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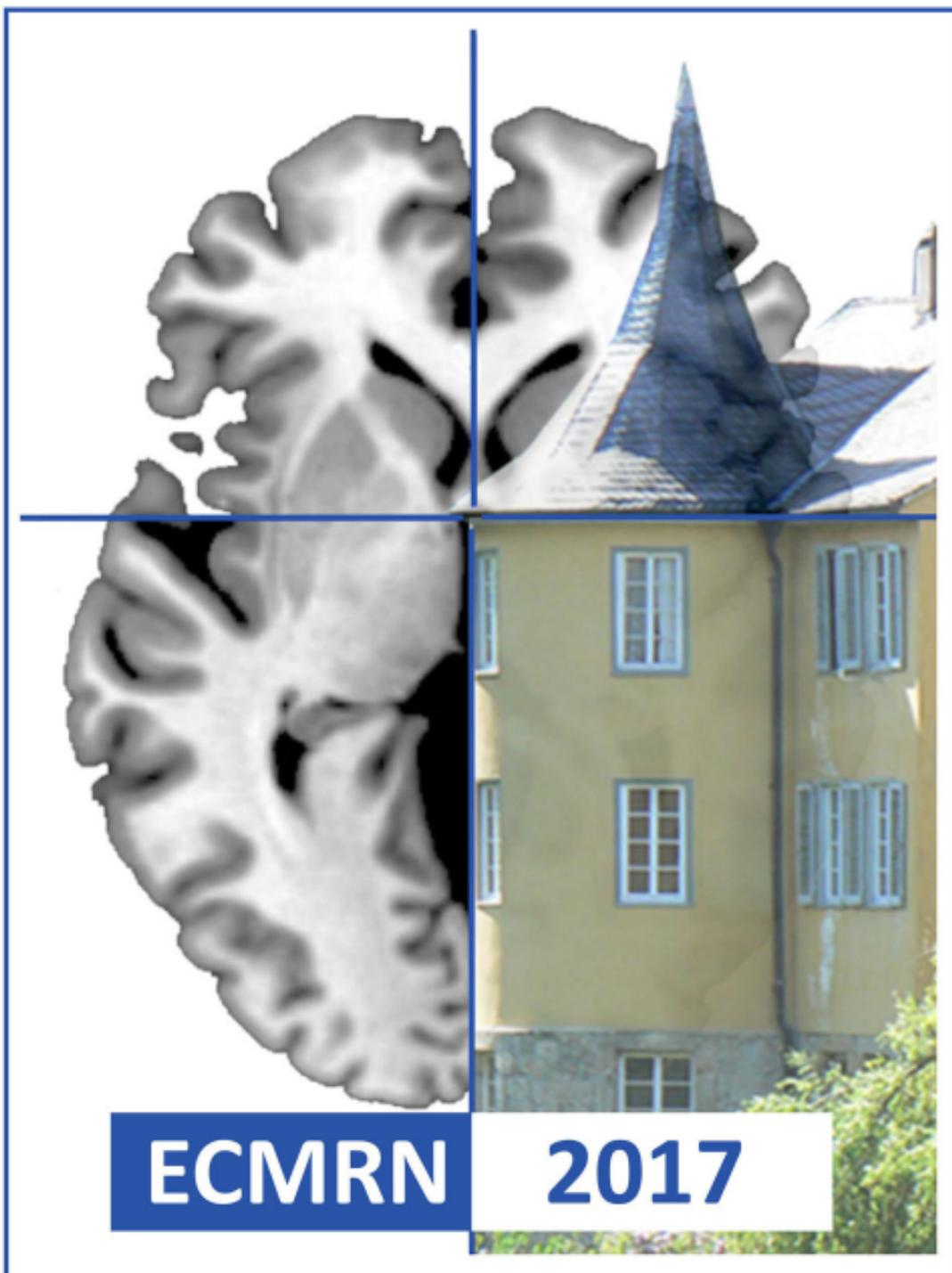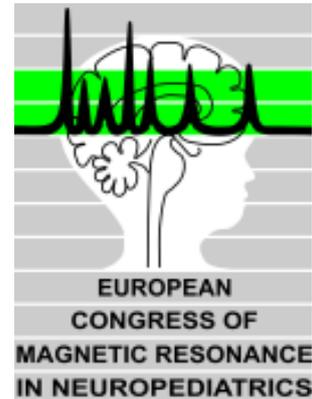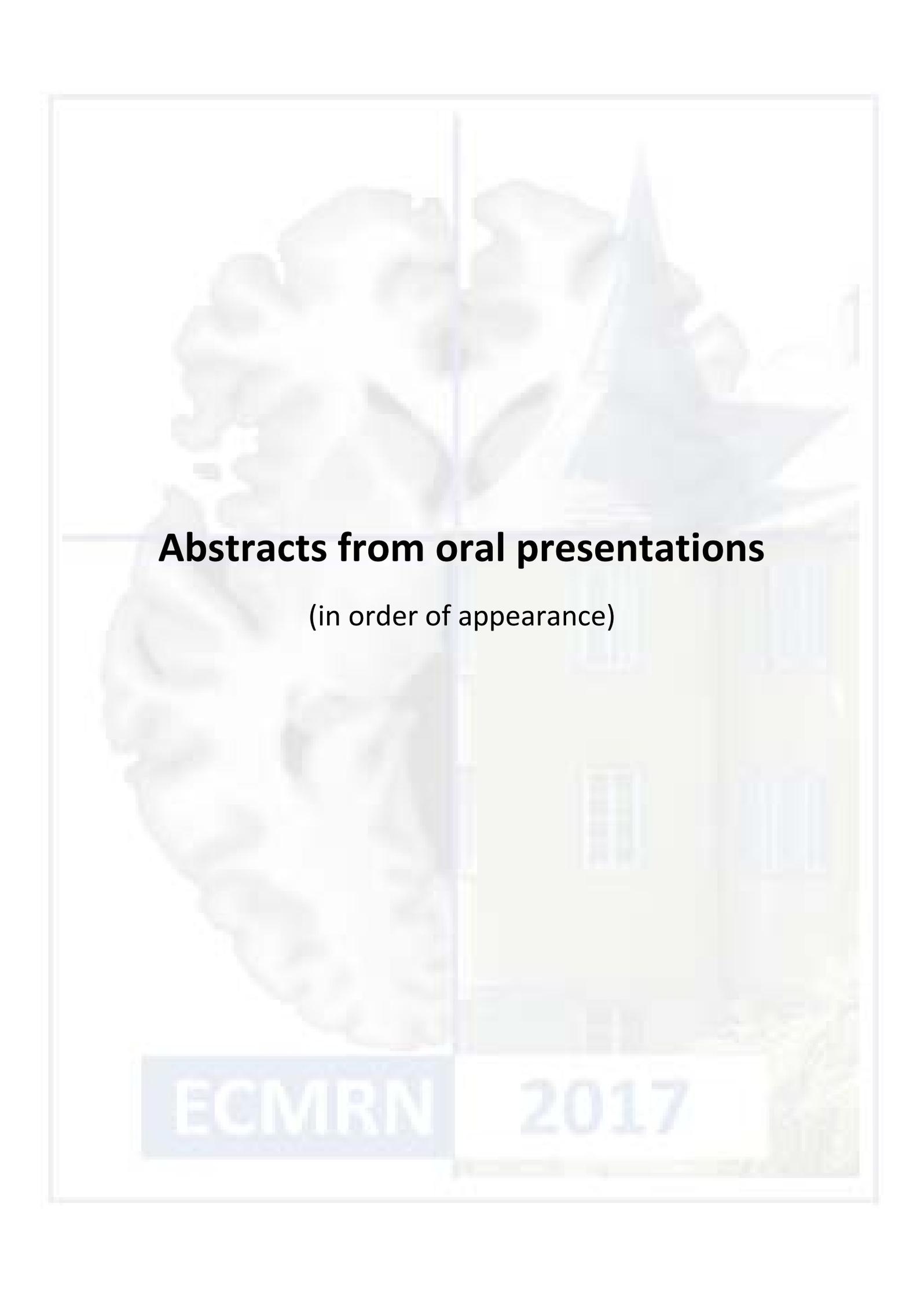
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Abstracts

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Abstracts from oral presentations

(in order of appearance)

SAGITTAL AXONAL STRATA OF THE HUMAN FETAL AND NEONATAL CEREBRUM

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Sagittal strata (SS) appear during early fetal life, form trajectories of projection fibers during midgestation and transform into one of the white matter segments during late fetal period. Aims: to analyze organization of SS on histological sections; to determine spatial relationship of SS with adjacent cerebral compartments; to find MRI correlations in vivo and in vitro.

Histological sections of postmortem brains, ranging between 8 to 34 postconceptional weeks (PCW), were "stained" for fibrillar and proliferative markers. 20 preterm infants, ranging from 27 to 43 PCW, were MRI examined immediately after preterm birth and at term age. Furthermore, 22 in vitro and 20 cases in utero were also scanned. MRI DTI images were obtained from postmortem brain base Code-No1-HD-4-3368.

The results show that early SS appear in the intermediate zone around 10 PCW consisting of thalamic projection and external capsule (EC) basal forebrain fibers. Between 18 to 22 PCW, SS show complex architecture with prominent regional variations and participate in local dispersion of proliferative subventricular zone (SVZ) and migratory waves of cells. External SS is interrupted by radially oriented glial-neuronal migratory stripes and represents important landmark of deep subplate zone during midgestation. In early preterm, basic organization of SS is maintained with increased thickness of external stratum, indicating development of associative fascicles. In vitro and in utero MRI show two bands, medial fibrillar and lateral cellular, which delineate SS. These bands were seen in all preterms with "normal" clinical parameters (SNAPP-II, SNAPP-E-II). At term age, lateral cellular band becomes less visible. In conclusion, projection fibers from basal forebrain and thalamus form SS during early fetal life. Contribution of associative fibers to SS occurs almost two months later. Architecture and developmental changes of SS reflect crucial neurogenetic events and may serve as fine indicator of integrity of the white matter in the human preterm infant.

Key words: axonal sagittal strata, transient cerebral compartments, development of cerebral connectivity, white matter integrity

Clinical Applications of Dynamic MRI in Pediatric Neuroradiology

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Dynamic cine magnetic resonance imaging (DC-MRI) is a rapidly developing technique, which has evolved from research and works in progress, into routine clinical imaging sequences. We demonstrate the contributions of this near real time MR technique in fetal and postnatal imaging. In our institution we utilize dynamic imaging for numerous indications including: 1. Functional assessment of intracranial/intraspinal cerebrospinal fluid (CSF) flow dynamics; 2. Evaluation of effectiveness of endoscopic procedures designed to divert CSF flow; 3. Dynamic evaluation of spinal instability in cases of congenital/acquired stenosis; 4. Assessment of phonation in children with suspected velo-pharyngeal dysfunction; and 5. Evaluation of swallowing patterns in fetuses with head and neck lesions. We present our data from studying swallowing patterns in 75 fetuses with facial clefts and 45 cases of fetal head and neck lesions. We demonstrate results of assessment of effectiveness of pediatric endoscopic third ventriculostomy (ETV) and intracranial arachnoid cyst fenestration in 60 cases. In addition, we demonstrate our method for dynamic imaging of the cervical spine with flexion/extension maneuvers in 40 cases and of phonation maneuvers in patients with 22q deletion and sleep apnea. DC-MRI offers many advantages over other dynamic imaging modalities due to its lack of ionizing radiation and short acquisition time, features of particular importance in prenatal and pediatric medicine. The dynamic sequences are based on fast acquisition and organization of images in a sequential loop, resulting in observation of a real-time movie. These sequences are easily obtainable from a technical standpoint and are easily tolerated by patients. DC-MRI provides clinically significant prognostic information for the planning of interventions and provides a method of evaluating the outcome of interventions.

Does prenatal structural brain asymmetry predict later language localization and abilities?

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The brain shows an asymmetry of its structures in most humans. The left hemisphere, especially the left temporal lobe, usually owns more volume and white matter bundles than the right hemisphere. An association between brain asymmetry and localization of language has already been proven. Furthermore, different studies underly the hypothesis that both brain structure and language localization are associated with language competence. In a previous study, we could demonstrate that most fetuses show a brain asymmetry already in the 20th to 30th gestational week (Kasprian et al., 2011). We are now interested in the relationship between prenatal asymmetry of brain structures and language localization and language competence in the same children several years later.

In an ongoing project, we investigate the relationship between prenatal anatomical asymmetry of the brain and later language localization, formation of language-related fiber bundles, and language abilities. At the conference, we will present preliminary data of 25 healthy children, aged 6 to 16, all of whom had a magnetic resonance imaging in utero between the 20th and 30th gestational week. We will report results of structural and functional magnetic resonance imaging investigating language localization, as well as results of an extensive language assessment in these children. We will report about the association between prenatal brain asymmetry and later language localization and language competence.

This study, for the first time, links prenatal data with later language abilities and language-related fiber bundles. With this knowledge, we hope to find early marker of later language abilities or language deficits.

Variability of functional connectivity architecture of the neonatal brain

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Functional connections within the human cortex show a broad range of inter-individual variance, which is especially high in association cortices that maintain higher order cognitive functions, and which is especially low in primary sensory-motor cortices (Mueller et al., Neuron 2013). Here, we investigated if this characteristic distribution of functional variability is already present in neonates.

We analyzed resting-state fMRI data of 25 preterm born infants, scanned around term (mean gestational age at birth 27,5±2.6 weeks, mean gestational age at birth 35,4±2.3 weeks, 12 female), and 25 adult control subjects (age 27.0±3.8 years, 13 female, 2 left-handed). MRI data were obtained at a magnetic field strength of 3.0 Tesla (Skyra VERIO, Siemens, Erlangen, Germany). MRI of preterm born infants was part of the AIRR study (Attention to Infants at Respiratory Risks), conducted by the German Center of Lung Research.

We found that the overall distribution of high functional variability in association cortices and low functional variability in sensory-motor areas was already present in neonates. Contrasting variability maps between adults and neonates revealed areas of lower variability in neonates as compared to adults in frontal and temporo-parietal association cortex areas. When comparing these areas to a map of developmental cortical expansion (Hill et al, PNAS, 2010), we found that most areas, where inter-individual variability will increase towards adulthood, fall within areas of most pronounced cortical expansion during development.

Our results indicate that individual differences in functional connectivity architecture are already prominent in the neonate brain. However, inter-individual variability is less pronounced than in adults, emphasizing the impact of post-natal development on functional brain architecture.

Neonatal MRI for prediction of neurological and cognitive outcome at age 2 years in neonatal hypoxic-ischaemic encephalopathy

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Background

Neonatal hypoxic-ischaemic encephalopathy (HIE) may be associated with brain injury and subsequent neurological and cognitive impairment. MRI can provide information on location, extent, and timing of injury. Validated MRI scoring systems can qualitatively assess injury severity and are promising tools to aid in early prediction of neurodevelopmental outcome.

Aims

The aims were to examine the correlation between an MR scoring system and neuromotor outcome in a cohort of infants with neonatal HIE at age 2 years, and in those participants without cerebral palsy, to examine associations with cognitive development.

Methods

Seventy-seven infants with HIE, 73 of whom underwent hypothermia treatment, born at mean gestational age 39.9, SD 1.56 weeks, admitted to a tertiary neonatal centre had neonatal MRI (1.5T; mean day 6 after delivery, SD 3.4) and neurodevelopmental assessment at age 2 years. MRI, including DWI, were scored according to Barkovich[1] and involvement of individual central grey matter structures, hippocampi and posterior limb of the internal capsule (PLIC) were also assessed. Neuromotor (assessed with standardised neurological examination) and cognitive development (Bayley Scales of Infant and Toddler Development-III) was assessed at mean age 25.07 (SD 3.15) months. Associations between MRI scores and outcome were examined using Kruskal-Wallis test, Chi-Square, and Spearman's correlation, with $p < 0.05$ indicating significant associations.

Results

Abnormalities in the basal ganglia, watershed areas, and the PLIC on T1-w, T2-w and DWI images were significantly associated with abnormal neurological status ($p < 0.001$). In the group of infants without cerebral palsy (n=65), there was weak evidence for an association between cognitive development and watershed area abnormalities on DWI (r=-0.265; p=0.06).

Conclusions

Qualitative standardised assessment of neonatal MRI is a useful tool for early prediction of abnormal neurology, but more sensitive methods are needed to predict cognitive outcome.

References: [1] Barkovich et al, AJNR 1998

Susceptibility weighted magnetic resonance imaging (SWI) in newborns with hypoxic ischaemic encephalopathy (HIE)

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Background and aims

Susceptibility-weighted imaging (SWI) MRI highlights contrast due to substances such as venous blood, blood products and iron. This study used SWI in newborns with hypoxic ischaemic encephalopathy (HIE), in addition to conventional MRI, for identifying infarcts, venous occlusion or brain oxygenation/metabolism changes. We explored associations between SWI findings and short-term neurological outcome to determine whether it is useful for predicting outcome.

Methods

46 newborns with HIE (25 male, mean gestational age 39.9 weeks) were scanned on a 1.5T MRI scanner (median age 6 (range 1-34) postnatal days) using our standard neonatal HIE MRI protocol plus SWI. SWI images were assessed using an in-house developed "prominence of veins" score, ranging from 0 (absent) to 3 (prominent), within the cortical, ependymal and deep medullary veins, plus a total score. The association between scores and neurological outcome (normal, non-specific signs, abnormal, i.e. Cerebral Palsy) at age 2 years was tested (using Chi-Squared and Spearman's correlation). We have also developed an automated analysis method (whole-brain ridge detection) for SWI images. This was tested on a SWI dataset of 61 infants; 51 with HIE and 10 healthy infants.

Results

Statistically significant correlations were found between ependymal, deep medullary and total SWI scores and neurological outcome at 2 years, with the most significant correlation found in the ependymal veins ($r=-0.387$; $p<0.05$). Using the automated method, the accuracy of classifying infants according to their SWI scores was 91.4%.

Conclusion

A low SWI score was associated with poor outcome. The effects of blood oxygenation and blood flow variations, which may occur in HIE, on SWI images should be investigated, e.g. using arterial spin labelling MRI. This will enable further validation of the categorical scoring and quantitative SWI analysis methods described above.

Voxel-based lesion symptom mapping of motor outcome after pediatric stroke

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Background
Stroke is less common in children than in adults, however this devastating disease is an important cause of neurological disabilities. In the pediatric population, little is known about prognostic factors of outcome in arterial ischemic stroke. The literature about the influence of stroke location on functional outcome is controversial. The aim of the study is to investigate structural lesion correlates of hemiparesis at stroke onset, at discharge and at 6 months follow-up.

Methods
All 62 children with unilateral stroke (aged 9.7 years ± 4.01) received an MRI including diffusion weighted images (DWI) at 2.61 ± 4.86 days after stroke. Binary lesion maps were obtained by manually tracing the lesions. All lesions were flipped to the right side. Voxel-based lesion symptom mapping (non-parametric Liebmeister-test) was used to identify lesion clusters associated with functional outcome.

Results
At discharge and at 6 months after stroke significantly associated voxels with hemiparesis were found in the capsula externa and the capsula interna. At stroke onset no significantly associated voxels with hemiparesis were found.

Discussion
In our sample the capsula externa and interna (e.g. part of the cortico-cortical association pathway and the tractus corticospinalis with ascending and descending tracts) are significantly associated with hemiparesis. The association between hemiparesis and the tractus corticospinalis, which is involved in motor control, becomes more pronounced over time (acute < discharge < 6 month follow-up). The present findings will improve our understanding of presenting symptoms in pediatric stroke and contribute on prognostic possibilities for affected children.

The mis-wired language network in rolandic epilepsy: role of the cerebellum

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The interplay between brain connectivity and language performance in rolandic epilepsy (RE) is poorly understood. This study explores the functional connectivity of the language network and its relation to the language profile in children with RE and typically developing (TD) children. Sixteen school-aged children with RE and 23 TD children (matched for age, gender and handedness) were included for final analysis. Language skills were evaluated using a standardized language test battery. Functional magnetic resonance imaging (fMRI) was carried out on a 3T Philips scanner. To assess intrinsic functional connectivity, resting state fMRI data were obtained. On the basis of a verb-generation fMRI paradigm the cortical language network was identified. Fourteen regions-of-interest were subsequently used as seed regions for the resting state connectivity analysis. Differences in language performance and functional organisation of the language network were statistically analysed. First, language was found to be impaired in children with RE. Second, although in RE epileptic activity is confined to the centro-temporal and perisylvian areas, we demonstrated widespread alterations in functional connectivity of the cortical language network, extending beyond the perisylvian area. In typically developing children, significant connectivity (α=0.05, FDR-corrected) was identified in 44 of 91 connectivity links, whereas children with RE demonstrated only 28 significant positive correlations. As no significant cortico-cerebellar connections with the right cerebellar crus were found in children with RE, a marked loss of cortico-cerebellar connectivity was found in these children. A relative dissociation of cerebral and cerebellar language regions was found in children with RE. The detachment from the normal modulatory control and automation function of the cerebellum might alter typical language functioning in these children. These insights contribute to the characterisation of the neuronal basis of language problems in RE, which is crucial for understanding the clinical phenomena of this complex neurodevelopmental disorder.

Very premature birth and the visuospatial working memory network in adolescence

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Visuospatial working memory (WM) refers to the temporary maintenance and manipulation of visual object location. Visuospatial WM is often impaired in very preterm-born children. By using fMRI it was shown, that very preterm-born children and term-born controls differ concerning the recruitment of frontal brain areas when performing a visuospatial WM task. Today, we investigate characteristics of the visuospatial WM network in very preterm-born and term-born adolescents.

38 very preterm-born (GA<32 weeks and/or BW<1500g) and 38 term-born adolescents were examined at 12-18 years. WM was measured outside the scanner and the WM network was assessed using the dot location fMRI task. Percent signal change (PSC) served to measure the intensity of brain activation. Multiple regression analyses were performed to examine the association between age, pubertal status, WM performance and WM activation.

Very preterm-born adolescents showed non-significantly lower WM performance than controls. In both groups, a comparable WM network was found over bilateral superior parieto-frontal brain areas. In controls, age correlated negatively with parietal brain activation and pubertal status correlated negatively with fronto-parietal brain activation. Further, the intensity of fronto-parietal brain activation correlated negatively with WM performance. In very preterm-born adolescents, no such associations appeared.

Our sample of very preterm- and term-born adolescents showed comparable visuospatial WM task performance and functional networks. In controls, higher age, higher pubertal status and better WM performance related to less brain activation. These associations were only apparent in controls but not in very preterm-born adolescents. On the one hand, this might point towards a larger variance in the very preterm group than in controls. On the other hand, it might indicate different neural characteristics of the WM network in very preterm-born adolescents.

SMPD4 mutations link microcephaly with simplified gyration, hypomyelination and congenital arthrogryposis to aberrant cytokinesis and membrane ceramide metabolism

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The importance of complex lipid metabolism in neurometabolic disorders has long been known in relation to deficiencies of lysosomal enzymes, i.e. linked to progressive neurodegeneration. Their role in neurodevelopmental processes, e.g. cell division, instead, starts to be explored, thanks to modern technologies such as mass spectrometry. A putative neutral sphingomyelinase, distinct from the acid lysosomal sphingomyelinase deficient in Niemann-Pick type A/B, is coded by SMPD4. SMPD4 knock-down by RNA interference in HeLa cells causes dysregulation of lipid composition and localization, with accumulation of different ceramide-containing lipids, but sphingomyelin, leading to abnormal cytokinesis, the latest phase of mitosis leading to final splitting into daughter cells (Ekin Atilla-Gokcumen et al. 2014). In four children from a large consanguineous pedigree we identified by RNASeq in the linkage area identical non-coding homozygote SMPD4 mutations leading to lack of normal transcript. The mutation was undetected by whole exome sequencing, being outside the captured coding areas, and by Sanger sequencing because of an interfering pseudogene. All children presented at birth with congenital arthrogryposis, microcephaly with consistent simplified gyration and mild cerebellar hypoplasia at MRI and died soon after birth of central hypoventilation and untreatable seizures. One girl survived up to three years: her OFC remained around – 5SD and her post-mortem brain MRI showed diffuse central hypomyelination, thin CC and simplified gyri, without signs of myelin destruction. Additionally, three similarly affected children from two unrelated families were found to have biallelic SMPD4 mutations, for a total of seven affected individuals. Immunocytochemistry of patient cells shows abnormal cytokinesis with abnormal mid-body structures leading to increased undivided multinucleated cells. Studies to identify the natural substrates of SMPD4 are ongoing. These data show the importance of membrane metabolism in mitosis during brain development and identify a novel pathway in the pathogenesis of cerebral malformation.

Post-mortem High Resolution Magnetic Resonance Imaging of the fetal brain: characterization of normal and pathological development

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Purpose
To describe the use of post-mortem high resolution magnetic resonance imaging (HRpmMRI) in the validation of prenatal MRI findings in CNS malformations.

Approach/Methods
We collected HRpmMRI of 40 fetuses (mean gestational age(GA) = 22 weeks(w); range = 17-33 weeks) after a voluntary termination of pregnancy (TOP) or after a spontaneous intrauterine death (IUD). Fetuses with CNS malformations were selected. The HRpmMRI was performed on a 3T scanner without any fixation and without removing the brain from the skull within 33 hours from delivery. Axial, coronal and sagittal T2 weighted HR images (voxel size 0.3x0.3x1.2mm) and T1 isotropic weighted images (voxel size 0.73 mm) were acquired. Fetuses with CNS malformations were previously studied with in utero fetal MRI at 1.5 T. The specimens' preservation status was assessed on HRpmMRI images. The HRpmMRI findings were compared with prenatal MR findings.

Findings/Discussion
Twenty-two fetuses with CNS malformations were studied with HRpmMRI. A positive correlation between brain swelling and time from delivery was observed: fetuses scanned more than 24 hours from delivery or after IUD were inadequate for diagnostic evaluation. HRpmMRI confirmed prenatal MRI findings in all cases with CNS anomalies with a more precise characterization of CNS malformations. The diagnostic accuracy of in vivo fetal MRI can be limited by the early gestational age and may needs autoptic confirmation. HRpmMRI shows some advantages over conventional autopsy: it is less sensitive to autolysis, it allows in-situ assessment without removing the brain from the skull and can be reviewed at a later stage.

Summary/Conclusion
The HRpmMRI overcomes the technical and diagnostic limitations of prenatal MRI allowing the precise depiction of the structural and signal changes involved in brain development. HRpmMRI do not replace conventional autopsy but shows advantages over it in the anatomical assessment of CNS malformations.

4H syndrome: Lessons from 3T MR Imaging

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Introduction
4H syndrome is a leukodystrophy characterized by hypomyelination, hypodontia and hypogonadotropic hypogonadism. With its variability in clinical symptoms, application of pattern recognition to identify typical MRI features proved to be useful for the diagnosis of 4H patients. We assessed MRI images of 4H patients acquired with 3T MRI to identify known and additional characteristic MRI features.

Methods
We collected 3T MR imaging data of 12 genetically diagnosed 4H patients (one with mutations in POLR3A, 8 with mutations in POLR3B and 3 with mutations in POLR1C). Imaging was performed at the same MRI scanner (GE Signa MR750) with the same protocol, including axial and sagittal T1- and T2-weighted images. We analyzed known and additional MRI features.

Results
Average age of patients at imaging was 17 years (3 – 37 years). Most of the patients displayed the known MRI features of 4H on T2-weighted images: hypointense signal of the optic radiation (n=11), relative hypointense signal of the ventrolateral thalamus (n=12), a small hypointense dot within the posterior limb of internal capsule (n=10) and hypointense signal of the dentate nucleus relative to the surrounding white matter (n=11). A new feature was a variable number of small T1 hyperintense and T2 hypointense dots, interpreted as myelin islets, mostly in the frontal and parietal white matter, in all patients. Interestingly, all patients had better myelination of the medial lemniscus with a relatively hypointense signal of this structure on axial T2W images ("closed eye sign"). Five patients had a small cystic lesion in the splenium.

Conclusion
In 4H leukodystrophy, MR imaging with 3T identified additional new imaging features such as myelin islets and the "closed eye sign", aiding the MRI diagnosis of this entity.

THE NEURO MRI PHENOTYPIC VS MITOCHONDRIAL GENOMIC OF PATIENTS DIAGNOSED WITH MITOCHONDRIAL DISEASES IN BAHRAIN.

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Bahrain is a small cosmopolitan island in the Arabian Gulf Sea. It covers an area of 770 sq. Km with a population of 1.3 million. Consanguineous marriage do contribute to a significant number of genetically transmitted disorders among which are mitochondrial diseases. Mitochondrial diseases are extremely challenging in their clinical presentation and can vary in the clinical, biochemical and imaging findings. The morphological or structural changes in the brain are non-specific, however there are important MRI findings that can aid in the early diagnosis.

This presentation will elaborate on the imaging characteristics along with the mitochondrial genomic correlation.

Methods:
Patients seen over a 16 years period classified according to their clinical presentation into three main groups, group that present mainly as encephalomyopathy that turn out to be either Leigh disease with different causative genes or other diseases that present with similar picture, the other group which present mainly as liver failure with variable degree of encephalomyopathy , and last group which present with significant lactic acidosis and encephalomyopathy

Results:
Over a period of 16 years , 22 patients were genetically confirmed to have diagnosed mitochondrial disease out of these patient 10 patients have Leigh disease (3 siblings with HIBCH , 2 siblings with NDUFV1 , 2 siblings with SUCLA2 , one patient with SURF1 , one patient with NDUFS4, and one patient with PDHA1) 4 patients were presented as encephalomyopathy but not classified as Leigh disease (3 siblings with SDHAF1, one patient with RRM2B, one patient with ETFDH) in the second group which the presentation were mainly with liver failure including 6 patients (4 patients with DGUOK, 2 patients with MPV17) the last group which include one patient with significant lactic acidosis which was diagnosed as pyruvate carboxylase deficiency (PC)

Conclusion:
The MRI findings of patients with mitochondrial disease are variable, however there are some disease that exhibit a pattern like recognition.

How to predict and interpret White Matter hyperintensities on FLAIR MR images in childhood non-CNS tumor patients and survivors?

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PURPOSE
Chemotherapy has been associated with neurocognitive sequelae in leukemia and brain tumors. By contrast, evidence for neurotoxicity remains limited for childhood solid non-CNS tumors treated with intravenous chemotherapy. We aimed to investigate risk factors for white matter (WM) lesions in these patients.

METHODS
We acquired longitudinal neuroimaging data in current solid non-CNS tumor patients (n=9). Cross-sectional data were acquired in combination with DNA samples for survivors (n=34) (age range = [16-35] years). Neuroimaging MR-scans included T2-weighted FLAIR images. DNA samples were examined for the MTHFRC677T and ApoE polymorphism. The risk for WM lesions was compared between the patient/survivor subgroups and healthy age-matched control participants. For all survivors, the risk for WM lesions was predicted by the ApoE genotype and by the MTHFRC677T genotype in osteosarcoma survivors. The extent of the lesions was predicted by methotrexate dose and time since diagnosis in the survivor group.

RESULTS
WM hyperintensities were present in 24% of the complete survivor group vs. in 3% of the controls, and in 56% of the current patient group after treatment vs. in no control. Of the survivor group and patients showing WM lesions, 87.5% and 80% were treated for an osteosarcoma. 37.5% of them were correctly predicted as lesion patient, based on the presence of Apoε4 allele (Model: χ^2= 8.708, p=.003). By contrast, the MTHFRC677T could not predict the presence of lesions (χ^2= 2.844, p=.410). Finally, the size of the lesions was significantly associated with MTX dose (β=.459, p=.017), but not with time since diagnosis (β=-.06, p=.730).

CONCLUSION
Our results suggest elevated risk for WM hyperintensities in solid tumor survivors, with the highest risk for osteosarcoma patients carrying the ApoE4 allele. We assume that high dose methotrexate causes diffuse WM alterations. Future research is necessary to investigate underlying the pathology and behavioral consequences of these hyperintensities.

FLAIR - A new sequence in the evaluation of normal and pathologic fetal brain

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Purpose:
Assessment of lamination is an essential aspect in the evaluation of the fetal brain. Given the subplate's high water content FLAIR images have a potential to ~~better~~ discriminate this layer from highly-cellular adjacent structures. Aim of our study was to compare routine T2 FSE and FLAIR images in assessing fetal brain lamination, using two groups: with and without brain malformations.

Methods and Materials:
Retrospective evaluation of fetal brain MRIs between 02/2014 and 05/2016 on 1.5T and 3T magnets, with availability of T2 FSE and FLAIR images in equivalent orthogonal planes. 147 cases and 102 controls were included. Sequences were analyzed for identification of the subplate by lobes in two gestational age (GA) groups; ≤28 gestational weeks (GW) and >29GW. For the cases, it was further assessed if anomalies were identifiable on T2 and/or FLAIR.

Results:
Mean GA was 28.2GW (SD±4.4) for cases and 26.9GW (SD±4.5) for normal fetuses. In all groups there was a statistically significant difference (p<0.001) in subplate identification in in favor of the FLAIR sequence, except in the temporal lobe assessment of the pathologic <28GW group (p=0.12). Lesions were at least partially identifiable on FLAIR images (91%), and better depicted on FLAIR in 17.5% of cases. FLAIR provided additional information in brain lesions in 42.3% of patients, and in excluding lesions in 71.5%.

Conclusions:
FLAIR provides a significant better visualization of lamination throughout gestation, when compared to T2 FSE images, in normal and pathologic fetal brains.

Tissue type segmentation of low contrast MR images using control based atlases.

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Objective:
Low contrast MR images seen in hypomyelinating disorders cannot be accurately segmented using existing methods. We aimed to develop a method for the tissue-type segmentation of these images using control based atlases.

Methods:
3DT1-weighted MR brain images of 20 control subjects were segmented using FAST and FIRST (FSL5.0.4) yielding brain masks of white matter (WM), grey matter (GM), cerebrospinal fluid (CSF) and subcortical regions (SR). All 20 brains and subsequently their masks were nonlinearly registered to each of the 19 other brains within the same group (20x19 registrations). The masks were then averaged and thresholded to obtain probabilistic atlases for each tissue type and CSF. To estimate the accuracy of the segmentation method, the probabilistic atlases and the FSL computed brain masks were compared and similarity was expressed using the Dice coefficient. Visual inspection of the atlases was also performed.

Results:
Mean Dice coefficients for WM, GM, CSF and SR were 0.75 (SD 0.03), 0.78 (0.03), 0.47 (0.05) and 0.68 (0.03), respectively. WM, GM and CSF volumes were consistently under-estimated and SR volumes overestimated using the probabilistic atlases. Visual inspection showed that the U-fibers were generally missing from the WM atlases.

Discussion:
The underestimation of WM is caused by U-fiber voxels being lost after probability thresholding due to inter subject variations in their location. The under- and overestimation of GM, CSF and SR are likely caused by varying accuracies in the registrations and/or probability thresholding. The high Dice coefficients of the different tissues show that the developed method of segmentation is effective in estimating tissue location. Currently, we are using this method to analyze a cohort of patients with hypomyelinating disorders.

Automatic clustering of white matter to anatomically meaningful fiber bundles

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Introduction

Novel diffusion MRI acquisition and modeling techniques, such as High-angular-resolution diffusion imaging (HARDI), allow an extended mapping of white matter orientations, successfully overcoming the obstacle of fiber crossings. With the so-called global tractography a „tractogram" of the entire brain can be reconstructed therefrom. Nevertheless, usually the clinical focus is only on certain fiber bundles that have to be segmented manually. We propose an automated method subdividing the whole-brain tractogram in the main fiber bundles and we present the segmentation of the pons to illustrate its anatomical precision.

Materials and Methods

80 HARDI datasets of healthy controls from the Human Connectome Project database (WU-Minn Consortium) were processed with an in-house global tractography algorithm (M. Reisert et al., 2011) and a tractogram group template was created. An statistical ordination method was then applied to cluster fiber trajectories following similar paths. As a result, trajectories belonging to the same anatomic bundle tend to appear in groups.

Results

Fiber bundles automatically clustered at the level of the pons were visually reviewed. The left and right sides had been correctly distinguished at the midline, the medial lemniscus and superior cerebellar peduncle in the posterior pons and the corticospinal tract in the anterior pons, the latter being subdivided in three parallel subbundles. In the transverse plane the middle cerebellar peduncles encircled the ascending and descending fibers as expected.

Discussion

We propose a method that subdivides fiber trajectories of the human brain in anatomically meaningful bundles without a priori knowledge. Avoiding the bias of manual fiber bundle segmentation is important, especially when anatomical deviations are expected, for example, in the presence of brain anomalies or during brain development. The proposed method could also prove useful in studying the bundle unfolding in the healthy and diseased brain during childhood and adolescence.

Long-term white matter tract reorganization following prolonged febrile seizures

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Objective:
Diffusion magnetic resonance imaging studies have demonstrated acute white matter changes following prolonged febrile seizures (PFS), but their longer-term evolution is unknown. We investigated a population-based cohort to determine white matter diffusion properties eight years after PFS.

Methods:
We used diffusion tensor imaging and applied Tract-Based Spatial Statistics for voxel-wise comparison of white matter microstructure between 26 children with PFS and 27 age-matched healthy controls. Age, gender, handedness, and hippocampal volumes were entered as covariates for voxel-wise analysis.

Results:
Mean duration between the episode of PFS and follow-up was 8.2 years (range 6.7 to 9.6). All children were neurologically normal, and had normal conventional neuroimaging. On voxel-wise analysis, compared to controls, the PFS group had (1) increased fractional anisotropy in early-maturing central white matter tracts, (2) increased mean and axial diffusivity in several peripheral white matter tracts and late-maturing central white matter tracts, and (3) increased radial diffusivity in peripheral white matter tracts. None of the tracts had reduced fractional anisotropy or diffusivity indices in the PFS group.

Significance:
In this homogeneous, population-based sample, we found increased fractional anisotropy in early-maturing central white matter tracts and increased mean and axial diffusivity with/without increased radial diffusivity in several late-maturing peripheral white matter tracts eight years post-PFS. We propose disruption in white matter maturation secondary to seizure-induced axonal injury, with subsequent neuroplasticity and microstructural reorganization as a plausible explanation.

Structural connectivity by diffusion MRI in childhood apraxia of speech

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Introduction
We recently demonstrated altered connectivity involving speech/language networks in a small sample of subjects with childhood apraxia of speech (CAS). Here, in a larger CAS sample, we applied an updated structural connectivity analysis as well as cortical thickness analysis as possible measures of altered brain development in CAS.

Patients and methods
We enrolled 32 children (16 of the previous report) with CAS and 14 age-matched controls. An updated whole brain probabilistic tractography analysis with constrained spherical deconvolution was performed. Fractional anisotropy (FA) and streamlines number (NUM) were used as a measure of connectivity. Relationship between structural connectivity and speech/language scores was also determined. Cortical thickness was assessed using FreeSurfer.

Results
Three subnetworks emerged with reduction of FA in CAS compared to controls. Subnetwork1 involved left frontal areas including middlefrontal regions and frontal operculum. Subnetwork2 involved left temporo-parietal areas including middletemporal, postcentral, supramarginal, inferiortemporal, precentral, inferiortemporal and hippocampal regions. Subnetwork3 involved right temporo-parietal and occipital areas including inferiorparietal, inferiortemporal, middletemporal, lateraloccipital and hippocampal regions. One subnetwork emerged with NUM reduction, involving left and right cerebellum cortices, right putamen, pallidum, right inferiorparietal and middlefrontal regions. Several regions in the left hemisphere showed thicker cortex in CAS, including superior and inferior parietal, frontal opercular, supramarginal, precentral and postcentral regions. Structural connectivity showed correlations with several clinical measures. Altered FA correlated with diadochokinesis, inconsistency speech focal and sequential control and phonetic inventory, altered NUM correlated with diadochokinesis, accuracy and expressive language.

Conclusions
Our findings support previous evidence of structural connectivity and cortical thickness anomalies in children with CAS across specific brain regions. Altered connectivity correlates with measures of CAS clinical dysfunction. These findings might reveal a possible epiphenomenon of complex pathogenic mechanisms in CAS involving speech/language networks that can be targeted by specific interventions.

Comparison of the Detectability of UBOs in Neurofibromatosis Type I patients with Proton density-weighted and FLAIR sequences in 3T MRI

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OBJECTIVE

In NF1 patients, significant numbers of so-called unidentified bright objects(UBOs) can be found , with predilection sites at the basal ganglia and the dentate nucleus. UBOs seem to develop at a very early age, contrary to other criteria leading to diagnosis. The detection of UBOs might therefore prove helpful in the early diagnosis. The aim of the study was to investigate whether the detectability of UBOs increases at 3T by comparing PDw with FLAIR.

PATIENTS AND METHODS

A total of 14 NF1 patients(7 male, 7 female, between 8 and 26 years old, mean age 15.4 years) were examined by a 3T-MRI. The presence of UBOs was evaluated on PD-w and FLAIR images by 4 evaluators(2 experienced neuroradiologists, 1 junior radiologist and 1 student in his final year). Detectability was rated by a three-point scoring system for dedicated regions: lesions which were "well defined/detectable", "suspicious" or "detected after a second look". The Wilcoxon signed-rank test was used for comparisons between the raters. The level of significance was P<0.05.

RESULTS

Significantly more lesions were marked as "well defined/detectable" in the PD-w Sequence compared to FLAIR(P<0,001 for all four evaluators). In particular, PD-w proved to be superior for detecting UBOs located in the medulla oblongata(P = 0,001) dentate nucleus(P=0,002) and hippocampal region(P=0,007), regardless of the level of the raters' experience.

CONCLUSION

This is the first study that compares FLAIR and PD-w at T3 for the diagnosis of UBOs in NF1. Significantly more UBOs are detected in the PD-w compared to FLAIR sequences, especially for the infratentorial regions. As UBOs occur at very early stages of the disease in patients with suspected NF1, PD-w might aid an early diagnosis in these patients.

Brain Functional Connectivity changes 7 years after Neonatal Arterial Ischemic Stroke (NAIS): A resting state fMRI study

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S NGuyen The Tich, CHU Lille, France

Objective
Resting state fMRI (rs-fMRI) enables to study brain functional connectivity, i.e. the intrinsic functional architecture of brain networks at rest. NAIS is an exquisite model to study long-term plasticity after early focal lesions. We studied brain functional connectivity with rs-fMRI in school-age children after NAIS, focusing on language networks.

Methods
From 100 newborns with NAIS followed until age 7 (n= 72, 2/3 boys, 85% MCA territory, 30% unilateral Cerebral Palsy, 49 % of atypical language profiles at N- EEL battery, without differences between left/right lesions, and with good global language performance), 38 patients and 29 age-matched controls underwent 3T rs- fMRI (exploitable in 32/26). After extended data preprocessing, we computed correlations (reflecting both direct and indirect connectivity) and partial correlations (direct connectivity only) within matrices of 64 bilateral homotopic regions grouped into 10 functional networks (the reference rs-fMRI functional atlas was derived from the controls data). Right lesions were flipped to the left side for group comparisons. Individual ROI volumes accounted for brain lesions, and statistics were corrected for multiple comparisons, FDR, $p < 0.05$.

Results
With both correlation and partial correlation, we found mostly reduced inter- hemispheric connectivity in the patient group as compared with controls (in motor, language and attentional networks). When restricting analysis to the language network, the reduction was strongest between homotopic inferior frontal and superior temporal regions ('broca' and 'wernicke'). In the contralesional hemisphere, only intra- hemispheric correlations were increased mostly in the language network with stronger connections with the basal ganglia and motor network and within the visual occipital network. No connectivity difference could be evidenced between patients with either typical or atypical language.

Conclusion
Rs-fMRI is useful to study the maturation of functional connectivity after NAIS, showing widespread reduction of inter-hemispheric connectivity and increased contralesional connectivity within the language network. The clinical correlates of this complex pattern remain to be fully understood.

Resting-state connectivity within the frontoparietal network relates to executive functions in children after arterial ischemic stroke and healthy controls

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Objective
The present study aims to investigate the relationship between core executive functions and frontoparietal network connections at rest in children who suffered an arterial ischemic stroke and healthy controls.
Methods
Children after chronic arterial ischemic stroke (stroke more than 2 years ago) registered in the Swiss Neuropediatric Stroke Registry and healthy controls were included. Executive function measures comprised inhibition, fluency, processing speed, divided attention, working memory and conceptual reasoning tasks. High-resolution T1-weighted MR structural images and rsfMRI were performed. FSL MELODIC was used for independent component analysis and definition of frontoparietal network components. Functional connections were obtained through correlation matrices, associations between cognitive measures and functional connections through Pearson's correlations.
Results
20 subjects after stroke (7 females; mean age 15.99y) and 22 controls (13 females; mean age 14.79y) were examined. Patients and controls performed within the normal range in all executive tasks. Children after stroke performed significantly lower in fluency (p=.048), processing speed (p=.023) and conceptual reasoning (p=.004) compared to controls. Resting-state functional connectivity between the left and right inferior parietal lobe was significantly reduced in children after stroke (p=.000). Fluency (r=.356, p=.021), processing speed (r=.403, p=.008) and perceptual reasoning(r=.405, p=.008) correlated significantly with the interhemispheric inferior parietal lobe connection in patients and controls.
Interpretation
Decreased interhemispheric resting-state connectivity after stroke in childhood may indicate a disruption of typical interhemispheric interactions necessary for higher level cognition. The present results emphasize the relationship between functional organization of the brain at rest and cognitive performance.

Correlations in resting-state functional networks and cognitive functions in children with perinatal stroke and healthy controls

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Perinatal stroke leads to congenital hemiparesis and often these children may have neurocognitive deficits, language impairment, behavioral disorders and epilepsy. Dysfunctions in the large-scale resting-state functional networks (RSFN) may underlie cognitive and behavioral disability in these children. The aim of the study was to identify RSNF and cognitive development in children with perinatal arterial ischemic stroke (AIS), periventricular venous infarction (PVI) and healthy controls and to find correlations between RSFN changes and cognitive function.

Methods

We studied RSFN in patients with perinatal stroke collected from the Estonian Pediatric Stroke Database using FMRIB Software Library (FSL) MELODIC tool. The preliminary study included 45 children (age range 7.6-17.9 years): 11 with leftside PVI, 12 with leftside AIS, and 22 age and sex matched healthy controls. Neurodevelopment of children was assessed by the Kaufman Assessment Battery for Children – II . RSFN of healthy controls were regressed back to individuals in control, AIS and PVI groups. The correlation (p<0.05) was calculated within each group between individual network representations and cognitive functions.

Results

No correlations were found between RSFN and general cognitive abilities. Correlations were only found in specific cognition process indices and RSFN. AIS group had more changes than PVI group and controls. For AIS group the task positive network correlated positively with both knowledge index and learning index, knowledge index also correlated positively with salience network and sequential processing correlated positively with precuneus. PVI group had only a negative correlation between mental processing index and right lateral network. In controls the knowledge index correlated positively with medial visual network and simultaneous processing index with default mode posterior network.

Conclusions

The findings demonstrate correlations in some specific networks and cognitive functions in children. RSFN changes found in children with stroke could serve as the underlying basis of cognitive brain function derangements of these children.
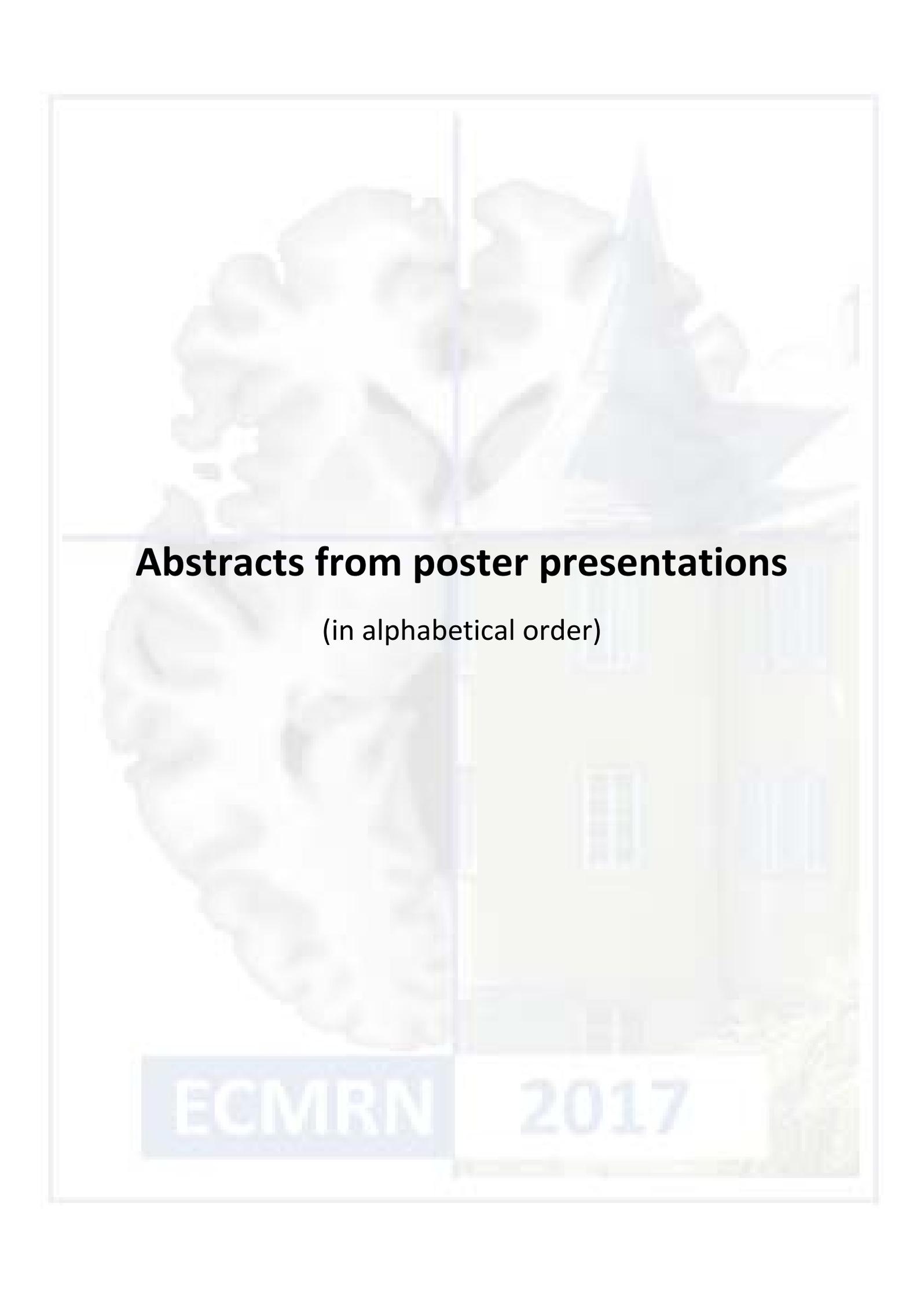
Abstracts from poster presentations

(in alphabetical order)

„Nora Imaging" – a web-based platform for medical imaging

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Imaging plays a significant role in the daily practice, both clinical and scientific, of the pediatric neurologist. Either for diffusion-, perfusion-, quantitative imaging or fMRI, it remains a challenge to keep up with the ever-evolving methods of image processing and visualisation. Especially the sharing of imaging data between sites poses difficulties, in part due to the lack of common analysis tools (JA Hernandez et al., IEEE Trans Inf Technol Biomed 2007). Here we introduce a web-based toolbox that simplifies the visualisation and processing of medical imaging.

Methods and Results

The toolbox (www.nora-imaging.org) is accessible from any webbrowser and operating system and does not require an installation. The data are loaded either locally per drag and drop or stored in a SQL-database. Through a self-explanatory interface it allows quick access and quality control of the images and the linking with clinical data. Numerous processing features are available beyond the classical, such as overlays for comparison of longitudinal data, lesion-segmentation and 3D surface rendering. For scientific purposes, hundreds of images are forwarded in parallel to processing pipelines of established software i.e. SPM, FSL, FreeSurfer and fiber tractography. Furthermore, the webtool can be utilised onsite in clinical routine, i.e. for a standardized calculation of the penumbra in stroke or the lesion load in multiple sclerosis. Our local database, that includes more than 250 brain MRIs of children and adolescents along with demographic data, has allowed us to widen our former scientific questions, mainly due to the centralized structure and the use of uniform postprocessing by mouse click.

Discussion

We introduce an in-house webtool for medical image visualisation and postprocessing. It is aimed to support the clinician in the handling of modern medical imaging data. Most importantly it provides a platform for the systematic processing and analysis of imaging studies with an emphasis on brain imaging.

Identification of SNORD118 mutations in patients with Leucoencefalopathy with cysts and calcifications

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Aim.
To describe a patient with leucoencephalopathy with cysts and calcifications (LCC), recently discovered as clinical and neuroimaging picture related to SNORD 118 gene.

Methods/Clinical Report.
Male, 6 years old, arrived to our Institute at age of 2 years for a mild paresis of left upper limb and speech delay. He was born after 4th pregnancy (the first two hesitated in spontaneous abortions) at 30 week of gestation with caesarean section because placental abruption. Mild respiratory distress and mild psychomotor developmental delay were reported. At 18 months a motor asymmetry of the upper limbs was noticed; at 24 months the boy presented a slight gross- and fine motor deficit at left side, expecially at upper limb, maintained more often flexed and adducted to the trunk.
Some diagnostic biochemical, electrophysiological and brain neuroimaging examinations were conducted. In collaboration with Colleagues of University of Manchester exome sequencing and Protein binding of U8 variants were performed.

Results.
First brain MRI performed at 2 years of age showed extensive and confluent, left-prevalent, signal abnormalities with SWAN hypointense components of periventricular and deep white matter, corona radiata and centrum semi-ovale. Signal abnormalities also involved the basal ganglia, thalami and left dentate nucleus. SWAN hypointensities were demontrated to be calcifications by CT. The proton spectroscopy study revealed no abnormal metabolites. MRI follow up performed at 30 months, 4, 5 and 6 years showed a gradual extension of signal changes with the appearance of cystic lesions, which showed contrast enhancement. Clinical picture resulted stable over time.
Our patient showed a compound heterozigous g.8076905A>G (n.2T>C) mutation in SNORD118.

Conclusions
Mutations in SNORD118 caused the cerebral microangiopathy LCC, a rare autosomal recessive, syndrome. In our patient, a completely new biallelic sequence variants was discovered (Nat Genet 2016). Despite the U8 snoRNA being ubiquitously expressed, germline mutations in SNORD118 cause an exclusively neurological, progressive microangiopathy, thus suggesting further subtleties in ribosomal activity directly relevant to human health and disease.

Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) – the first Polish patient

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A female infant was referred to MRI at the age of 7 months due to psychomotor delay, generalized hypotonia and nystagmus. Brain MRI, performed outside our centre, was interpreted as normal except for somewhat widened lateral ventricles although delay of myelination/hypomyelination has already been evident with unmyelinated posterior limbs of the internal capsules. At the age of 15 months the girl was admitted to our centre and scanned again. Neurological examination showed nystagmus, axial hypotonia, pyramido-extrapyramidal (mainly dystonic) syndrome, secondary microcephaly. No progression of myelination was noted. Additionally, the putamen was thinned and T2-hyperintense bilaterally, the frontal horns of the lateral ventricles were wider than before, reflecting most likely atrophy of caudate heads, and cortical atrophy of the cerebellum appeared. The globi pallidi and thalami were normal. The patient showed features of a severe form of H-ABC, so did the analysis of the TUBB4A gene (direct Sanger sequencing of all exons and exons/introns boundaries). The heterozygous de novo substitution c.755A>G in the exon 4 was identified - missense variant p.Lys252Arg in the tubulin protein. This is a new mutation, not described until today. In silico analysis predicts its damaging impact on the protein's structure and function. To our knowledge this is the first case of H-ABC reported in Poland.

Cerebellar cortico-subcortical signal alterations – do they indicate specific pathology?

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Objective:
To draw attention to a specific pattern of cerebellar pathology characterized by signal hyperintensity on T2w images affecting cortico-subcortical cerebellar structures and to discuss possible aetiology.

Methods:
MRIs with such pathology presented at our department during the last 2 years were analyzed; prerequisite for MRI: axial and coronal T2w images. Medical history and aetiological work-up were systematically analysed. A literature review was performed.

Results:
Four patients were identified who fulfilled the inclusion criteria.
- A 12 year old girl presented with primary developmental delay, mild mental retardation and unspecific neurological signs; additional MRI signs: bilateral parietal corticosubcortical lesions in parasagittal distribution. The girl was classified as Cerebellar Bottom-of-Fissure Dysplasia (Poretti et al. 2015).
- A 9 months old girl, and a 9 months old boy, both with primary developmental delay, presented with acute or subacute dyskinetic movement disorder; additional MRI signs: bilateral striatal and multifocal cortico-subcortical lesions. They responded to thiamine treatment and qualified as thiamine-transporter defect.
- A 1 year old boy developed spastic movement disorder after being shaken at the age of 2 months; additional MRI signs: widespread cortico-subcortical lesions.

Conclusion:
Cerebellar cortico-subcortical signal alterations do not indicate a specific aetiology. Additional MRI signs and medical history give clues to the different aetiologies; e.g. dysplastic, metabolic or postischemic.

Functional Connectivity of the Cerebellum in Preterm born Neonates

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The cerebellum of the premature infants appears to be at risk for impaired growth and development. Recent evidence has highlighted a crucial role for the cerebellum also for higher order cognitive processing along with the development of crucial motor abilities.

Applying resting state functional MRI (RS fMRI) technique, we investigated cerebellar functional connectivity (FC) of 3 different cerebellar regions in preterm infant brain within the cerebellum and with different cortical regions responsible for both motor and cognitive functions Twenty healthy preterm newborns were studied (13 males/7 females; median post-menstrual age at birth: 31weeks+5days; range age: 27-34 weeks).

FC between cerebellar seed-regions (vermis, CrusI, dentate nucleus) (i.e. intracerebellar) and between the cerebellum and cerebral regions (i.e. extracerebellar) relevant for cognitive and motor processing were explored , applying a seed-to-voxel correlational approach. Spatial connectivity maps for every seed-region showed significant positive RSFC with ipsi- and contralateral cerebellar areas. For CrusI and dentate nucleus, positive extracerebellar correlations were observed with ipsilateral occipital and inferior temporal regions and contralateral parietal and prefrontal regions. Negative correlations were observed with contralateral occipital, inferior temporal and inferior frontal areas as well as ipsilateral superior parieto-frontal regions.

Resting State FC showed both an ipsilateral and contralateral pattern of activity between cerebellum and cerebrum evident early in the development. Connectivity between the cerebellum and prefrontal areas and heteromodal areas may represent, at this very early age, a core neural foundation of functional architecture necessary for the development of higher-order cognitive functions, such as language.

Resting State fMRI and Cognitive Outcome at 6 and 12 months of age in Healthy Preterm Infants

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At rest, the brain shows spontaneous activity in the form of dissociable networks that have been recently assigned important behavioral relevance. Preterm children are at increased risk for subtle disabilities that can impact on cognitive outcomes. The default mode network (DMN) is a distributed network of brain regions that are more active during rest than during the performance of a task (Raichle et al., 2001). The existence of a fragmented DMN, including Posterior Cingulate Cortex (PCC) and the Medial PreFrontal Cortex (mPFC), has been suggested as early as 30 weeks post-mestrual age (PMA) by Doria et al. (2010).

A cohort of 15 healthy neonates born prematurely with median PMA 31 weeks + 5 days, distributed in a range between 27 and 34 weeks, was studied. After having probed the connectivity at rest between the two DMN seeds and a set of frontal brain regions associated to task activity, we have investigated how these functional measures correlate to scores of general cognitive outcome (Bayley-III Scales of Infant and Toddler Development) at 6 and 12 months of age.

Performance measures on the Cognitive Scale (Bayley-III) at 6 months were significantly correlated to mPFC connectivity to both left ($r= .683$, $p=.005$) and right inferior frontal gyri ($r= .543$, $p=.037$) and to the frontopolar region ($r= .759$, $p=.001$). Interestingly, at 12 months cognitive measures were still associated to mPFC connectivity to right inferior frontal gyri ($r= .531$, $p=.042$) and fronto-polar region ($r= .644$, $p=.001$). PCC connectivity measures instead were not significantly associated with cognitive scores at 6 months or at 12 months.

These findings suggest that resting state connectivity in preterm infants at birth between non-task and taskrelevant areas may already reflect the developmental trajectory of cognitive functioning assessed as early as 6 or 12 months of age.

Temporal lobe dysgenesis in fibroblast growth factor receptor 3 (FGFR3) gene

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Background:
Mutations in in the fibroblast growth factor receptor 3 (FGFR3) gene are responsible for a number of osseous dysplasias (achondroplasia, hypochondroplasia, thanatophoric dysplasia (TD), SADDAN), and craniosynostotic syndromes (Cruzon, Muenke). Temporal lobe dysgenesis has been described associated with all of these syndromes, most often on a case-report or pathology specific basis.

Methods:
Retrospective review (2009–2016) of patients with achondroplasia, hypochondroplasia, TD, SADDAN, Cruzon and Muenke syndromes, who had brain imaging performed. Pre- and postnatal brain MR images were reviewed and appearance of the hippocampus, dentate gyrus, amygdala and temporal and medial occipital lobes, deep transverse sulci, megalencephaly, temporal lobe enlargement were described and recorded.

Results:
All of the FGFR3-related syndromes were associated with temporal lobe dysgenesis. The most common finding was a deep vertically oriented collateral sulcus. This was most notorious in TD; temporal lobe dysgenesis was overlooked during the initial MRI in the majority (82%) of the other cases. Temporal lobe dysgenesis was reported in all but one fetal brain MRI; no specific meaning was attributed to these finding in 68% of cases. In Achondroplasia, findings were unilateral in 3/7 patients. A pictorial review of our findings in each entity will be presented.

Conclusion:
Temporal lobe dysgenesis is a transversal yet underdiagnosed feature of FGFR3 mutation syndromes. This is partly because of the lack of recognition of these entities, even in tertiary centres. These anomalies are still of uncertain clinical relevance, but propagation of FGFR3-related brain dysgenesis characteristics would facilitate proper diagnosis of similar cases.

The neuroimaging features in two patients with hypomyelinating leukodystrophy-13 associated homozygous mutation in the C11ORF73 gene

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Hypomyelinating leukodystrophy-13 is an autosomal recessive neurodegenerative disorder characterized by infantile onset of delayed psychomotor development, axial hypotonia, spasticity, post-natal microcephaly and optic atrophy. Patients may experience life-threatening cardiac failure during acute febrile illness.

The genetic basis is a homozygous missense mutation, p.Val54Leu, in C11ORF73 encoding HSP70 nuclear transporter protein, Hikeshi, which leaves the cells unprotected during heat shock stress.

We describe the neuroimaging features in two unrelated patients, demonstrating progressive hypomyelination and periventricular white matter abnormalities.

Patient 1

MRI at age 1 year 4 months revealed non-homogeneous increased T2 signal and mildly decreased T1 signal in periventricular white matter and centrum semiovale, as well as in the splenium of the corpus callosum. Internal capsule, thalami, midbrain, pons, medulla, middle cerebellar peduncles and cerebellar white matter showed abnormal T2 signal. DWI images suggested mild restriction along the medial longitudinal fasciculus.

Brain CT at age 2 years demonstrated mild diffuse white matter hypodensity.

At 2 years and 4 months MRI showed progression of diffuse T2 hyperintensity, involving the subcortical white matter and corpus callosum, with interval volume loss in the splenium, findings indicative with progressive white matter disease.

CT of the head at age 3 years 9 months demonstrated progressive white matter changes with significant periventricular and deep white matter hypodensity, as well as progressive volume loss expressed by mild ex vacuo ventriculomegaly.

Patient 2

MRI scan at age 1 year 5 months revealed diffuse increased T2 signal in periventricular white matter and centrum semiovale, extending to, and involving the internal capsule anterior and posterior limbs, the thalami, brainstem and cerebellar white matter. There was a prominent symmetrical high T2 signal along the medial longitudinal fasciculus, with mild DWI diffusion restriction. A subtly decreased T1 signal was noted in affected areas. Mild pons flattening was noted on sagittal view.

Comparative analysis of Cerebral Magnetic Resonance Imaging changes in infantile, juvenile and adult patients with Niemann-Pick disease type C

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Aim:
To describe cerebral MRI in different onset forms of Niemann-Pick type C (NPC), because systematic MRI analyses in this rare lysosomal storage disease are lacking, in particular in the infantile and juvenile onset forms.

Methods:
32 cerebral MRI scans from 19 patients with NPC were assessed using a newly established and validated scoring system which addresses white matter changes and supratentorial versus infratentorial atrophy.

Results:
Seven scans were from 6 NPC patients with an early infantile onset (< 2 years of age), 6 scans from 3 patients with late infantile onset (>2-6 years), 6 from 4 with juvenile onset (>6 - 15 years), and 13 from 6 with adult onset (>15 years). While supratentorial atrophy was the leading sign in the infantile groups, the juvenile and adult form was characterized by both, infra- and supratentorial atrophy. White matter changes were found in nearly every patient; they increased with disease duration in the earlier forms and were prominent in the later forms already early in the disease course.

Conclusion:
This is the first systematic and comparative MRI analysis in the different onset groups of NPC using a scoring system. Early during disease course, MRI showed different patterns in infantile compared to juvenile and adult onset NPC patients, e.g. only supratentorial versus global atrophy in juvenile and adult onset patients. MRI changes provide an additional, early biomarker for NPC.

Language plasticity after Neonatal Arterial Ischemic Stroke (NAIS): clinical and fMRI evaluation at 7 years of age

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Objective

NAIS is an exquisite model to study longterm brain plasticity after early focal lesions, which are reputed to carry frequent contralesional language specialization and little language deficits. We describe language outcome and functional MRI (re)organization in school-age children after NAIS.

Methods

AVCnn cohort: 100 newborns with NAIS followed until age 7 (2/3 boys, 85% MCA territory, 30% unilateral Cerebral Palsy, uCP). 72 children underwent clinical (handedness, uCP) and neuropsychological assessment (WISC-IV: VCI; N-EEL battery: lexical vs syntaxic processing, in expressive vs receptive language, Speech). Thirty of them (and 29 age-matched controls, TCDs) also underwent 3T language production fMRI study, which was successful in 19 children.

Results

Over the 72 children, daily language was well preserved in the vast majority, mean VCI was 97 +/-16. However, at least one abnormal N-EEL score (i.e. atypical clinical profile) was found in 49% of them, without clear differences between left and right lesions. Among the 19 children with successful language fMRI studies, 8 (42%) had lesions in the left posterior MCA territory (language areas), of which 7 (88%) were left-handers (3 right hemiparesis) and 5 (62%) showed right-sided activated regions (mirroring the left network found in the TCDs) with abnormal clinical profile. Lesions in other left territories (n=5) rarely led to atypical language (n=1), atypical hemispheric specialization (n=1), or left-handedness (n=2). Children with right lesions (n=6) showed both right-handedness and left language fMRI lateralization with abnormal clinical profile in 3 (50%).

Conclusion

Language outcome after NAIS is good. Normal VCI does not exclude subtle language deficits. Left posterior MCA territory infarcts often lead to right language specialization, especially in left-handers, then always with an atypical clinical profile, but lesion side does not appear a good predictive factor. These findings might eventually shed light on outcome assessment in the neonatal period to plan appropriate rehabilitation.

Dynamic functional network connectivity in BECTS - Effects of focus localization

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There is evidence that epileptic activity in the course of brain development influences the organization of functional networks within the brain. Children with benign epilepsy with centro-temporal spikes (BECTS) show a more bilateral or right hemispheric organization of language processes than healthy children (HC); nevertheless, knowledge about dynamic aspects of functional connectivity in these children is lacking. The aim of our study is to gain first insights into dynamic connectivity patterns in children with BECTS and the impact of focus localization.

FMRI data during sentence reading of 41 children with BECTS and 36 HC from two study sites (Basel, Montreal) were pre-processed using SPM12 and afterwards decomposed into 75 functional networks using a group-level spatial independent component (GIFT toolbox, Calhoun, 2004). We further used a sliding-window approach on individual time courses of 41 functional intrinsic connectivity networks and computed covariance matrices per window and participant. K-means clustering algorithm was used on the windowed covariance matrices to obtain group centrotypes of four different connectivity states (S1 to S4).

All BECTS showed less connectivity in one network-pair during S2 in comparison to healthy controls. By splitting up the BECTS group according to localisation of epileptic focus, even more differences became evident: children with a left hemispheric focus showed reduced connectivity in S2 and S3, whereas children with right-sided focus had less connectivity during S3 and within the central network during S4. Children with a left hemispheric focus had a significantly reduced dwell time in S3 and a higher number of transitions between states during sentence reading.

Children with BECTS show reduced connectivity compared to HC. Affected stages differ with respect to focus localization, which implies diverse adaption processes. Children with a left-sided focus are affected most during sentence reading: they show less connectivity between different networks and a more fluctuating utilisation of states.

Isolated Globus Pallidi hypointensities in type 2 GM1 gangliosidoses

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An 8-year-old boy, born to consanguineous parents, presented with developmental delay, unclear speech, abnormal gait and recent worsening in gait and swallowing function. There was no dysmorphic features or hepatosplenomegaly. He had extrapyramidal rigidity with severe dysarthria because of oromandibular dystonia. His two elder sisters had similar problems and were bed-bound from 8-years of age. Routine blood tests, fetoprotein, vitamin E, copper, and ceruloplasmin titers were negative. Metabolic work-up, including blood and urine chromatography of amino acids and urinary organic acids, were unremarkable. A careful look at the MRI which was reported normal revealed that the globus pallidi were hypointense more evident in FLAIR and DWI images. There was no cerebral atrophy or white matter hyperintensities. The MRI changes have been reported in late-infantile and juvenile GM1 gangliosidoses earlier however in view of rarity of the condition many are not aware of this finding.[1] This prompted genetic testing which showed homozygous mutation in GLB gene. Lysosomal enzyme assay in cultured skin fibroblasts revealed a -galactosidase activity of 5.8 nmol/mg/h (normal mean, 145 -32 nmol/mg/h).

Neurodegeneration with brain iron accumulation which includes conditions like pantothenate kinase-associated neurodegeneration, neuroferritinopathy, infantile neuroaxonal dystrophy, and aceruloplasminemia is characterized by evidence of focal brain iron accumulation in the extrapyramidal nuclei; the globus pallidum is consistently involved. Age of onset of the symptoms, involvement of additional nuclei and pattern of involvement helps in differentiation of different disorders.[2] Globus pallidum T2 hypointensity is also a known feature of thalassemia major and human immunodeficiency virus, in which it is caused by iron deposition, and of Wilson disease, in which it reflects the paramagnetic properties of copper. Isolated globus pallidum hypointensity in children is always abnormal and should point towards GM1 gangliosidoses and prompt appropriate investigations.

The impact of Necrotising Enterocolitis on brain development in preterm infants: Preliminary report

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Background and Aims
Necrotising Enterocolitis (NEC) is an inflammatory bowel disease causing intestinal gangrene, resulting in septicaemia. Infants born very preterm (<32 weeks of gestation; GA) are at high risk of developing NEC; around 50% of these infants require surgery. Surgically treated infants have 60% greater risk of neurodevelopmental impairment than other babies born at similar GA. This study aims to investigate how NEC impacts the developing brain and neurodevelopmental outcome.

Methods
This study included 7 preterm born infants (3 male, mean GA 26 +4 weeks) with confirmed NEC (Bell stage II/III), treated at a tertiary neonatal centre. Two controls groups were recruited; a preterm control (PTC) group without NEC (PTC; n=8, matched for at least two; GA +/- 2 weeks, birth weight Z-score, sex, and intraventricular haemorrhage), and a term control (TC) group of n=11 healthy term-born infants. Infants were scanned on a 1.5T MRI scanner at term equivalent age (37-44 weeks GA). Diffusion MRI data were acquired and Tract-based Spatial Statistics (corrected for multiple comparisons and adapted for newborns) was used to compare fractional anisotropy (FA) in white-matter tracts on a whole-brain level between groups.

Results
Correcting for post-menstrual age at scan, preliminary findings showed that infants in the NEC and PTC groups have a significantly lower FA in central WM tracts compared to term-born infants ($p<0.05$ and $p<0.05$ respectively). There was a weak trend of decreased FA in the splenium of the corpus callosum in NEC infants compared to preterm controls ($p<0.20$).

Conclusions
These preliminary findings indicate microstructural white-matter changes associated with NEC, particularly in the corpus callosum. However, a larger sample is required for further confirmation. Thereafter, associations with neurodevelopmental outcome measures can be explored.

Brain volume and cognitive functions in healthy very preterm born children

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Background
There is limited knowledge in healthy very preterm children whether gray matter volume (GMV) and white matter volume (WMV) increase linearly with advancing GA or whether there is a threshold of GA above which cognition and brain volume remain unaffected.
Objective: To determine whether subgroups of very preterm children defined by GA differ regarding brain volume and cognitive functions during school-age.
Study design
We studied 106 children (M=10 years 1 month, SD=16 months; 40 females) enrolled in primary school including 57 generally healthy very preterm children (24 born 24th -29th weeks of GA and 33 born 30th – 32nd weeks of GA), all born appropriate for GA and 49 term-born children. Neuroimaging implicated a structural sequence analysed with voxel-based morphometry with the SPM8 software. Cognitive functions were assessed with the WISC-IV.
Results
Compared to children born 30th-32nd weeks of GA and full-term controls, children born < 30th week of GA had lower GMV, WMV and poorer cognitive functions including decreased full scale IQ, verbal comprehension and processing speed. A regional difference in GMV was found in the right middle and superior temporal lobe where a cluster of 2134 voxel was significantly decreased in cortical GMV in preterms < 30th weeks of GA compared to preterms > 30th weeks of GA and controls. No differences were found between children born 30th – 32nd weeks of GA and full-term controls.
Conclusions
Healthy very preterm children born 30th – 32nd week of GA showed no decrements in GMV and WMV or cognitive functions in comparison to full-term children. In general, the 30th week of GA appears to be a relevant threshold above which brain and cognitive development is less affected than previously thought. In contrast, decrements in GMV, WMV and cognitive functions were evident in children born < 30th week of GA.

Atypical fetal superior temporal sulcus depth asymmetry predicts extraordinary language processing in childhood

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Hemispheric specialization serves as marker for healthy brain development in humans. The most clearly lateralized cognitive function in humans is language. Magnetic resonance imaging (MRI) allows investigating early structural asymmetries in the human fetus in vivo and in utero. In our ongoing work following a sample of healthy children that had fetal MRI, we observed a special case exposing atypical asymmetry of the superior temporal sulcus (STS) compared to 1) her "typical" twin brother and 2) a sample of four age-matched "typical" controls.

The sample of six children at the age of seven exposing no familial left-handedness underwent comprehensive neurolinguistic and neuropsychological assessment, language functional magnetic resonance imaging (fMRI) and task-free resting state fMRI.

Compared to "typical" reference sample, the "atypical" female twin exposed a significantly differing rightward shift concerning language lateralization in the frontal and temporal lobes. Regarding language localization the "atypical" twin showed increased activity in left parahippocampal, fusiform and lingual gyri and left ventral occipito-temporal LO area, compared to the control sample. Additional seed voxel correlations using seed voxels derived from the language paradigm revealed a "typical" strongly overlapping Broca network for both twins. However, the "atypical" twin showed additional stronger connectivity between the right inferior frontal gyrus (IFG) and the contralateral homologous area as compared to her brother. All children had normal cognitive profile.

This investigation depicts long-term outcome of fetal MRI regarding language processing in childhood. We were taking advantage of a case of atypical asymmetric development of the STS in combination with her twin brother sharing the same intra- and extrauterine environment and parts of their genes. We could show that the case exposing strong differences in cortical folding of language relevant brain areas also exposes differences in terms of language lateralization and localization in childhood compared to children withl typical prenatal cortical folding. This study is a first step towards extensive outcome research on prenatal biomarkers revealed by fetal MRI.

Unusual MRI findings in the spinal cord in a case of Kearns-Sayre syndrome

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Aim:
To describe unusual MRI spine findings in a case of Kearns-Sayre syndrome

Abstract:
Kearns-Sayre syndrome (KSS), is a rare multisystem mitochondrial disorder. The classic imaging findings include calcific deposits in the basal ganglia and/or sub cortical white matter, with supra and infratentorial atrophy. Nearly symmetric T2 prolongation in the subcortical white matter, basal ganglia, thalamus, corpus callosum, brainstem and cerebellum have been described in KSS.

We describe MR imaging findings in the cervical spinal cord in addition to findings in the white matter, basal ganglia, thalami and brainstem, in a proven case of KSS.

Brain volumes and developmental trajectories after preterm birth

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Background
Cognitive outcome after preterm birth is heterogeneous. We have previously shown in a cohort of very preterm children that cognitive ability at 5½ years was highly predictive of ability at age 18. However, a substantial proportion of preterm individuals improved their relative performance, i.e. in comparison to term born peers. This was not conclusively explained by perinatal or environmental factors (Stalnacke, 2015).

Aim
To investigate whether the relative improvement in cognitive abilities could be explained by variations in regional brain volumes measured in adolescence.

Methods
As part of a prospective longitudinal study, 118 preterm individuals (birth weight < 1500 g) participated in neuropsychological assessments at age 5½ and 18 years. Sixty (34 female) underwent MRI (including 3D T1-weighted images) at mean age 15.1 years. Twenty-one participants did show relative improvement of cognitive abilities, while 39 did not. Brain volumes (corrected for intracranial volume) were calculated using Freesurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). Regression analyses, controlling for sex and age at MRI, were performed to investigate associations between brain volumes and improvement of cognitive abilities.

Results
Improvement in cognitive abilities was significantly ($p<0.05$) associated with larger cortical grey matter volumes, larger volumes of the right thalamus, right hippocampus, right amygdala; insula and accumbens, bilaterally. There were no significant correlations between relative improvement and supratentorial white matter, cerebellar volumes, or corpus callosum volume. Analogous findings were obtained when eight participants with periventricular white matter abnormalities were excluded, except for the hippocampus, left accumbens and left insula.

Conclusions
There was a correlation between cognitive development and brain volumes, measured in adolescence. Individuals who improved had larger grey matter volumes compared to those who showed no cognitive catch-up.

Case series: Bilateral periventricular nodular heterotopia (BPNH) as detected on fetal and maternal MRI, caused by a previously undescribed Filamin A mutation

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We present a case series of X-linked bilateral periventricular heterotopia in a 31-year-old, neurologically unremarkable mother and her two consecutive female fetuses. During the first pregnancy, fetal MRI at 23+0 gestational weeks (gw) revealed severe bilateral periventricular nodular heterotopia (BPNH) and megacisterna magna, raising suspicion of X-linked BPNH. Post-mortem workup confirmed subependymal heterotopia During the second pregnancy, fetal MRI at 25+2 gw showed less pronounced periventricular heterotopia and megacisterna magna, further fostering the suspicion if X-linked BPNH. Additional cranial MRI of the mother revealed severe BNPH, but no megacisterna magna. As mutations in the X-chromosomal filamin A gene (FLNA) are by far the most common cause of X-linked BPNH (Parrini et al., Brain, 2006), DNA samples derived from maternal blood and chorionic villi biopsy during the first pregnancy were analyzed and revealed a previously undescribed FLNA mutation. Apart from the detection of this novel FLNA mutation this case is remarkable as it demonstrates high phenotypic variance of the mutation, with the first fetus displaying much more severe BPNH on MRI than the second fetus. Despite heavy BPNH burden on maternal MRI, the mother did not suffer from epilepsy or any other neurological or mental disorder. This furthermore demonstrates that the imaging phenotype does not necessarily predict the clinical phenotype, a notion that has to be taken into account when estimating neurological significance of findings on fetal MRI.

Hypoplastic olfactory nerve in a patient with SOX2 anophthalmia syndrome

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Introduction

SOX2 anophthalmia syndrome is an uncommon autosomal dominant syndrome caused by mutations in the SOX2 gene and clinically characterized by severe eye malformations, anophthalmia and/or microphthalmia that is usually bilateral, severe, and apparent at birth. Other common findings include brain malformations, esophageal atresia, hypogonadotropic hypogonadism and/or pituitary hypoplasia, postnatal growth failure, delayed motor development, and learning disability, however, there has been no report of olfactory nerves.

Case

A 4-year-old girl who was born at 40 weeks of gestational, and weighted 2,922 g, as a first child of healthy unrelated parents. At birth, she exhibited bilateral microphthalmia confirmed by CT. SOX2 gene analysis revealed a mutation (c.70_89del20), leading to a diagnosis of SOX2 anophthalmia syndrome. She presented delayed psychomotor development, meaningful words at 3 years, walking alone independently at 4 years, and probable olfactory disturbance. MRI at 4 years showed hypoplasia of eye balls, optic nerves and chiasma; hypoplasia and malrotation of bilateral hippocampus; and hypoplasia or apalasia of olfactory nerves.

Discussion

We firstly report hypoplasia/apalasia of olfactory nerves in a patient with SOX2 anophthalmia syndrome. It is known that SOX2 also expresses in olfactory epithelium, thus, SOX2 mutation may cause hypoplasia/apalasia of olfactory nerves. Olfactory nerves should be carefully checked when MRI is performed in patients with SOX2 anophthalmia syndrome.

Symptomatic neonatal arterial ischemic stroke: correlation of diffusion weighted imaging and clinical outcome at two years follow-up

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Background
Neonatal arterial ischemic stroke (NAIS) is known to be associated with cerebral palsy, epilepsy and cognitive impairment. Research on clinical outcome prognosis is scarce.

Aim
The aim of the study was to test the prognostic value of diffusion weighted imaging (DWI) findings at stroke onset regarding motor and mental development at 2 years follow-up (mean 23.3 months, SD 4.3 months).

Methods
Two different methods were used to correlate imaging data with clinical outcome: stroke lesions were localized in 58 cases (mean age of 2.2+/-2.1 days) and stroke lesion volumetry was carried out in a subgroup of 41 cases. Both findings were correlated with motor and mental development at 2 years follow-up.

Results
40% of the children developed CP and 25% showed delayed mental development.
The highest odds ratio (OR=17.0, 95% CI 3.26-88.77) regarding CP was found for involvement of thalamus and basal ganglia. Regarding cognitive outcome (OR 8.1, 95% CI 1.99-33.05) involvement of thalamus alone was shown to be most predictive.
Volumetry data showed a correlation between stroke lesion volumes and motor (r=.551, p<.001) and mental (r=-.398, p<.005) outcome.
In the case of occurrence of CP, lesion location remained more predictive than lesion volume (Wald=5.519, p=.019, Exp(B)=16.0).

Conclusion
Early DWI in children with neonatal ischemic stroke has a prognostic value regarding later clinical outcome. Both lesion localization and lesion volumetry data are related to motor and mental outcome at two years follow-up.