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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

also possible to use 1.5 T scanners for the DTI analysis, which are more prevalent for clinical use; though, it should be taken into account that the signal to noise ratio is increased in 3 T compared to 1.5 T.

2.3. DTI analysis

DTI analysis was conducted using FSL software (FMRIB, Oxford, UK, www.fmrib.ox.ac.uk/fsl) and the neonate DTI atlas (Oishi et al., 2011), and performed for major cerebral WM tracts (corpus callosum [CC], posterior limb of the internal capsule [PLIC], optic radiations [OR], CR, cerebral peduncle [CP]) and tracts in the cerebellum (superior cerebellar peduncles [SCP], middle cerebellar peduncles [MCP], and inferior cerebellar peduncles [ICP]) (Oishi et al., 2011). Motion and eddy current corrections were performed using FSL software. The realignment and re-slicing of the diffusion calculated maps were performed using affine transformation via the FSL linear image registration tool. An FA threshold of 0.2 was used for extracting the major WM skeleton in order to correct partial volume effects. Mean values of FA, MD, Da, and Dr were averaged within each VOI. Fig. 1 presents the DTI analysis stages. Fig. 2 presents an example of the VOIs used in the DTI analysis. Six subjects were excluded from the analysis due to movement artefacts. The DTI analysis was performed by a neuropsychologist (M.W.) with 7 years of experience in advanced MRI methods, and under the supervision of the head of the Developmental Neuropsychology Unit (R.G.), the Deputy Director of the Functional Brain Center (D.B.B.) and a Senior Pediatric Radiologist (L.B.S.).

2.4. Quality assurance

Diffusivity maps were visually inspected. In addition, the volumes of each VOI per subject were calculated relative to the volume of the VOI in the WM atlas. VOIs that occupied $< 50\%$ of the atlas VOIs were excluded from the analysis, resulting in 12% exclusion.

2.5. Neonatal Neurobehavior Assessment Procedure

RNNAP testing was conducted by two senior neurologists who were trained in using the tool. This assessment was performed in the presence of the participant's mother, in the neonatal intensive care unit (NICU) at term and at the Child Development Centre at 44 weeks. The assessment was typically conducted before noon and after feeding. The RNNAP is a clinical evaluation of infant neurobehavioral functioning, which assesses the integrity and organization of the infant's sensory–motor system. It is one of the few assessments that implement the use of both passive and activated motor patterns, as well as assessment of sensory reactivity, which enables a more complete evaluation of the neonate, who may be sensitive to changes during this dramatic period (Gardner, Karmel, Norton, Magnano, & Brown, 1990; Silberstein et al., 2009). This integrative clinical evaluation of activated motor behaviors and passive tone evaluations increases the sensitivity and specificity of the RNNAP.

The RNNAP has proven reliable and valid in differentiating premature infants at various levels of neurological risk and in predicting developmental outcomes (Gardner, Karmel, & Freedland, 2001; Gardner et al., 1990; Karmel et al., 2010a; Silberstein et al., 2009). The assessment includes 17 items, clustered into nine behavioral categories (each consisting of several sub-categories), that test the integrity of neonatal reflexes, reactivity to visual and auditory stimulation, passive and activated motor responses, and state control. The infant's performance in each subcategory is rated as normal or abnormal based on clinical criteria. The criteria for abnormality are determined according to previously published guidelines (Gardner et al., 2001). Briefly, visual attention is considered abnormal if the infant is unable to differentially fixate on a pattern paired with a blank stimulus, or is

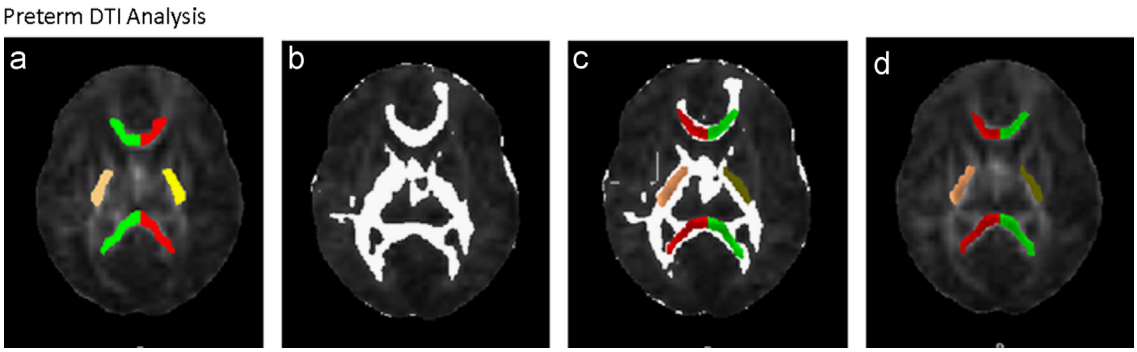

Fig. 1. DTI analysis steps. (a) Stage 1: coregistration between preterm brain and atlas template in chosen ROIs. (b) Stage 2: FA threshold of 0.2 for extracting major WM skeleton (correcting for partial volume effects). (c) Stage 3: extraction of areas that the template overlapped with the WM skeleton. (d) Stage 4: extraction of diffusion parameters from ROIs.

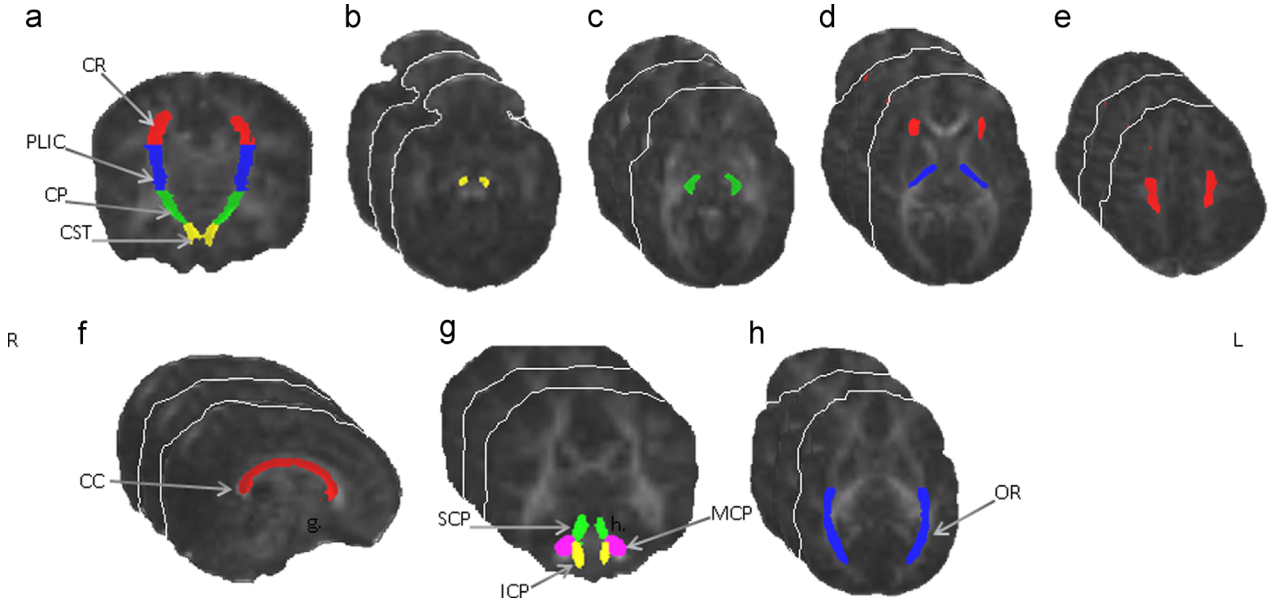

Fig. 2. Volumes of interest (VOIs). (a) Coronal view of motor pathway VOIs. (b) Corticospinal tract (CST). (c) Cerebral peduncle (CP). (d) Posterior limb of internal capsule (PLIC). (e) Corona radiata (CR). (f) Corpus callosum (CC). (g) Superior (SCP), middle (MCP), and inferior (ICP) cerebellar peduncles. (h) Optic radiations (OR).

unable to follow a pattern smoothly across midline. Auditory attention is considered abnormal if the infant is unable to consistently turn his/her head from midline toward a rattle and/or a voice presented on the right and the left. Sensory asymmetry is present when the infant is better able to orient to visual or auditory stimuli from one direction. Head/neck control is considered abnormal if the infant is floppy, weak, and shows little attempt to lift or pull its head up. Extremity movements and tone (i.e. hypo- or hyper-tonus of the arms, legs, and trunk) were assessed as well. Motor asymmetry is present when the infant demonstrates better tone and/or a greater amount or quality of movement on one side of the body. State control is assessed as either very highly aroused, very irritable, very low arousal, difficult to arouse, or unresponsive. Jitteriness is present if fine or gross tremors of arms and legs (either spontaneous or elicited) are present. A higher RNNAP total score reflects lower neurobehavioral functioning. The RNNAP has been specifically designed for high-risk newborns, though reports of large cohorts of low-risk infants born preterm indicate that a number of neurobehavioral abnormalities are expected, even in low risk the low risk preterm population (Gardner et al., 1990, 2001). The advantage of the RNNAP is its high sensitivity in the evaluation of neonatal neurodevelopment.

2.6. Statistical analysis

Comparison of the total RNNAP scores at term versus at 44 weeks was performed using a paired *t*-test. The proportion of preterm infants with neurobehavioral abnormalities in each RNNAP sub-category was calculated both at term and at 44 weeks, and McNemar's test was used to study the differences between the two time points (Mc, 1947). In addition, sensory reactivity and tonic regulation categories were divided into two groups: infants with normal performance and infants with abnormal performance in that RNNAP category.

To study maturational differences between the different WM tracts, the Da and Dr values of the different tracts were plotted and analyzed using a repeated measures analysis of variance (ANOVA). This analysis served to infer early and late maturing tracts. To test the hypothesis that lower WM integrity of major WM tracts is associated with lower neurobehavioral performance at term and at 44 weeks, correlations were assessed between mean diffusivity values (Da, Dr, MD, and FA) in the WM pathways (CC, PLIC, OR, CR, CP, SCP, MCP, and ICP) and total RNNAP score at term and at 44 weeks of age. A one-way multiple ANOVA was performed to investigate differences in DTI parameters of early maturing and late maturing WM tracts between preterm infants with normal and abnormal performances in the sensory and motor RNNAP categories. Finally, hierarchical regression analysis was performed taking into account Da of WM VOIs that correlated with RNNAP and maturation factors (GA, age at RNNAP assessment).

3. Results

3.1. Neurobehavioral functioning of the preterm infant

Data from the RNNAP at term and at 44 weeks was available for 46 preterm infants. No significant differences were detected between the RNNAP total score at term and at 44 weeks. The mean ($\pm$SD) RNNAP score at term was 20.21 ($\pm$2.42; range 17–25) and at 44 weeks was 20.23 ($\pm$2.36; range 17–25). Only one-fifth of the participants (21.7%) had a normal score on the RNNAP assessment at term (i.e. performed optimally in all tested neurobehavioral sub-categories). The remaining 78.3% had abnormalities in one or more sub-categories of the RNNAP. At 44 weeks, one-third of the participants (30.4%) had a normal RNNAP assessment score, and the remaining 66.6% had some degree of RNNAP abnormality. The most frequently affected domains were auditory attention, sensory asymmetry, extremity movement/tone, and jitteriness. The sub-categories with abnormal performance were not similar between the two age groups, demonstrating that although no differences were detected in the total score, there were changes in the susceptibility of the different domains as the infants matured. The proportion of infants with abnormal performance in each sub-category is presented in Table 2.

The McNemar test showed that neurobehavioral performance changed significantly over the first month post-term age in the domain of sensory reactivity, specifically in visual attention ($p < 0.008$); and in the domain of motor regulation, specifically in the hypotonic trunk sub-category ($p < 0.021$). On the RNNAP assessment, preterm neonates were more likely to improve their visual attention and to demonstrate less trunk hypotonia at 44 weeks than at the term.

Table 2
Proportion of infants with NB abnormalities.

NB category	Sub-category	% Abnormal ~40 weeks	% Abnormal ~44 weeks	McNemar *p* value
Attention	Visual	22.5	2.6	*0.008
	Auditory	35.7	26.3	1.0
Sensory asymmetry	Visual	0	0	
	Auditory	26.2	21.1	0.607
Head–neck control	Extension	21.4	7.9	0.388
	Flexion	16.7	26.3	0.388
Extremity movement/tone	Hypotonic arms	38.1	28.9	0.804
	Hypertonic arms	4.8	7.9	1.0
	Hypotonic legs	14.3	13.2	1.0
	Hypertonic legs	4.8	7.9	1.0
	Hypotonic trunk	35.7	13.2	*0.021
	Hypertonic trunk	4.8	2.6	1.0
	Asymmetric tone	29.3	39.5	0.581
State control	Peak excitement	11.9	13.5	1.0
	Alertness	9.5	2.6	0.63
Feeding		2.4	0	1.0
Jitteriness		23.8	18.9	1.0

NB = neurobehavioral.
Note: The McNemar *p*-value is computed between performance on the RNNAP1 at term and the RNNAP2 at 44 weeks in each category.

3.2. Findings on conventional MRI

The most common MRI findings detected in the 49 infants that were included in the study were: diffuse excessive high signal intensity (DEHSI) in the cerebrum (63%), cerebellar punctate lesions (17.4%) and grade I hemorrhage (18%). For detailed MRI findings see Table 3.

3.3. Integrity and maturation of WM tract VOIs

Forty-three infants had DTI data fit for analysis; from the remaining six, no DTI data were available due to sub-optimal imaging data related to movement artifacts. No significant differences were detected between homolog (right and left) VOIs ($p > 0.05$), except for in the left and right optic radiations. Therefore, all homolog VOIs were averaged to obtain mean values for Da, Dr, MD, and FA. Table 4 presents the means and standard deviations of the diffusivity parameters in each VOI. The diffusivity parameters in the table show that the different WM tracts have different levels of maturation at TEA.

3.4. Maturation of WM tracts

To test the hypothesis of differential maturation of WM tracts, the Da and Dr values were plotted. A linear trend was detected in a manner compatible with the known progression of myelination (i.e. from the caudal to the rostral direction; Fig. 3).

Fig. 3 shows differences in the level of maturation of the WM VOIs at TEA, as reflected in lower Da and Dr values, which indicates a higher maturation level. The figure shows a linear trajectory demonstrating that inferior tracts precede the more superior tracts

at TEA. Comparisons were conducted among the 9 VOIs: ICP, CP, CST, SCP, PLIC, MCP, CR, CC, and OR; and revealed significant differences in Da and Dr among almost all VOIs. These results imply different maturation rates of specific tracts in the neonatal period. Mauchly's test (Mauchly, 1940) indicated a violation of the assumption of sphericity for Da only ($\chi^2_{(35)}=127.3$, $p=0.039$; Dr: $\chi^2_{(2)}=104.457$, $p=0.069$). Therefore, the degrees-of-freedom for Da were corrected using Greenhouse–Geisser estimates of sphericity. There was a significant main effect for region on the diffusivity parameters values (overall $p<0.0001$ l; Da: $F_{(4.7,199.07)}=219.494$; Dr: $F_{(8,336)}=223.74$). Bonferroni-corrected post-hoc tests demonstrated that diffusivity parameters in most of the 9 regions were significantly different from each other ($p<0.0001$). No significant differences were detected between the CC and OR; among the CST, CP and SCP; or among the PLIC, MCP and SCP. The most early maturing tracts, as indicated by lower values in both Da and Dr, were the CP and ICP, while the late maturing tracts, as indicated by higher values of both Da and Dr, were the OR, CC, and CR. The PLIC showed markedly lower Dr than Da.

3.5. Correlation between WM integrity and total RNNAP scores

To test the hypothesis that lower WM integrity of major WM tracts is associated with lower neurobehavioral performance at term and at 44 weeks, a correlation analysis was conducted. The analysis showed that higher diffusivity values, indicative of lower integrity, in cerebellar and several cerebral fiber tracts were associated with poorer RNNAP performance at term and at 44 weeks. Moderate correlations were detected between RNNAP scores at term in both FA and Da for the CST ($r=0.372$, $p<0.030$ and $r=0.384$, $p<0.025$, respectively). No other significant correlations were detected for other tracts.

At 44 weeks, more correlations were identified. At this age correlations between RNNAP scores and cerebral WM were detected in MD, Da, and Dr for the CC ($r=0.373$, $p<0.021$; $r=0.367$, $p<0.024$; and $r=0.361$, $p<0.026$; respectively). In the cerebellum, RNNAP scores at 44 weeks also correlated with MD, Da, and Dr for the SCP ($r=0.354$, $p<0.029$; $r=0.353$, $p<0.030$; and $r=0.335$, $p<0.040$; respectively) and with MD, Da, and Dr for the ICP ($r=0.373$, $p<0.023$; $r=0.350$, $p<0.033$; and $r=0.340$, $p<0.039$; respectively). These correlations indicate that reduced maturation of major WM tracts is associated with overall lower neurobehavioral performance at term, and more so at 44 weeks. This provides support for the hypothesis that specific neurobehavioral impairments are related to altered maturation of specific tracts.

Table 3
MRI findings.

MRI findings	% abnormalities
White matter abnormalities	
Cerebral DEHSI	63
Cerebellar DEHSI	8.7
Cerebral punctate lesions	11
Cerebellar punctate lesions	17.4
Periventricular white matter volume loss	0
Cystic abnormalities (PVPC)	4
Mild ventricular dilatation	10
Thinning of the corpus callosum	0
Abnormal integrity of Myelin within PLIC	8.2
Abnormal basal ganglia and thalami (BGT)	6.1
Gray matter abnormalities	
Presence of gray matter cortical signal abnormality	0
Quality of gyral maturation	0
Mildly enlarged size of the subarachnoid space	6.1
Hemorrhages	
Grade 1	18
Grade 2	2
Grade 3	0
Grade 4	0

DEHSI=diffuse excessive high signal intensity; PVPC=congenital periventricular pseudocysts.

3.6. Relation between early and late maturing WM fibers as a function of typicality in sensory and motor neurobehavior

To examine the hypothesis that sensory neurobehavioral impairments are related to early maturing WM tracts, and that motor neurobehavioral impairments are related to late maturing WM tracts, group comparisons were conducted between WM integrity of early and late maturing tracts in preterm infants with and without abnormal performances in sensory and motor neurobehaviors. Results showed that sensory reactivity neurodevelopmental difficulties were related to differences in maturation of early developing WM tracts, such as the CP, and that motor regulation difficulties were related to late maturing WM tracts, such as the CC and OR. These relationships were similar when examining neurobehavioral performance at 40 weeks and at 44 weeks (Tables 5 and 6).

In the sensory reactivity domain, lower Dr values for the early-maturing CP tracts were detected in preterm infants with normal visual attention at term (Table 5), indicating lower WM integrity in preterm infants with abnormal performance. This relationship was maintained at 44 weeks, such that preterm infants with normal sensory reactivity had significantly higher Dr values for the CP, compared to neonates with abnormal sensory reactivity (Table 6). In the motor-tone regulation domain, significantly lower diffusivity values in the late maturing CC and OR were detected at both ages, in preterm infants with normal tonic regulation as compared with preterm infants with abnormal tonic regulation (Table 6).

Table 4
DTI parameters in WM VOIs of preterm infants with mild WM abnormalities.

	VOI	MD ($\times 10^{-3}$ mm^2/s)	Da ($\times 10^{-3}$ mm^2/s)	Dr ($\times 10^{-3}$ mm^2/s)	FA (a.u.)
Cerebrum	CR	1.40 (0.09)	1.70 (0.10)	1.26 (0.09)	0.20 (0.02)
	PLIC	1.18 (0.07)	1.57 (0.06)	0.99 (0.08)	0.29 (0.04)
	CP	1.15 (0.07)	1.48 (0.08)	0.98 (0.08)	0.26 (0.04)
	CST	1.23 (0.09)	1.49 (0.12)	1.10 (0.08)	0.20 (0.03)
	CC	1.57 (0.10)	1.97 (0.12)	1.37 (0.10)	0.24 (0.02)
	OR	1.61 (0.14)	1.99 (0.17)	1.42 (0.13)	0.22 (0.03)
Cerebellum	SCP	1.25 (0.09)	1.53 (0.10)	1.11 (0.09)	0.21 (0.03)
	MCP	1.29 (0.11)	1.61 (0.13)	1.14 (0.10)	0.23 (0.03)
	ICP	1.09 (0.09)	1.32 (0.09)	0.98 (0.06)	0.21 (0.03)

DTI=diffusion tensor imaging; WM=white matter; VOI=volume of interest; CC=corpus callosum; PLIC=posterior limb of internal capsule; OR=optic radiations; CR=corona radiata; CST=corticospinal tract; SCP=superior cerebellar peduncle; ICP=inferior cerebellar peduncle; MCP=middle cerebellar peduncle; MD=mean diffusivity; Da=axial diffusivity; Dr=radial diffusivity; FA=fractional anisotropy, and a.u.=arbitrary units.

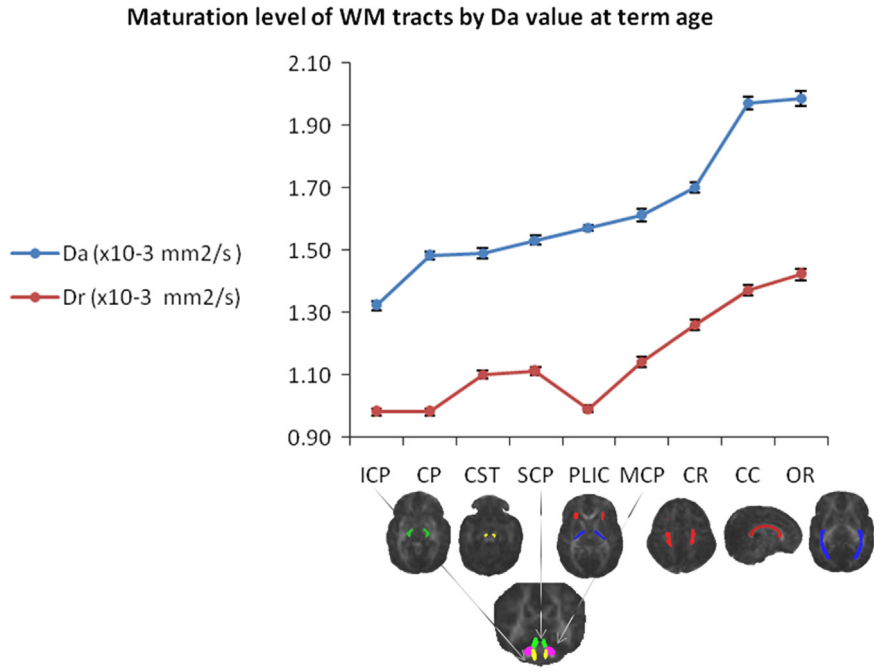

Fig. 3. Maturation level of WM tracts by Da value at term age. ICP=inferior cerebellar peduncles; CP=cerebral peduncles; CST=corticospinal tracts; SCP=superior cerebellar peduncles; PLIC=posterior limb of the internal capsule; MCP=middle cerebellar peduncles; CR=corona radiata; CC=corpus callosum; OR=optic radiations. Error bars represent standard error. Note, the maturation level of WM tracts is indicated by the Da (blue) and Dr (red) values. WM tracts are arranged from lowest-to-highest Da value. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 5
Differences in DTI parameters of WM tracts as a function of NB performance at term.

NB domain	Sub- category	VOI	Diffusivity parameter	Normal NB mean ± SD	Abnormal NB mean ± SD	*F*	*p*-value
Sensory reactivity	Visual attention	CP	Dr	0.97 ± 0.08	1.03 ± 0.04	5.02	0.031
Tonic regulation	Hypo-/ hyper-/ asymmetry	CC	Da	1.91 ± 0.12	1.99 ± 0.10	4.88	0.033
			Dr	1.33 ± 0.09	1.39 ± 0.09	4.89	0.033
		CR	Dr	1.28 ± 0.11	1.34 ± 0.09	4.2	0.047
		OR	Dr	1.38 ± 0.13	1.46 ± 0.09	4.18	0.048

DTI=diffusion tensor imaging; WM=white matter; NB=neurobehavioral; VOI=volume of interest; SD=standard deviation; MD=mean diffusivity ($\times 10^{-3}$ mm^2/s); Da=axial diffusivity ($\times 10^{-3}$ mm^2/s); and Dr=radial diffusivity ($\times 10^{-3}$ mm^2/s).

Table 6
Differences between preterm infants in DTI parameters of WM tracts based on NB performance at 44 weeks.

NB domain	NB sub-category	VOI	Diffusivity parameter	Normal NB mean ± SD	Abnormal NB mean ± SD	*F*	*p*-value
Sensory reactivity	Auditory attention	CP	Dr	0.97 ± 0.07	1.03 ± 0.09	4.92	0.033
Tonic regulation	Hypo-/ hyper-/ asymmetry	CC	Da	1.91 ± 0.10	2.00 ± 0.11	7.43	0.01
			Dr	1.32 ± 0.09	1.41 ± 0.09	9.05	0.005
		OR	Da	1.92 ± 0.13	2.03 ± 0.14	6.75	0.013
			Dr	1.37 ± 0.11	1.46 ± 0.11	6	0.019

DTI=diffusion tensor imaging; WM=white matter; NB=neurobehavioral; VOI=volume of interest; SD=standard deviation; Da=axial diffusivity; ($\times 10^{-3}$ mm^2/s); Dr=radial diffusivity ($\times 10^{-3}$ mm^2/s); CP=cerebral peduncle; CC=corpus callosum; and OR=optic radiations.

See Fig. 4 for bar graphs demonstrating sensory reactivity and tonic regulation as a function of typicality in 40 and 44 weeks.

3.7. Hierarchical regression analysis

To examine the hypothesis that integrity of specific WM tracts and maturation factors would be uniquely predictive of infant neurobehavior in the neonatal period, a hierarchical regression model was computed. Predictors included Da of the tracts and maturation factors, and were entered in 4 blocks: Blocks 1, 2 and 3 included Da of the CC, SCP, and ICP, respectively (continuous variables that reflect WM integrity); Block 4 included GA and age at RNNAP assessment (maturation factors that should be accounted for). The model was highly significant and explained 40.2% of the variance in RNNAP performance at 44 weeks, mostly due to the Da for CC ($F_{(1,39)}=11.89$) and SCP ($F_{(2,38)}=9.574$, $p<0.005$; Table 7), supporting the final hypothesis.

4. Discussion

This study shows that subtle neuronal integrity changes in specific tracts may underlie fine neurobehavioral difficulties in neonates. Our findings also demonstrate the contribution of the level of WM maturation in specific major tracts to neurobehavioral performance during the neonatal stage.

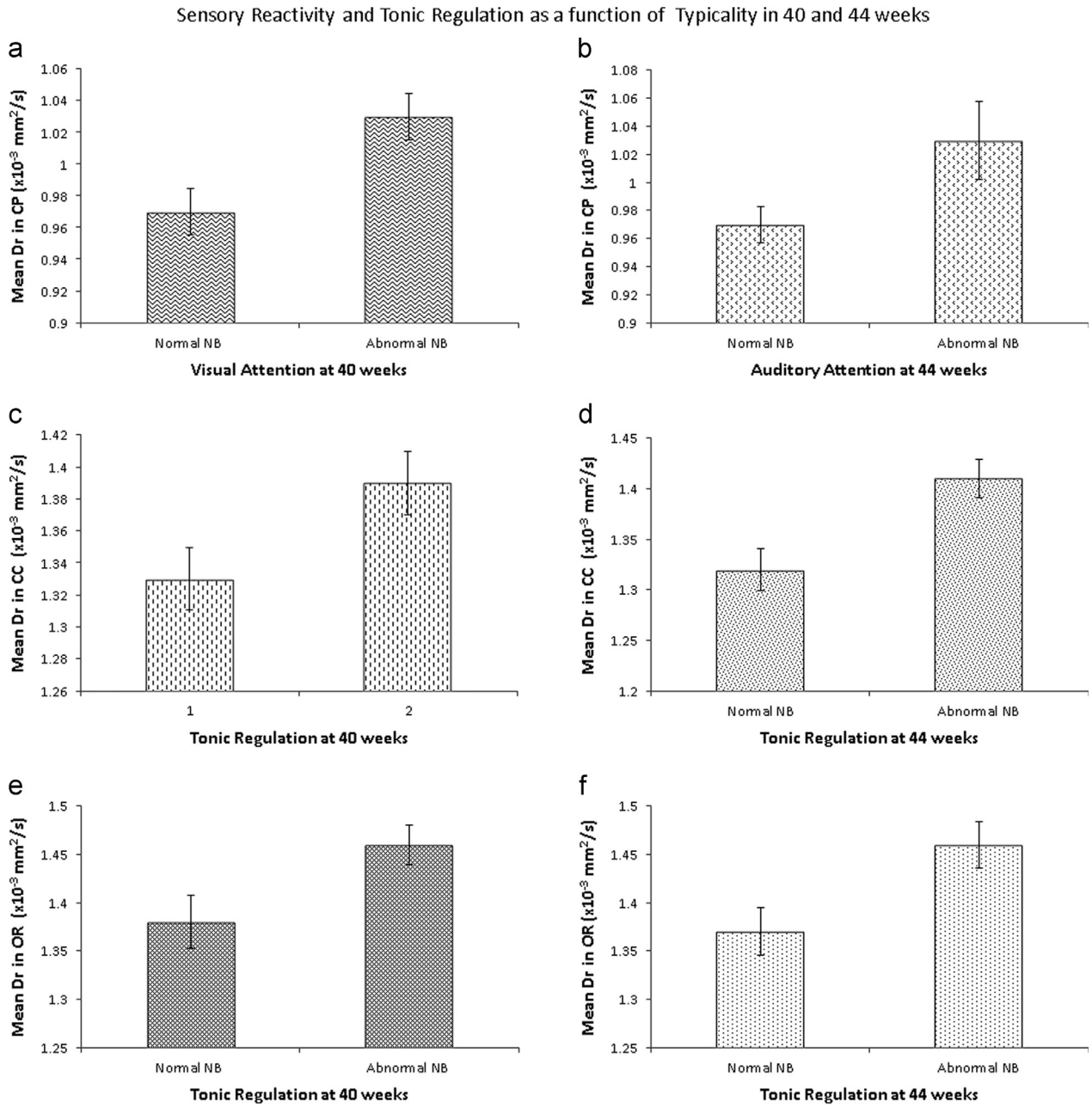

Fig. 4. Sensory reactivity and tonic regulation as a function of typicality in 40 and 44 weeks. (a, b) Children with abnormal sensory reactivity scores, visual attention at 40 and auditory attention at 44 weeks display higher Dr ($p < 0.05$) in the cerebral peduncle. Children with abnormal tonic regulation at 40 and 44 weeks display higher Dr ($p < 0.05$) in the corpus callosum (c, d) and in the optic radiations (e, f). Mean and std error are shown.

4.1. Progression of late-term and neonatal neurodevelopmental maturation

The newborn infant develops rapidly, both in the sensory (auditory and visual) and motor reactivity domains, during the intrauterine and neonatal periods. Maturational changes in auditory perception seem to precede those in visual perception. The peripheral auditory system is ready to send afferent stimulation to the central nervous system by at least 23–24 weeks of fetal development (Geva et al., 2011; Jiang, Brosi, & Wilkinson, 2006), and some motor responses to sound can be recorded at this time as well (Gray & Philbin, 2004). Development of the auditory system is such that by term age fine auditory discrimination between expected and unexpected sounds is behaviorally evident (Gray & Philbin, 2004). Regarding visual development, the healthy normal preterm infant is able to discriminate and show differential looking and visual preference to appropriate temporal and spatial stimuli as early as 33–34 weeks post-conceptual age (Dubowitz, Dubowitz, Morante, & Verghote, 1980; Geva, Gardner, & Karmel, 1999). Although, the visual sensory–motor processes involved in detecting and shifting gaze to visual targets are functional by term age (Hunnius, Geuze, Zweens, & Bos, 2008), the balance between engaging and shifting attention to visual stimuli develops from birth through the first few months of life (Geva et al., 1999; Harel, Gordon, Geva, & Feldman, 2011; Hunnius et al., 2008).

In both infants born at term and healthy preterm infants, the motor repertoire evolves beginning in the prenatal period and continues to develop during the neonatal period through the first two months of post-term life (Einspieler et al., 2008). The developmental course of spontaneous movements consists of

Table 7
WM integrity and maturation factors: prediction of NB at 44 weeks.

	Beta	r^2 change	*F* change
CC-Da	0.444**	0.234	11.887**
SCP-Da	0.235	0.101	5.799*
ICP-Da	0.120	0.023	1.306
GA at birth	−0.048		1.294
		0.044	
GA at RNNAP	−0.229		

r^2 total = 0.402; $F_{(5,40)} = 4.705$, $p < 0.002$.
WM = white matter; NB = neurobehavior; Da = axial diffusivity; ($\times 10^{-3}$ mm^2/s); CC = corpus callosum; SCP = superior cerebellar peduncle; ICP = inferior cerebellar peduncle; GA = gestational age; and RNNAP = Rapid Neonatal Neurobehavioral Assessment Procedure.

* $p < 0.05$.
** $p < 0.001$.

spontaneous general movements (Einspieler et al., 2008), followed by specific neuromotor patterns (Karmel & Gardner, 2005; Katona, 1989; Zelazo, Zelazo, Cohen, & Zelazo, 1993). These neuromotor patterns emphasize non-reflex type responses, similar to those seen in subsequent motor activity at later ages, and can indicate neonatal neuromaturational changes or brain dysfunction, necessitating direct intervention (Karmel & Gardner, 2005).

Budding expressions of these developmental progressions were noted in the current results, depicted by a discrete profile at each age. Most preterm infants in this study displayed abnormal function in at least one neurobehavioral domain both at TEA and at 44 weeks. The prospective follow-up showed that the total mean score and range of neurobehavioral function were not significantly different between the two time points. This general finding may seem to be compatible with the notion of 'stability', as previously reported (Einspieler et al., 2008); however, it is important to note that there were changes in susceptibility of the different domains as the infants matured. Indeed, differences were noted in the composition of the total score at term and at 44 weeks; a finding that may indicate a specific developmental course for the various neurobehavioral domains that develop during the neonatal period.

In general, our findings concerning sensory–motor susceptibility were consistent with other research in terms of the overall behavior of NBs studied (Gardner et al., 1990; Karmel & Gardner, 2005). However, there were some differences in performance in the current sample from what was reported in other preterm infant cohorts, mainly in the lack of visual asymmetry abnormality, the larger proportion of infants with auditory attention and asymmetry problems and the higher incidence of state control and jitteriness seen in the current work. These differences may arise from different demographic sources and care protocols that were used in the current study, possibly meriting further research. More specifically, these differences may reflect changes in the characteristics of today's cohorts of NICU infants compared to those in previous studies (Gardner et al., 1990; Karmel & Gardner, 2005); or they may stem from changes in the NICU environment and care practices, such as differences in touch, light and noise level exposure. Importantly, it should be noted that this study cohort is not a random sample of preterm NICU infants, but rather it includes infants with mild to moderate echogenicity detected on their cranial cUS. Pending replication, these differences may unveil susceptibility that is related to the DEHSI phenomena.

Compatible with the first hypothesis of this study, some sensory categories (specifically visual attention) showed improvement with age during the neonatal period, while motor regulation categories (e.g. unilateral muscle tone and hypertonicity) showed changes that were hardly recognizable at term, but emerged later during the neonatal period. The pattern was such that there were more hypotonic preterm infants at TEA than at 44 weeks and more infants at 44 weeks with hypertonicity. Moreover, regulation differences in unilateral muscle tone emerged during the neonatal period (e.g. asymmetry between the arms and legs) and were more prevalent at 44 weeks, indicating that many behavioral changes occurred during the neonatal period and that a special trajectory of neurobehavioral maturation for each sensory–motor domain might be expected.

4.2. Progression of late-term and neonatal neuronal maturation

Myelination is an important part of WM maturation. Myelination is a long sequential nonlinear process that begins in the last trimester of gestation, peaks in the first postnatal year, and continues until at least 20 years of age (Dubois et al., 2008). There are temporal and spatial differences in axonal maturation and myelination of different fiber tracts. Myelination advances in the infero-superior and caudo-rostral directions, and progresses from central to peripheral regions (Dubois et al., 2008; Huang et al. 2006a, b). For example, cerebellar WM begins to myelinate during the third trimester of gestation and continues after birth, whereas the middle cerebellar peduncles (MCP) myelinate later on, around the time of birth, and demonstrate the most prolonged sequence of myelination (Brody, Kinney, Kloman, & Gilles, 1987; Saksena et al., 2008). The internal capsule and cerebral peduncle are well developed in the early phase of development and are already visible at 20 months of gestation, while the corona radiata (CR) is not well visible in the fetal brain (Huang et al., 2006a, b). This is due to low diffusion anisotropy in the superior regions of the CR in the neonatal stage (Hermoye et al., 2006; Huang et al., 2006a, b).

Overall, for WM tracts, limbic fibers develop first, association fibers develop last, and both commissural and projection fibers form the anterior to posterior parts of the brain (Huang et al., 2006a, b). The brainstem, cerebellum, basal ganglia, and thalamus also myelinate in a caudal-to-rostral order (Connolly, Forssberg, & Mac Keith Meeting, 1997). However, the neurobehavioral correlates of these maturational spurts were not yet known and were investigated in the current project. The second hypothesis of this study postulated differential maturation levels for the major tracts that could be detected during the neonatal period. Indeed, comparison of diffusion parameters in the different cerebral and cerebellar WM tracts revealed a spatial and temporal WM maturation pattern that corresponded to neurobehavioral development. In this cohort, the most mature tracts (indicated by reduction in both Da and Dr) were the CP and the ICP, while the less mature tracts (indicated by higher values of both Da and Dr) were the OR, CC, and CR. The PLIC showed a more pronounced reduction of Dr compared to Da, which may indicate that accelerated myelination is more dominant than axonal growth. In neonates born at 35–42 weeks GA and examined at age 22 ± 10 days, Gao et al. (2009) reported that the general maturation pattern at the neonatal age began centrally (CC), followed by the CST, PLIC, OR, and peripheral WM development from the occipital to the frontal lobes. The current results are generally in accord with Gao et al., in terms of the CST, PLIC, and OR, with the exception of a difference in regard to the CC, which was less mature in the current cohort. This latter difference may arise from the different ranges of GA used in the two cohorts (the group in the study by Gao et al. was somewhat more mature, GA = 35–42 weeks, relative to the current study, GA = 24–34 weeks). Moreover, there were also differences in ages at the time of MRI scans between the cohorts (Gao et al.: 45 ± 1.5 weeks; current study: 37 ± 1.7 weeks).

When focusing on the motor system, different levels of WM maturation were detected in the CR, PLIC, and CP, with the lowest

Da and Dr values in the CP, intermediate in the PLIC, and the highest in the CR. The reverse expected trend was detected in the FA values. These results for maturation of the motor system are in line with previous studies that have supported maturation progression along the infero-superior axis (Hermoye et al., 2006; Huang et al., 2006a,b).

Having shown different trajectories of discrete neurobehavioral domains and differences in maturation levels of the major tracts at TEA, the third hypothesis in this study postulated a relationship between diffusion parameters of WM tracts and general neurobehavioral performance. Discrete relationships were found at term and the number of relationships increased dramatically at 44 weeks. These results seem to indicate that WM structure at term predicts the behavioral progression during the neonatal period.

Overall, a correlation was first found between WM diffusion parameters in the cerebral CST and neurobehavioral performance at TEA. In addition, a correlation was found between diffusion parameters in the CC and cerebellar pathways (the SCP and ICP) and neurodevelopment performance at 44 weeks of age. Previous studies have detected comparable associations between the integrity of major WM fibers and outcome at later ages (Messerschmidt et al., 2008; Thompson et al., 2011; van Kooij et al., 2012). Krishnan et al. demonstrated that higher WM apparent diffusion coefficient (ADC) values at centrum semiovale level at TEA in preterm infants without overt lesions were negatively correlated with the developmental quotient at two years, pointing to preterm birth-related susceptibility even in the absence of significant risk (Krishnan et al., 2007). The current findings pinpoint these maturation levels of the major tracts to neurobehavioral performance already in the neonatal age, pointing to their validity in detecting susceptibility of specific neurobehavioral patterns at such an early age.

It is plausible that the lower maturational level of the WM tracts at TEA may reflect an altered course in development rather than a lag in maturation, in the sense that preterm infants never "catch up" with the typical developmental trajectory, and thus display altered connectivity throughout life. This was shown by reports of altered connectivity in studies of structural and functional connectivity conducted on children and adolescents born preterm, suggesting that there is long lasting effect of preterm birth on brain development (Constable et al., 2008, 2013; Ment, 2009; Schafer et al., 2009; Vangberg et al., 2006). It is important to keep in mind that an altered course of development does not necessarily mean adverse outcome since development of compensatory neural networks in response to injury in the premature brain may preserve overall function through plasticity (Schafer et al., 2009). In order to determine whether this conception is accurate, a serial imaging paradigm can be employed. Future studies with long term follow-up are needed to determine whether the WM abnormalities reflect a lagged developmental effect, indicating that recovery eventually will reach the expected normal levels of central nervous system (CNS) connectivity, or whether it will result in long-term effects on development. The latter is more probable, as studies reported altered connectivity in children and adolescents born preterm (Constable et al., 2008, 2013; Ment, 2009; Schafer et al., 2009; Vangberg et al., 2006) as well as increasing incidences of long-term effects on development indicated by syndromes such as ADHD (Gurevitz, Geva, Varon, & Leitner, 2014) or ASD (Johnson & Marlow, 2014; Karmel et al., 2010a) in children born preterm.

The relationship between sensory and motor domains and level of maturation of WM tracts was also investigated, with the hypothesis that preterm infants with abnormal performance in sensory reactivity will have lower WM integrity in early-maturing tracts, while preterm infants with abnormal performance in tonic regulation will have lower WM integrity in late-maturing tracts. Our results supported this notion by demonstrating reduced WM integrity and maturation in cerebral peduncles in preterm infants with poorer sensory reactivity, evidenced by difficulty engaging attention at TEA and at 44 weeks of age. Compared to preterm infants with normal attention, those with poor attention showed elevated Dr. These findings considerably extend findings from other studies that have reported reduced FA in the CP and MCP in children with attention deficit hyperactivity disorder (ADHD) during childhood [at 9 (Ashtari et al., 2005) and 10 years of age (Bechtel et al., 2009)]. WM microstructure of the cerebellar peduncles has also been associated with sustained attention in healthy adolescents and adults (Takahashi et al., 2010). These reports link the microstructure of the CP and MCP tracts to attention and validate the notion that the seeds for attention are set neonatally due to microstructural changes in the CP and MCP. Pending replication, further work in this direction may enable earlier detection of infants who are at risk for development of ADHD.

As for motor regulation changes, this study demonstrated reduced WM integrity/maturation in later-maturing pathways (the OR and CC) in preterm infants with poorer regulation of muscle tone at term and at 44 weeks of age, compared to preterm infants with normal tonic regulation at this early age. This finding extends previous reports on preterm infants scanned at TEA that found that the maturation of the splenium (as reflected by FA values) was significantly lower in children with abnormal versus normal neurological assessments performed at 18 months (Rose et al., 2009). Regarding the OR, decreased WM integrity in children and adolescents was found in older participants with inferior visuomotor tracking performance (Caeyenberghs et al., 2010). The current results present a comparable picture with neonates, enabling deduction of a more general brain–behavior relationship with regard to the role of these particular tracts and early motor development.

Finally, the regression model used in this study highlighted the important roles that the maturation levels of the CC and the cerebellar peduncles, together with maturation factors, played in predicting neurobehavioral performance at 44 weeks of age. The correlations among the CC, ICP, and SCP with the total RNNAP score at 44 weeks provide a neurostructural basis underlying neonatal neurobehavioral performance and offer a way to explore the relationships between early WM maturational level at TEA and development of discrete sensory–motor reactivity patterns in preterm neonates. Using sensitive neurobehavioral evaluations and new DTI methods with neonates enabled us to demonstrate that the integrity/maturational level of major WM tracts is predictive of neurobehavioral development that occurs at such an early age. This suggests that the neonatal period is a sensitive time, characterized by significant and diagnosable neuromaturational and neurobehavioral changes that were to-date elusive and generally thought of as relatively stable (Hunnius et al., 2008).

It should be noted that a high proportion of the preterm infants in this study had WM signal changes such as diffuse excessive high signal intensity (DEHSI) at term-equivalent MRI. In a previous study we have shown that preterm infants with DEHSI demonstrated altered regional WM integrity compared to those without DEHSI (Weinstein et al., 2014). Volpe (2009) introduced their thesis suggesting that the "encephalopathy of prematurity" is a complex amalgam of primary destructive disease and secondary maturational and trophic disturbances that may be elusive to conventional methods. The fine grained axonal/neuronal disease may account for some of the changes documented in this report.

From a theoretical perspective, since these early neurodevelopmental changes precede many effects of socio-economic and environmental factors and long-term brain compensation mechanisms, such an early outcome assessment may be highly valuable in its ability to enable the study of the WM integrity–neurobehavior

maturation relationship while minimizing the effect(s) of these confounding factors.

In light of the discrete relationship between specific pathways, neonatal sensory reactivity, and motor regulation performance, this research suggests that there may be a beneficial impact from early intervention (Zelazo et al., 1993). The current findings point to specific target WM tracts and the specific neurobehavioral domains that may be the focus of neonatal interventions. For example, one method of neonatal intervention was based on Ferec Katona's observation that neuromotor patterns in the neonate could be elicited through active feedback mechanisms from the appropriate sensory input (Karmel & Gardner, 2005; Zelazo et al., 1993). Preterm infants with reduced maturation/integrity in major WM tracts may benefit from such interventions and future studies should assess the impact of early intervention on WM integrity and on long-term outcome.

The limitations of this study include a relatively small number of participants, which limited our ability to test more elaborate predictive models. Further, this study focused on preterm infants and therefore a confounding factor of neurological insults related specifically to preterm birth should be taken into account. Future studies should be extended to infants born at term as well.

It should also be noted that the effect of exposure to the NICU during critical periods of brain development is increasingly implicated as a contributor to attentional difficulties of preterm infants (Gray & Philbin, 2004). Most likely, a combination of tools including the neurobehavioral examination, neuroimaging, and neurophysiological studies will be needed to accurately and reliably account for the dramatic changes occurring during the late term (Geva, Eshel, Leitner, Valevski, & Harel, 2006) and neonatal period (El-Dib, Massaro, Glass, & Aly, 2011).

In summary, neurobehavioral attention and motor performance evolve during the neonatal period in a manner that is related to level of maturation of specific major WM fiber tracts. Early maturing tracts were related to sensory reactivity while late maturing tracts were related to tonic regulation, which correspond with the development of these neurobehavioral abilities. Perturbed neurobehavioral maturation in preterm neonates during the neonatal period is associated with higher diffusion values of these WM major fiber tracts, even when maturational factors are taken into account. Since WM maturation is an on-going process, early identification of changes in WM integrity along with neurobehavioral difficulties may deepen the understanding of the very early neurodevelopmental milestones of the postnatal period and may afford early intervention during this sensitive time window.

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