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Neonatal neuropsychology: Emerging relations of neonatal sensory–motor responses to white matter integrity

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ABSTRACT

The neonatal period is considered to be essential for neurodevelopment and wellbeing throughout the life span, yet little is known about brain–behavior relationships in the neonatal period. The aim of this study was to evaluate the association between neonatal sensory–motor regulation and white-matter (WM) integrity of major fiber tracts in the neonatal period. We hypothesized that WM integrity of sensory–motor systems would predict neurobehavioral maturation during the first month of life.

Forty-nine premature neonates underwent magnetic-resonance-imaging at term. Diffusion-tensor-imaging analysis was performed in major WM tracts along with repeated neonatal neurobehavioral evaluations assessing sensory reactivity and motor regulation.

Difficulties in one or more behavioral sub-category, mostly in auditory and visual attention, hypotonicity and jitteriness, were documented in 78.3% infants at term. Sixty-six percent of infants experienced difficulties, mostly in auditory attention, head–neck control, hypotonicity and motor asymmetry, at 44 weeks.

Attention difficulties were associated with reduced integrity of cerebral and superior cerebellar peduncles; while tonicity was associated with reduced integrity of the corpus-callosum and inferior–posterior tracts. Overall, results showed that early maturing tracts were related with the degree of typicality of sensory reactivity status while late maturing tracts were related with the degree of typicality of tonic regulation. WM integrity and maturation factors explained 40.2% of the variance in neurobehavior at 44 weeks.

This study suggests that in preterm neonates, deviant sensory–motor reactivity can be detected very early in development in manners that are related to lower integrity/maturational level of early and late maturing fiber tracts.

1. Introduction

The neonatal period is considered to be essential for neurodevelopment and wellbeing throughout the life span, yet very little is known regarding the association between neuromaturational changes and the neurobehavioral development occurring during the neonatal period. Literature indicates continuity from prenatal to postnatal life, with little changes in the form and pattern of movement from the late gestation period to 8–10 weeks of postnatal age, even though fundamental changes occur during this period (Einspieler, Marschik, & Prechtl, 2008). At approximately 8–10 weeks, characteristics of distinct motor and sensory behavior patterns change, making the infant more fit and adapted

Abbreviations: MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; MD, mean diffusivity; FA, fractional anisotropy; Da, axial diffusivity; Dr, radial diffusivity; GA, gestational age; VOI, volume of interest; TEA, term-equivalent age; CC, corpus callosum; PLIC, posterior limb of the internal capsule; OR, optic radiations; CR, corona radiata; CP, cerebral peduncles; CST, cortico spinal tract; SCP, superior cerebellar peduncles; MCP, middle cerebellar peduncles; ICP, inferior cerebellar peduncles; RNNAP, Rapid Neonatal Neurobehavioral Assessment Procedure; WM, white matter

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to the extrauterine environment (Einspieler et al., 2008). Developmental neuroscientific frameworks postulate relationships between behavioral changes during the first postnatal month and maturation properties of the neural tracts that lead to this significant change. Preterm birth offers a unique model to study this important developmental period, as it enables examination of development during late gestation and throughout the neonatal period, as well as neurobehavioral performance at term age, independent of birth-related experiences.

Little is known regarding the susceptibility of discrete neural pathways in the neonatal period in infants born preterm, or the relationship between such susceptibility and the neonatal developmental course. Yet, given the marked brain plasticity during this period (Limperopoulos, 2010), early behavioral evaluation in the neonatal period is critical for enabling early interventions that may improve outcomes in preterm infants. Therefore, it is important to study the relationship among maturation changes during the neonatal period, the integrity of neonatal neural pathways, and the early neurobehavioral development of the neonate.

Diffusion tensor imaging (DTI) allows evaluation of the integrity, quantity, and pace of the developing white-matter (WM) tracts (Basser & Pierpaoli, 1996). Quantitative diffusivity measures, derived from DTI, characterize the directional preference of diffusion and provide non-subjective measures that reflect tissue microstructure. For example, mean diffusivity (MD) reflects the amplitude of water diffusion, fractional anisotropy (FA) reflects the directionality of water diffusion, axial diffusivity (Da) represents diffusion along the tensor ellipsoid main axis ($\lambda_{//}=\lambda_1$), and radial diffusivity (Dr) represents diffusion perpendicular to that axis ($\lambda_{\perp}=(\lambda_2+\lambda_3)/2$). MD and FA have been widely used to characterize diffusion anisotropy in various brain tissues, but they lack the ability to provide more insights into underlying WM microstructural changes. Da and Dr may be more useful in this respect, as Da is found to be indicative of axonal growth and Dr is related to myelination (Gao et al., 2009; Song et al., 2003). Therefore, these measures may provide more specific physiologic information regarding the WM microstructural changes and maturational processes than is available using only FA and MD.

Several WM tracts were shown to be more susceptible to damage in preterm infants compared to control infants born at term. Compared to infants born at term, preterm infants were reported to show lower FA values in central WM regions (Anjari et al., 2007, 2009) and higher FA values in the fiber tracts of the neurosensory pathways (Gimenez et al., 2008). Changes in diffusivity parameters, especially altered Dr, have been detected in preterm infants with extensive WM signal intensity abnormalities in the internal capsule, inferior frontal regions, sensorimotor areas, and superior occipital regions (Cheong et al., 2009). WM microstructure in preterm infants at term equivalent age (TEA) was associated with cognitive, fine motor, and gross-motor performance at a corrected age of 2 years (van Kooij et al., 2012), and with poorer developmental performance at 18 months of age (Rose et al., 2009). However, the relationship between the integrity of central WM tracts and very early neurobehavioral outcomes is not well established.

The current study tested the relationships between WM integrity and neurobehavioral performance at two ages within the neonatal period; term and 44 weeks post-conception. The first hypothesis of this study was that preterm neonates in this cohort would show neurobehavioral abnormalities, primarily in the sensory reactivity and motor-regulation domains, even in the absence of major cerebral injury documented using conventional methods. An additional goal was to study maturational differences between the different WM tracts, hypothesizing that differences in the diffusivity parameters would reflect level of maturation. The third hypothesis was that altered integrity of major WM tracts would be associated with lower overall neurobehavioral performance at term and at 44 weeks. Specifically, it was postulated that early maturing WM tracts would be related to the degree of typicality of sensory reactivity status, while late maturing tracts would be related to the degree of typicality of tonic regulation. The final hypothesis of this study was that both WM integrity of specific tracts and maturational factors would be uniquely predictive of an infant's neurobehavioral status in the neonatal period.

2. Methods

The Ministry of Health and the local Institutional Review Board approved this study, and informed consent was obtained from parents prior to participation.

2.1. Participants

This study was part of an on-going prospective study that began in December 2009. Participants included 58 preterm infants born < 34 weeks' gestational age. In order to create a relatively homogenous study group, only parents of infants who had mild to moderate echogenicity on routine cranial US (cUS) performed within a week after birth in the neonatal intensive care unit (NICU), and who had no additional major abnormalities as detected by their NICU cUS, were approached. The full description of echogenicity assessment is available from Weinstein et al. (2014). Of the parents who were approached, five declined to participate.

The exclusion process consisted of two levels: the first level was based on the cUS examination, and included: significant findings such as > grade II intraventricular hemorrhage, cystic periventricular leukomalacia, periventricular hemorrhagic infarction, cerebral malformations; cerebellar malformation or cerebellar injury; as well as exclusion based on genetic disorders, congenital infections (e.g. cytomegalovirus and rubella), central nervous system infection, unstable medical condition or any contraindication to MRI (such as recent surgery or implants). The second level was based on the TEA MRI findings, such that infants with structural brain abnormalities were excluded (i.e. marked cerebellar asymmetry, and intraventricular hemorrhage > grade II). Nine infants were excluded based on the second level of exclusion criteria. All twins in this study were dizygotic. Table 1 presents the demographic and clinical characteristics of the participants.

2.2. MRI protocol

MRI was performed on a 3-T MRI scanner (HDX, GE Healthcare, Little Chalfont, UK). The protocol included anatomical sequences (Sagittal T1, Axial T2, and T2* weighted images) as well as axial fluid-attenuated inversion recovery and high resolution 3-dimensional T1 weighted images for volume measurements. DTI images were acquired along 33 non-collinear gradient directions with b values of 700 s/mm^2, and one that served as a reference with no applied diffusion gradient. Other acquisition parameters included: TR/TE=8000/88 ms, matrix of 64×64, FOV=160 mm and 2.5 mm slices with no gap, in-plane resolution 2.0×2.0 mm^2. Axial slices were prescribed to cover the entire brain, including the cerebellum. It is

Table 1
Clinical characteristics.

Variable	Mean ± SD	Frequency
A (w)	29.2 ± 2.6	
GA at MRI test (w)	37.3 ± 1.7	
GA at RNNAP1test (w)	38.26 ± 1.72	
GA at RNNAP2 test (w)	43.9 ± 1.3	
Birth weight (g)	1267 ± 442	
Arterial pressure at entrance to NICU	40.4 ± 7.2	
Male	28	57%
Twin*	34	69%
IUGR	3	6%
Respiratory distress syndrome	34	69%
Hypotension	2	4%
Bronchopulmonary dysplasia	12	25%
High frequency ventilation	18	39%
Antenatal steroids	40	82%
Postnatal sepsis	8	16%

n=49; GA=gestational age; MRI=magnetic resonance imaging; SD=standard deviation; w=weeks; g=grams; RNNAP=Rapid Neonatal Neurobehavioral Assessment Procedure; NICU=neonatal intensive care unit and IUGR=intrauterine growth restriction.

* All twins are dizygotic