Transient structural MRI patterns correlate with the motor functions in preterm infants

Katušić, Ana; Žunić Išasegi, Iris; Radoš, Milan; Raguž, Marina; Grizelj, Ruža; Ferrari, Fabrizio; Kostović, Ivica

Source / Izvornik: **Brain and Development, 2021, 43, 363 - 371**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.braindev.2020.11.002

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:445023

Transient Structural MRI Patterns Correlate with the Motor Functions in Preterm Infants

Ana KATUŠIĆ*, PhD, Assis. Prof.[a]; Iris ŽUNIĆ IŠASEGI, MD, PhD[a] ; Milan RADOŠ , MD, Assoc. Prof.[a]; Marina RAGUŽ, MD, PhD[b]; Ruža GRIZELJ, MD, Assoc. Prof.[c]; Fabrizio FERRARI, MD, Prof.[d]; Ivica KOSTOVIĆ, MD, Prof Emeritus[a]

Affiliations:

[a] Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience, Croatian Institute for Brain Research, University of Zagreb, School of Medicine, Croatia

[b] University Hospital Dubrava, Department of Neurosurgery, University of Zagreb, School of Medicine, Croatia

[c] Clinical Hospital Centre Zagreb, Department of Pediatrics, University of Zagreb, School of Medicine, Croatia

[d] Neonatal Intensive Care Unit, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

12 text pages, 4 figures, 3 tables, 41 references

***Corresponding author:**

Ana Katušić, Assist. Prof.

Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience, Croatian Institute for Brain Research, University of Zagreb, School of Medicine,

Šalata 12, 10000 Zagreb, Croatia

Email address: akatu@hiim.hr

ORCID iD: https://orcid.org/0000-0002-7648-131X

ABSTRACT

Aim To explore the relationships between transient structural brain patterns on MRI at preterm and at term-equivalent age (TEA) as a predictor of general movements (GMs) and motor development at 1-year corrected age (CA) in very preterm infants.

Methods In this prospective study, 30 very preterm infants (median=28wks; 16 males) had structural magnetic resonance imaging (MRI) at preterm (median=31wks+6d) and at TEA (median=40wks) and neuromotor assessments. The quality of GMs was assessed by Prechtl's general movements assessment and a detailed analysis of the motor repertoire was performed by calculating a motor optimality score (MOS), both at term age and at 3 months post-term. Motor development at 1-year CA was evaluated with the Infant Motor Profile (IMP). Associations between qualitative MRI findings and neuromotor scores were investigated.

Results Abnormal GMs and low motor performance at 1-year CA were associated with the poor visibility of transient structural pattern, that is with sagittal strata.

Interpretation Transient structural MRI pattern, sagittal strata, at preterm age is related to the quality of GMs and later motor development in preterm infants. This transient fetal brain compartment may be considered as a component of neurobiological basis for early neuromotor behavior, as expressed by GMs.

Keywords: general movements, motor functions, preterm infants, sagittal strata, periventricular crossroads, neonatal MRI

Abbreviations

CA, corrected age; CP, cerebral palsy; GMs, general movements; GMOS, general movements optimality score; IMP, Infant Motor Profile; MRI, magnetic resonance imaging; MOS, motor optimality score; TEA, term-equivalent age; SS, sagittal strata; WM, white matter

One of the most challenging pursuit in clinical neuroscience is to find reliable criteria for prediction of neurological and neurobehavioral outcome in preterm infants. Brain magnetic resonance imaging (MRI) conducted at term-equivalent age (TEA) is a sensitive tool that can provide important information about brain injury and structure, which is associated with long-term neurodevelopment [1]. Although MRI of the neonatal brain has improved our understanding of the nature and extent of cerebral abnormalities in preterm infants [2], it alone cannot completely predict the functional outcome for individual infant. In this respect, neurodevelopmental assessments have an important role in identifying infants at risk for later neurological impairment and may enhance the prognostic utility of MRI when used in combination [3-5].

Spontaneous activity resulting in general movements (GMs) is described as one of the best qualitative indicators of normal neurological outcome in preterm infants [6,7]. Correlation of GMs with structural MRI was proposed to be one of the most accurate predictors of severe motor impairments, as manifested in cerebral palsy (CP) in preterm and term infants [8-11].

Although neurobiological and neural substrate in GMs has not been documented convincingly so far, several studies indicate the role of transient circuitries of the subplate [12]. Other developing neurophysiological mechanisms were also considered [13]. One of the obstacles in the analysis of GMs and MRI is lack of longitudinal studies and MRI shortly after preterm birth. From neurobiological point of view, interpretational difficulties are related to different reorganizational processes, such as reduction in projection and restructuring of pathways, and to the nature of developmental lesions. This latter was considered in studies claiming that developmental lesions will eventually result in changes in neuronal reorganization during long period of postnatal brain development [14].

In order to shed some light on these clinical and biologically relevant questions, we have started our long-term project in which we have correlated structural MRI findings at preterm and TEA, with the quality of GMs and later motor development for the cohort of preterm born infants. Next to conventional methods of assessing brain injury [15], we have applied additional scoring of transient fetal compartments and white matter (WM) segments [16-20]. These specific

transient compartments of the fetal brain in the third trimester are the major site of navigation for many axonal pathways during the early and late preterm periods [16,19].

While there is evidence that MRI abnormalities are associated with the neuromotor performance in very preterm born infants [4,5], the relationship between transient fetal brain patterns and early neuromotor behavior, as expressed by GMs, has yet to be explored. Additional studies in this area might help to improve knowledge of the neural correlates of early motor performance in preterm born infants.

Accordingly, the aims of our prospective study were to explore the relationship between the transient structural brain patterns at preterm and TEA and (1) the qualitative and quantitative assessments of GMs at writhing and fidgety period and (2) motor development at 1-year CA in very preterm born infants.

METHODS

Participants

This study was based on a longitudinal design to follow the neuromotor development in preterm infants throughout 12 months CA and it is part of a multidisciplinary, longitudinal research project of Zagreb neurodevelopmental research group. The participants were recruited from consecutive newborn admissions to the Neonatal Intensive Care Unit at the University Hospital Centre Zagreb between September 2015 and February 2017. The infants were included if they were born very preterm (<32 weeks gestational age). The preterm infants with known congenital or chromosomal abnormalities, higher-graded hydrocephalus and massive infarctions, likely to affect their neurodevelopmental outcome, were excluded. Thirty-eight very preterm born infants were recruited for the study.

Written informed parental consent was obtained for all participants. Ethical approval was obtained from Institutional Review Board of the University of Zagreb, School of Medicine and in accordance with Declaration of Helsinki.

Procedure for MRI

This study used a 1.5T MRI scanner (Symphony, Siemens) and a 3T MRI scanner (Magnetom Prisma^{FIT}, Siemens) for MR imaging.

MRI was done twice: (1) Early MRI at preterm age, between 27 and 33 wks PMA, and (2) Late MRI at TEA, between 37 - 44 wks PMA. Early MRI was done shortly after birth on a 1.5T MRI scanner in the Clinical Hospital of the University of Zagreb (T2-weighted turbo spin-echo, TR/TE = 5050 ms/116 ms, FOV = 200 × 104 mm; resolution = 448 × 152; voxel size = 0.5 × 0.6 × 5 mm; duration 2:46 min), and then again at TEA on 3T MRI scanner (T2-weighted turbo spin-echo TR/TE = 6000 ms/96 ms, FOV = 220 × 96 mm; resolution = 512 × 179; voxel size = 0.4 × 0.4 × 1.5 mm).

MRI scanning was performed after regular feeding; infants were wrapped/half-fixed within linen diapers and blanket.

The scoring of transient fetal compartments and WM segments [16,18] was performed on MR images obtained at preterm and TEA. They were categorized as non-visible (0), poorly visible (1) and fairly visible (2) for subplate, sagittal strata (SS), periventricular crossroads and borders between WM segments (Figures 1 and 2). All images were assessed independently by one of two experienced neuroradiologist and neuroanatomist with excellent interrater and intrarater reliability, and who were unaware of the infant's prenatal history.

Neurological and Motor Assessments

All assessments were administered according to their standardized procedures by trained and advanced certificated assessors who were unaware of the infants' clinical characteristics. Both assessors (A.K. and J.G.) are certified by the GM Trust.

General Movements Assessments

Video recordings of GMs were obtained on 2 occasions. The first was conducted at 2 - 4 weeks CA, in the period of writhing GMs, and the second at 12 - 16 weeks CA, when GMs have fidgety character.

Writhing GMs were described as normal or abnormal (poor repertoire, cramped synchronized, or chaotic). Normal GMs involve the infant's entire body, can last from a few seconds to several

minutes and are characterized by a complex and variable sequence of arms, legs, neck and trunk. Writhing GMs were scored as abnormal if they lacked complexity, variability and fluency [8]. A detailed analysis of motor repertoire at term-age was performed by calculating a GMs optimality score (GMOS) [21]. Eight different aspects, including GMs quality, were distinguished. GMOS ranges from 5 to 42 (low to high optimality).

General movements of a fidgety nature were described as normal, abnormal, or absent [8]. Normal fidgety movements are circular movements of small amplitude, moderate speed and variable acceleration of the neck, trunk and limbs in all directions. Fidgety movements were scored as being abnormal when circular movements were present, but with exaggerated speed, amplitude or jerkiness. They were scored as absent if they were never observed. The Motor Optimality List for Fidgety Movements [22] was used to assess a Motor Optimality Score (MOS). Five aspects, including fidgety movement quality, were distinguished. During this period, MOS ranges from 5 to 28 (low to high optimality).

Infant Motor Profile

Infant motor profile (IMP) assessment was obtained at 12 months CA. A video recording of 15 minutes of spontaneous and elicited play behavior was made. The 80 items of the IMP constitute five domains: variation (the size of the motor repertoire), adaptability (the ability to select efficient strategies from this repertoire in order to perform the movement), fluency, symmetry, and motor performance (motor milestones) [23]. The IMP results in domain scores and a total score, which is calculated as the mean of the five domain scores. All scores are expressed as percentages, with 100% as maximum. For the aim of our study we analyzed the total IMP score. Total IMP score of 85 at 12 months CA presents median value in children who later develop minor neurological dysfunction [24], so we considered the score below 85 as a cut-off score for indicating infants with normal, that is with low motor score at 12 months CA.

Statistical analysis

Data analysis was performed using Stata version 10.0 (Stata Corp, College Station, TX).

Relations between MRI patterns and GMs optimality scores and motor outcome (total IMP score) were assessed with the Spearman's rank correlation coefficient (r). Interpretation of the Spearman's correlation coefficient was as follows: ρ<0.25, weak relationship; 0.25–<0.50, fair relationship; 0.50–0.75, moderate relationship; and ρ>0.75, good relationship. For significant correlations, the relations were further tested with the Kruskal-Wallis test to test for differences between the groups with distinctive visibility of transient brain patterns and neuromotor scores. Throughout the analyses, differences and correlations with p<0.05 were considered to be statistically significant (two-tailed testing).

RESULTS

Participants characteristics

During the study period, 38 very preterm infants fulfilled the inclusion criteria; 8 infants were not included in final analysis (5 were excluded due to poor image quality and 3 did not return for motor assessment). Accordingly, the study group comprised 30 preterm infants (16 males, 14 females), with a median gestational age of 28 weeks. Participants characteristics are shown in Table 1. The incidence of brain injury remains stable between early and term MRI. Six (20%) infants had mild WM abnormalities. In four (13%) infants MRI findings showed deep GM abnormality and three (10%) infants had evident abnormalities on cerebellum. There were no infants with moderate or severe brain injury.

General movements and Infant Motor Profile

At the assessment at term age (median = 2 weeks CA), 14 (47%) infants showed normal GMs and 16 (53%) showed poor repertoire. Median GMOS was 28 (interquartile range (IQR), 24 - 40). At fidgety age (median = 14 weeks CA), the quality of fidgety movements was scored as absent in five (16%) infants, abnormal in three (1%) and normal in 22 (73%) infants. Median MOS for fidgety movements was 22 (IQR, 19 - 26).

The total IMP score ranged between 70 and 97. At 1-year CA, 9 (30%) infants had total IMP score below 85, so they were classified as having low motor score for CA (Table 2).

The visibility of transient brain patterns and general movements

At early MRI, only visibility of SS had significant correlations with the GMOS at term-age and with MOS at 3 months post-term. The relationship was stronger for occipital ($r = 0.55$, $p = 0.002$ for GMOS; $r = 0.62$, $p = 0.001$ for MOS) than for the frontal SS ($r = 0.43$, $p = 0.017$ for GMOS; $r = 0.48$, $p = 0.015$ for MOS). The median GMOS and MOS scores were the highest in the group of infants with fairly visible SS at early MRI, suggesting that a clear visibility of SS may be predictive of higher motor optimality score at writhing and fidgety age (Table 3, Kruskal-Wallis $p < 0.01$ for frontal and occipital SS).

There was no evidence for any of transient structural patterns at term MRI being related to GMOS or MOS.

The distribution of normal and abnormal GMs at writhing and fidgety age according to the visibility of SS at early MRI is presented in Figure 3.

The visibility of transient brain patterns and motor outcome at 1-year CA

The analysis again revealed that only poor SS visibility at preterm age increased the risk of adverse motor outcome, with occipital SS ($r = 0.87$, $p < 0.01$) being stronger related to outcome than frontal SS ($r = 0.68 = p < 0.01$).

No linear relationships were found between visibility of any of transient brain patterns at term MRI and total IMP score.

We next compared total IMP scores between infants with differential visibility of frontal and occipital SS at preterm age. Infants with better visibility of SS had significantly higher total IMP scores at 1-year CA (Table 3, Figure 4, Kruskal-Wallis $p < 0.01$ for frontal and occipital SS).

DISCUSSION

In this prospective study, we have shown the advantage of an early MRI scan in predicting early neuromotor behavior and motor outcome in the cohorts of very preterm infants [25]. Our

findings identify the potential neuroimaging markers for abnormal GMs trajectory and poor motor development in infancy. The obtained results suggest structure – function relationship between transient fetal brain pattern and neuromotor behavior.

Using this structural-functional approach, we have found that visibility of SS, an indicator of structural integrity of motor and sensory associative pathways [18], at preterm age correlates strongly with the quality of GMs trajectory and motor outcome at 1-year CA. Furthermore, we have shown that differential significance of frontal versus occipital SS correlates with functional outcome at 3 months and 1-year CA.

The role of transient compartments and transient circuitry as a neural basis for GMs was discussed in recent reviews of Hadders-Algra [12,13]. Transient functional activity, intrinsically spontaneous, is the main feature of developing brain and neurological basis for this was described in cortex, driven by both synaptic [26] and non-synaptic electrical mediated semi-channel activity [27]. It may also exist on the lower level due to the early synapses development [28].

GMs may be considered as a special form of spontaneous activity [29,30]. Spontaneous activity of cortical circuitries in cerebral wall may modulate the central pattern generator (CPG) control of GMs. Basic requirements for prospective integrative function of spontaneously active developing brain is the existence of real connectivity of different structures. In the light of possible anatomical connectivity, it is interesting to point that major efferent and afferent pathways are located exactly in SS.

In the present paper we have shown that SS, as the major gateway of intracerebral trajectory of both sensor and motor associative pathways, situated at the deep border of the subplate [18], are prospective vulnerable structure which may lead to abnormality of GMs and adverse motor development. This transitional fibre-rich lamina consists of different pathways, which are likely in control of CPG of GMs; supraspinal pathways, including subcortical pathways from pyramidal neurons cortical layer VI to various brainstem targets; corticopontine, corticospinal and corticonuclear pathways from layer V; and somatosensory pathways connecting thalamus and cortex [31].

In the early prenatal brain development, subplate neurons may serve for differentiation and specification of deep projection neurons [32], where efferent fibres [31] from the subplate may use SS as a trajectory for their projection. The fact that the most superficial stratum of SS, which borders with subplate, serves for growth of associative cortico-cortical pathways opens the possibility that these pathways may be also injured at this topographical point. Thus, the finding of correlation between alteration of SS and quality of GMs is in an accordance with proposed morphogenetic and connectivity role of transient fetal compartments.

When discussing the role of supraspinal central control of GMs generator, one should not exclude changes in developmental reorganization of different pathways. It was proposed that the crucial role of early developing corticospinal pathway [33] is in providing control before and after the period of GMs age. In the context of changing development of central control of GMs generator [34], it is crucial to emphasize that the transition of GMs from early to writhing to fidgety movements requires understanding of changing pattern of central physiological control and reorganizational events in pathway projections. It is known that bilateral projections of corticospinal pathway are being changed from bilateral to predominantly unilateral pathway, which can be partly explained by the change in the central control [33].

Furthermore, cerebellum, which develops during the period of spontaneous movements, may also be involved through different motor activity in ascending and descending pathways [12]. The most important circuit involving cerebellum is corticopontine-cerebellar pathway which develops very early [35], since these pathway and numerous interstitial collaterals of corticospinal pathways terminate in various pontine nuclei, throughout period characterized by GMs.

In revealing which neuronal circuitries may be active before, during or immediately after GMs phase, it is obvious that there are significant events along motor axis. First, pyramid neurons of layer V shows development of dendritic trees as a parameter of functional maturity [36]. Second, intensive myelination occurs along the primary motor descending pathways indicating different physiological efficiency in transmission. Furthermore, a major reorganization involves subplate neurons, which remain incorporated in the gyral WM and have important functions in somatosensory cortex “gating” [37]. Also, subplate remnant (SPr) is important as a growth and ‘mini waiting’ compartment for cortico-cortical pathways which finish their growth around 3

months in somatosensory cortex [48]. The short intracortical connections between different loci of somatosensory and motor cortex are another significant, however, neglected parameter [39]. Thus, the complex development and sequential involvements of different pathways between 9 and 18 PCA weeks and 3 months postnatal, during the period of existence and changing patterns of GMs, suggest possible relationship with GMs, but requires further studies and new spatiotemporal correlates necessary in search of GMs neural substrate in developing infants.

Our analysis of predictive value of MRI in early preterm age extended previous studies which preformed MR scanning at term age [40,41]. In the context of predictive value of structural scans, it is interesting that visibility and integrity of SS show strong correlation with alterations of GMs and motor outcome. These findings support our standpoint that SS may be used for qualitative MRI scoring additional to standardized criteria.

Considering the research design and population, we find the size of our cohort relevant for research question, but the novelties of our study need to be considered with respect to some limitations. The number of included participants was small and thus multivariate analysis, that would introduce the cofounding parameters which potentially affect GMs quality, could not be conducted. In this regard, one may consider that the quality of GMs can be affected by the maturational stage of transient brain structure. As preterm and term period is a time of rapid changes in brain development, it is challenging to attribute the visibility of transient fetal patterns, or lack of it, to maturational (age-dependent), that is to pathological (injury-induced) process. The continuous research work on the association between transient fetal compartments and neurobehavioral outcomes, may contribute in defining underlying structure-function relationship.

In conclusion, this study demonstrated that the transient fetal fibrillary compartment SS, as the major gateway of intracerebral trajectory of both sensory, motor and associative pathways, are prospective vulnerable structure which may lead to abnormality of GMs and adverse motor development. Accordingly, this transient brain pattern may be considered as a component of neurobiological basis of GMs and as a potential neuroimaging marker for early motor behavior of preterm infants.

ACKNOWLEDGMENTS

We thank Mrs J. Gagula for her contribution in neuromotor assessments. We also thank infants and their families for their participation.

All phases of this study were supported by Croatian Science Foundation projects CSF-IP-09 2014-4517 and CSF-DOK-10-2015; co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience- project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund.

CONFLICT OF INTEREST DISCLOSURES

The authors declare no competing interests.

REFERENCES

1. Anderson PJ. Neuropsychological outcomes of children born very preterm. Semin Fetal Neonatal Med 2014; 19: 90-6.
2. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: A qualitative magnetic resonance imaging study. J Pediatr 2003; 143: 171–9.
3. Constantinou JC, Adamson-Macedo EN, Mirmiran M, Fleisher BE. Movement, imaging and neurobehavioral assessment as predictors of cerebral palsy in preterm infants. J Perinatol 2007; 27: 225–9.
4. Spittle AJ, Boyd RN, Inder TE, Doyle LW. Predicting Motor Development in Very Preterm Infants at 12 Months' Corrected Age: The Role of Qualitative Magnetic Resonance Imaging and General Movements Assessments. Pediatrics 2009; 123: 512–7.
5. Skiöld B, Eriksson C, Eliasson AC, Ådén U, Vollmer B. General movements and

magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. Early Hum Dev 2013; 89: 467–72.

6. Prechtl HFR. State of the art of a new functional assessment of the young nervous system. An early predictor of cerebral palsy. Early Hum Dev 1997; 50: 1–11.
7. Einspieler C, Prechtl HFR, Ferrari F, Cioni G, Bos AF. The qualitative assessment of general movements in preterm, term and young infants - Review of the methodology. Early Hum Dev 1997; 50: 47-60.
8. Guzzetta A, Mercuri E, Rapisardi G, Ferrari F, Roversi MF, Cowan F, et al. General movements detect early signs of hemiplegia in term infants with neonatal cerebral infarction. Neuropediatrics 2003; 34: 61-6.
9. Ferrari F, Todeschini A, Guidotti I, Martinez-Biarge M, Roversi MF, Berardi A, et al. General movements in full-term infants with perinatal asphyxia are related to basal ganglia and thalamic lesions. J Pediatr 2011; 158: 904–11.
10. Einspieler C, Marschik PB, Bos AF, Ferrari F, Cioni G, Prechtl HFR. Early markers for cerebral palsy: Insights from the assessment of general movements. Future Neurol 2012; 7: 709–17.
11. Kwong AKL, Fitzgerald TL, Doyle LW, Cheong JLY, Spittle AJ. Predictive validity of spontaneous early infant movement for later cerebral palsy: a systematic review. Dev Med Child Neurol 2018; 60: 480–9.
12. Hadders-Algra M. Putative neural substrate of normal and abnormal general movements. Neurosci Biobehav Rev 2007; 31: 1181–90.
13. Hadders-Algra M. Neural substrate and clinical significance of general movements: an update. Dev Med Child Neurol 2018; 60: 39–46.
14. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009; 8: 110-24.
15. Kidokoro H, Neil J, Inder T. A New MRI assessment tool to define brain abnormalities in very preterm infants at term. Am J Neuroradiol 2013; 34: 2208–14.
16. Judaš M, Radoš M, Jovanov-Miloševic N, Hrabac P, Štern-Padovan R, Kostovic I. Structural, immunocytochemical, and MR imaging properties of periventricular

crossroads of growing cortical pathways in preterm infants. Am J Neuroradiol 2005; 26: 2671–84.

17. Kostović I, Jovanov-Milošević N, Radoš M, Sedmak G, Benjak V, Kostović-Srzentić M, et al. Perinatal and early postnatal reorganization of the subplate and related cellular compartments in the human cerebral wall as revealed by histological and MRI approaches. Brain Struct Funct 2014; 219: 231-53.
18. Žunić Išasegi I, Radoš M, Krsnik Ž, Radoš M, Benjak V, Kostović I. Interactive histogenesis of axonal strata and proliferative zones in the human fetal cerebral wall. Brain Struct Funct 2018; 223: 3919-43.
19. Kostović I, Judaš M. Prolonged coexistence of transient and permanent circuitry elements in the developing cerebral cortex of fetuses and preterm infants. Dev Med Child Neurol 2006; 48: 388–93.
20. Pittet MP, Vasung L, Huppi PS, Merlini L. Newborns and preterm infants at term equivalent age: A semi-quantitative assessment of cerebral maturity. Neuroimage Clin 2019; 24: 102014.
21. Einspieler C, Marschik PB, Urlesberger B, Pansy J, Scheuchengger A, Krieber M, et al. The General Movement Optimality Score - a detailed assessment of general movements during preterm and term age. Dev Med Child Nuerol 2016; 58: 361-68.
22. Einspieler C, Bos AF, Krieber-Tomantschger M, Alvarado E, Barbosa VM, Bertoncelli N, et al. Cerebral palsy: Early markers of clinical phenotype and functional outcome. J Clin Med 2019; 8: 1616-43.
23. Heineman KR, Bos AF, Hadders-Algra M. The infant motor profile: A standardized and qualitative method to assess motor behaviour in infancy. Dev Med Child Neurol 2008; 50: 275-82.
24. Heineman KR, Middelburg KJ, Bos AF, Eidhof L, La Bastide-Van Gemert S, Van Den Heuvel ER, et al. Reliability and concurrent validity of the Infant Motor Profile. Dev Med Child Neurol 2013; 55: 539–45.
25. George JM, Fiori S, Fripp J, Pannek K, Guzzetta A, David M, et al. Relationship between very early brain structure and neuromotor, neurological and

neurobehavioral function in infants born <31 weeks gestational age. Early Hum Dev 2018; 117: 74-82.

26. Molliver ME, Kostović I, Van Der Loos H. The development of synapses in cerebral cortex of the human fetus. Brain Res 1973; 50: 403–7.
27. Singh MB, White JA, McKimm EJ, Milosevic MM, Antic SD. Mechanisms of Spontaneous Electrical Activity in the Developing Cerebral Cortex—Mouse Subplate Zone. Cereb Cortex 2019; 29: 3363-79.
28. Okado N, Oppenheim RW. The onset and development of descending pathways to the spinal cord in the chick embryo. J Comp Neurol 1985; 232: 143-61.
29. Hadders-Algra M, Prechtl HFR. Developmental course of general movements in early infancy. I. Descriptive analysis of change in form. Early Hum Dev 1992; 28: 201–13.
30. Ferrari F, Prechtl HFR, Cioni G, Roversi MF, Einspieler C, Gallo C, et al. Posture, spontaneous movements, and behavioural state organisation in infants affected by brain malformations. Early Hum Dev 1997; 50: 87–113.
31. McConnell SK, Ghosh A, Shatz CJ. Subplate neurons pioneer the first axon pathway from the cerebral cortex. Science 1989; 245: 978-82.
32. Ozair MZ, Kirst C, van den Berg BL, Ruzo A, Rito T, Brivanlou AH. hPSC Modeling Reveals that Fate Selection of Cortical Deep Projection Neurons Occurs in the Subplate. Cell Stem Cell 2018; 23: 60-73.
33. Eyre JA. Corticospinal tract development and its plasticity after perinatal injury. Neurosci Biobehav Rev 2007; 31: 1136–49.
34. Einspieler C, Marschik PB. Central Pattern Generators und ihre Bedeutung für die fötale Motorik. Klin Neurophysiol 2012; 43: 16-21.
35. Vasung L, Huang H, Jovanov-Milošević N, Pletikos M, Mori S, Kostović I. Development of axonal pathways in the human fetal fronto-limbic brain: Histochemical characterization and diffusion tensor imaging. J Anat 2010; 217: 400-17.
36. Petanjek Z, Judaš M, Kostović I, Uylings HBM. Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. Cereb Cortex 2008; 18: 915-29.

37. Kostovic I, Judas M, Sedmak G. Developmental history of the subplate zone, subplate neurons and interstitial white matter neurons: relevance for schizophrenia. Int J Dev Neurosci 2011; 29: 193-205.
38. Kostović I, Kostović-Srzentić M, Benjak V, Jovanov-Milošević N, Radoš M. Developmental dynamics of radial vulnerability in the cerebral compartments in preterm infants and neonates. Front Neurol 2014; 5: 139.
39. Ouyang M, Kang H, Detre JA, Roberts TPL, Huang H. Short-range connections in the developmental connectome during typical and atypical brain maturation. Neuroscience and Biobehavioral Reviews 2017; 83: 109-22.
40. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants. N Engl J Med 2006; 355: 685–94.
41. Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at Term and White and Gray Matter Abnormalities in Very Preterm Infants. J Pediatr

FIGURE LEGENDS

FIGURE 1

Coronal sections of T2 weighted MR images of prematurely born children scanned at corrected 35 (**A**), 28 (**B**) and 34 (**C, D**) PMA, where one can note periventricular crossroads C1, C2 (**A**), C4 (**B**), C5 (**C**) and C6 (**D**). We did not examine C3 because of its inconsistency on MRI scans. Please, note occipital sagittal strata (asterisk, **C**) as continuation of periventricular crossroad (C5), both being components of white matter segment II. Arrows (**A, B, D**) mark conspicious cellular cluster positioned above corpus callosum (CC). ''Broken'' lines represent borders between different transient compartments/Von Monakow segments which can be particularly in places seen in younger examinee (**B**), especially at the dorsal part of the brain. In older specimens (**A**), subplate zone gradually decreases in size and in MR intensity, remaining visible only as a subplate remnant (SPr).

FIGURE 2

Coronal sections of T2 weighted MR images of prematurely born children from our cohort as examples for evaluation of visibility of frontal **(A, C, E**) and occipital (**B, D, F**) sagittal strata. Examinees are MRI scanned shortly after birth, respectively at corrected age of 28 (**A, B**), 34 (**C**), 33 (**D**), 31 (**E**) and 34 (**F**) PMA. In our study, we marked sagittal strata (segment II of white matter;[26]) as fairly visible (arrow; **A, B**), poorly visible (arrow; **C, D**) and non-visible (**E, F**). In addition, figures **A** and **B** represent examinee with great visibility of borders between transient compartments/future Von Monakow segments of white matter (delineated with ''broken'' line), such as segment I, which mainly consists of corpus callosum (**A**); developing centrum semiovale (segment III); and subplate compartment (SP), whose neurons will gradually be incorporated into the segment IV. Note combination of corpus callosum (CC) and occipital periventricular crossroad C5, where CC constitutes great part of C5 visibility on MRI scans.

FIGURE 3

Distribution of infants with abnormal or normal general movements at writhing and fidgety age according to visibility of frontal and occipital SS at early MRI. The number inside the column presents the number of cases within each group.

FIGURE 4

The comparison of total IMP scores between preterm infants with differential visibility of frontal and occipital SS. The IMP scores were significantly higher in the infants with fairly visible SS than in infants with poorly visible SS (Kruskal-Wallis $p < 0.01$). Bold horizontal lines indicate median values, boxes represent 25th and 75th centiles and whiskers represent range.

TABLES

Table 1. Demographic and clinical data of participants

Characteristics (n=30)	Median (IQR) / number
Gestational age at birth (wk)	28 (26^{+4} – 30^{+4})
Gestational age at Early MRI (wk)	31^{+6} (30^{+4} – 32^{+6})
Gestational age at Term MRI (wk)	40 (39^{+3} – 41^{+4})
Birth weight (g)	1125 (871.50 - 1428.75)
Male – n	16
Multiple pregnancies – n	5
Bronchopulmonary dysplasia – n	8
Mild WM abnormality*	6
Deep GM abnormality	4
Cerebellar abnormality	3

GM, gray matter; WM, white matter.

* Brain injuries were assessed according to conventional MRI scoring system.[15]

Table 2. General movements assessments and total IMP score at 1-year CA

Neuromotor assessment	Median (IQR) / number (%)
GMs at writhing age	
Normal	14 (47%)
Poor repertoire	16 (53%)
GMOS	28 (24 - 40)
GMs at fidgety age	
Fidgety	22 (73%)
Abnormal	3 (1%)
Absent	5 (16%)
MOS	22 (19 - 26)
IMP Score	
Total IMP Score	88 (80 - 94)
Total IMP Score < 85	9 (30%)
Total IMP Score in the group of infants with normal motor score for CA	92 (88 - 96)
Total IMP Score in the group of infants with low motor score for CA	79 (75 - 82)
CA at IMP assessment (mos)	12 (12- 14)

GMs, General Movements; GMOS; General Movements Optimality Score;
MOS, Motor Optimality Score; IMP, Infant Motor Profile; CA, Corrected Age

Table 3. The visibility of sagittal strata at early MRI and corresponding GMs optimality and IMP scores

Neuromotor assessment Median (IQR)	Fairly visible		Poorly visible		Non-visible	
	SS - F	SS - 0	SS - F	SS - 0	SS - F	SS - 0
n (%)	9 (30%)	16 (53%)	10 (33%)	10 (33%)	11 (37%)	4 (13%)
GMOS	26 (24 - 27)	32 (27 - 35)	22 (19 - 24)	25 (22 - 26)	20 (17 - 21)	20 (17 - 21)
MOS	24 (21 - 25)	26 (22 - 26)	21 (17 - 22)	20 (18 - 22)	17 (15 - 19)	16 (13 - 15)
Total IMP score	92 (91 - 95)	94 (93 - 95)	91 (90 - 94)	85 (84 - 86)	77 (75 - 79)	74 (73 - 75)

SS - F, sagittal strata frontal; GMs, General Movements; GMOS; General Movements Optimality Score; MOS, Motor Optimality Score; IMP, Infant Motor Profile; SS - O, sagittal strata occipital.