are sensitive to development, ageing and disease state (Hagmann et al., 2008; Robinson et al., 2010; Sporns et al., 2005; Stam et al., 2007; Van Essen et al., 2012). These recently developed

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techniques define networks with spatial resolution typically in the millimetre-range and may provide complementary evidence to micro-scale connectome studies concerned with the connections of individual neurons on a cellular level (Felleman and Van Essen, 1991). Indeed, tractography-based connectivity has previously been shown to parallel observations based on experimental animal studies, or post mortem histology and dissection (Behrens et al., 2003a; Goldman-Rakic and Porrino, 1985; Morel et al., 1997; Scannell et al., 1999).

The formation of cerebral pathways through axonal growth, neuronal differentiation and synaptogenesis during the perinatal period is essential for normal brain development and function (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010). Tractography has successfully been applied in neonates to delineate major white matter tracts including the cortico-spinal tracts and corpus callosum (Aeby et al., 2009; Bassi et al., 2011; Berman et al., 2005; de Bruine et al., 2011; Hasegawa et al., 2011; Partridge et al., 2005; Thompson et al., 2011), and thalamocortical pathways in the optic radiations (Bassi et al., 2008; Groppo et al., in press). Recently, structural connectivity networks have also been described in small numbers of infants from as young as 2 weeks (Yap et al., 2011). However, rapid anatomical changes over time and lack of a universally-accepted method for parcellation of the brain into nodes or landmarks has limited attempts to define a perinatal connectome (Fan et al., 2011; Tymofiyeva et al., 2012).

Preterm birth represents a major risk factor for adverse neurodevelopmental outcome in childhood (Delobel-Ayoub et al., 2009; Marlow et al., 2005). The neural substrates that underlie these deficits are not known but due to the timing of key developmental processes, disruption of the thalamocortical system is thought to represent a major component of preterm brain injury (Kostovic and Judas, 2010; Volpe, 2009). In recent years, quantitative magnetic resonance (MR) studies have shown that regional tissue loss, primarily in the cortical and subcortical grey matter, accompanied by diffuse white matter injury predicts early neurodevelopmental outcome after preterm birth (Boardman et al., 2006, 2010; Inder et al., 2005; Kapellou et al., 2006; van Kooij et al., 2012). Additionally, we have demonstrated that prematurity is associated with a pattern of altered brain development that is predominant in frontotemporal structures, inclusive of reduced cortical volume and impaired white matter microstructural development and dependent on the volume of the thalamus at term-equivalent age (Ball et al., 2012), suggesting that preterm birth has an adverse effect on the developing thalamocortical system.

In order to test the hypothesis that thalamocortical connectivity is significantly decreased following preterm birth, we present a novel method for mapping the connective pathways between the whole cortex and the thalamus in the neonatal brain. By providing the first detailed description of the neonatal human thalamocortical connectome, we aim to comprehensively map the effects of a major environmental influence – premature extrauterine life due to preterm delivery – on the development of thalamocortical connectivity, and determine regions where connectivity is significantly altered by term-equivalent age.

2. Methods

Ethical permission for this study was granted by the Hammersmith and Queen Charlotte's and Chelsea Hospital (QCCH) Research Ethics Committee. Written parental consent was obtained for each infant.

2.1. Subjects

Eighteen healthy term-born control infants (seven males) were examined between October 2006 and February 2011 as part of ongoing studies at QCCH. Median gestational age at birth was 39^{+2} (36^{+0}–41^{+6}) weeks, median postmenstrual age at scan was 39^{+0} (41^{+6}–44^{+4}) weeks and median birth weight was 3.20 (2.68–4.20) kg.

Forty-seven preterm infants (26 males) born at less than 36 weeks gestational age (as defined by the last menstrual period) between March 2005 and October 2008 were included. The cohort had a median gestational age of 28^{+3} (range: 23^{+4}–34^{+6}) weeks, a median age at scan of 41^{+3} (38^{+2}–44^{+1}) weeks and median birth weight of 1.11 (.63–2.37) kg. Infants were excluded if cystic periventricular leukomalacia (PVL; four infants) or haemorrhagic parenchymal infarction (HPI; four infants) was apparent on the term-equivalent magnetic resonance imaging (MRI). All preterm infants were included in a previously reported study (Ball et al., 2012).

2.2. Imaging

Each infant successfully underwent T1- and T2-weighted MRI and 32-direction diffusion tensor imaging (DTI) acquisition at term-equivalent age. MRI was performed on a Philips 3-Tesla system (Philips Medical Systems, Netherlands) using an eight-channel phased array head coil. T1-weighted MRI was acquired using: repetition time (TR): 17 msec; echo time (TE): 4.6 msec; flip angle 13°; slice thickness: .8 mm; field-of-view: 210 mm; matrix: 256 × 256 (voxel size: .82 × .82 × .8). T2-weighted fast-spin echo MRI was acquired using: TR: 8670 msec; TE: 160 msec; flip angle 90°; slice thickness 1 mm; field-of-view: 220 mm; matrix: 256 × 256 (voxel size: .86 × .86 × 1). Single shot echo planar imaging (EPI) DTI was acquired in the transverse plane in 32 non-collinear directions using the following parameters: TR: 8000 msec; TE: 49 msec; slice thickness: 2 mm; field-of-view: 224 mm; matrix: 128 × 128 (voxel size: 1.75 × 1.75 × 2 mm); *b*-value: 750 sec/mm^2; SENSE factor of 2.

All examinations were supervised by a paediatrician experienced in MRI procedures. Infants were sedated with oral chloral hydrate (25–50 mg/kg) prior to scanning and pulse oximetry, temperature and electrocardiography data were monitored throughout. Ear protection was used for each infant, comprising earplugs moulded from a silicone-based putty (President Putty, Coltene Whaledent, Mahwah, NJ, USA) placed in the external ear and neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA, USA).

2.3. Cortical parcellation

For each infant a cortical mask was derived from tissue segmentation performed using an expectation-maximisation